Anti-ribosomal P antibodies in large cohort of autoimmune hepatitis with no evidence of lupus: A common underlying mechanism targeting liver?

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The 10th International Congress on SLE
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Oral Presentations

19/04/13

10:40 - 11:40

Oral Presentations 1

Pacífico A

O01

The PREDICTS panel of biomarkers is associated with 28-fold increased risk for the presence and progression of atherosclerosis in women with SLE

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Purpose: There is up to a 50-fold increased risk of coronary artery disease in patients with SLE that is not fully explained by traditional Framingham cardiac risk factors. Several non-traditional biomarkers, including pro-inflammatory HDL (piHDL), elevated leptin, and homocysteine have been individually associated with subclinical atherosclerosis (ATH) in SLE. It is unknown whether these biomarkers and others can be combined into a risk profile (the PREDICTS panel) that better predicts future progression of ATH.
Methods: 210 female SLE and 100 age-matched control women not taking statins were studied. B-mode and Doppler scanning of carotid arteries was performed at baseline and at 24-36 months (mean 29.6 ± 9.7 months). Antioxidant function of HDL was measured as the change in fluorescence intensity caused by oxidation of DCFH by LDL in the presence or absence of test HDL. Fluorescence in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL. Plasma leptin and sTWEAK were measured by ELISA, and homocysteine was determined by HPLC in the UCLA clinical lab.
Results: 29% (61) of SLE patients had plaque on follow-up ultrasound. Factors associated with plaque on multivariate analysis included increased age (p=0.002), piHDL (OR 9.1 95% C.I. 3.3-24.6, $p < 0.001$), high leptin (OR 7.3, 95% C.I. 2.2 – 24.0, p=0.001), high plasma soluble TNF-like weak inducer of apoptosis (sTWEAK) (OR 28.8, 95% C.I. 2.9 – 281.1, p=0.004), and diabetes (OR 61.8 95% C.I. 6.4-598.1 $p < 0.001$). However, no single variable demonstrated full predictive capacity (e.g., negative predictive value (NPV) of piHDL was 89%, but positive predictive value (PPV) was 46%). We next used Salford Predictive Modeling software to determine which variables and cutpoints were most predictive for plaque: age ≥48, piHDL, leptin values ≥ 34ng/dL, homocysteine (≥12mmol/L), and sTWEAK ≥373 pg/mL. We defined high risk PREDICTS as ≥ 3 predictors or diabetes + ≥ 1 predictor. PPV for high PREDICTS was 94%, NPV 64%, sensitivity 89%, and specificity 79%. In multivariate analysis patients with high PREDICTS had a 28- fold increased odds for the longitudinal presence of carotid plaque (95% CI 10.6 – 72.7 $p < 0.001$), and also demonstrated an increased rate of plaque progression ($p < 0.001$)and IMT progression ($p < 0.001$). All 5 SLE subjects with a cardiac event had high baseline PREDICTS. High PREDICTS was also a significant predictor for plaque in controls (OR 8.1, 95% C.I. 1.8 - 36.4, p=0.006).
Conclusions: A high PREDICTS score confers 28-fold increased odds for the presence of any current, progressive or acquired carotid plaque in SLE subjects, and also significantly associated with higher rates of plaque and IMT progression.

O02

Neutrophil Gelatinase Associated Lipocalin (NGAL/lipocalin-2) regulates the onset of serum autoantibodies in pristane induced lupus

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Background: NGAL (lipocalin-2), a member of the lipocalin superfamily, is expressed by neutrophils, hepatocytes, and renal resident cells following ischemia or inflammatory conditions, and is involved in innate immune responses during infection. Previously, we found that NGAL worsens renal disease in nephrotoxic serum nephritis. However, its relevance to adaptive immunity has not been fully explored.
Materials and methods: To investigate a possible role for NGAL in autoreactive antibody responses in an experimental lupus model, we injected pristane (0.5 ml/mouse i.p.) into wild type B6 (n=10) and NGAL-deficient (NGAL-/-) (n=10) mice.
Results: Analyzing the levels of serum autoantibodies at 3 months post injection, we found that B6 NGAL-/- mice had significant increases in IgG2a and IgG2b anti-double stranded DNA antibodies. Similarly, the titers of IgG2a and IgG2b antibodies to single stranded DNA and histone were significantly increased in pristane challenged NGAL-/- mice as compared to NGAL sufficient mice. Furthermore, elevated serum anti-ribonucleoprotein antibodies were found in pristane treated NGAL-/- mice by immunoprecipitation. Although autoantibody titers in NGAL-/- mice were not increased at baseline, our results are

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consistent with the apoptotic defects and accumulation of lymphoid cells reported previously in these mice. We also found significant upregulation of interferon regulatory factor-5 (IRF5), IP-10, CXCL13, CXCR5, CxCR3, PD-1, PD-L1, and activation induced cytidine deaminase (AID) in spleens of NGAL-/- mice compared to WT mice. In vitro, we found that pristane and other inflammatory mediators promoted NGAL secretion by splenocytes.
Conclusions: NGAL deficiency accelerates the onset of anti-nuclear antibodies in pristane induced lupus, suggesting that blocking NGAL may be effective in spontaneous or induced humoral autoimmunity.

O03

Serum levels of B-Lymphocyte Stimulator and A PRoliferation Inducing Ligand in patients with lupus nephritis: APRIL as a candidate biomarker
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Background: B-lymphocyte activity has a pivotal role in the pathogenesis of Systemic Lupus Erythematosus (SLE). B-Lymphocyte Stimulator (BLyS), also known as B-cell activating factor (BAFF), is known for its role in the activation, differentiation, and maintenance of activated B-lymphocytes. BLyS is overexpressed in patients with SLE and its levels have been demonstrated to correlate with levels of autoantibodies and with SLE disease activity. In the circulation, BLyS appears as a homotrimer or a heterotrimer together with A PRoliferation Inducing Ligand (APRIL), a plasma-cell survival factor. The aim of our study was to investigate serum levels of BLyS and APRIL in patients with lupus nephritis (LN) and how these levels are affected by immunosuppressive treatment.
Patients and Methods: 64 patients with active biopsy–proven LN (55 females, 9 males, median age 31) were included in the study. The kidney samples were evaluated and rated according to the WHO classification system for LN (class II, n=1; class III, n=19; class IV, n=31; class V, n=13). All patients were treated with corticosteroids combined with cyclophosphamide (n=44), mycophenolate mofetil (MMF, n=13), rituximab (n=6) or azathioprine (n=1). The patients underwent a second renal biopsy after completed induction therapy. Serum and urine were collected before (baseline) and after induction treatment. Gender- and age-matched healthy individuals were recruited as controls (n=64). Serum levels of BLyS and APRIL were assessed by ELISA (R&D Systems and eBioscience, respectively).
Results: Soluble (s)BLyS and sAPRIL levels were significantly higher in patients compared to controls at baseline ($p < 0.001$ and $p < 0.01$, respectively). After induction treatment, a significant decrease in serum levels of APRIL was observed (p=0.034) but sBLyS levels remained unchanged (p=0.45). At baseline, median sBLyS levels in the patient and in the control group were 1512.1 and 1112.4 pg/mL respectively and median sAPRIL levels in the patient and in the control group were 7.1 and 3.6 ng/mL respectively. After induction therapy, median sBLyS and sAPRIL levels were 1734.3 pg/mL and 5.4 ng/mL respectively. Among patients with a proliferative nephritis (PN, class III/IV) at baseline, we observed decreased sAPRIL levels (p=0.005) but no difference in sBLyS levels (p=0.39) after induction therapy. In the patient group with membranous LN (class V), a trend towards decreased sAPRIL levels was noted (p=0.08) but no difference for sBlyS was seen (p=0.37). A greater decrease in sAPRIL levels was observed in patients who received MMF compared to cyclophosphamide.
Conclusions: Our findings demonstrate that both BLyS and APRIL are upregulated in patients with LN compared to healthy subjects. Serum levels of APRIL, but not BLyS, decreased after immunosuppressive therapy. This observation suggests that sAPRIL should be further evaluated as a biomarker for LN disease activity and as a candidate target for future drug therapy. Further studies of clinical and histopathological response to treatment need to be performed.

O04

Systemic sclerosis and systemic lupus erythematosus pan-meta-GWAS reveals six new shared susceptibility loci
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Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are two archetypal systemic autoimmune diseases which have been shown to share multiple genetic susceptibility loci. In order to gain insight into the genetic basis of these diseases we performed a pan-meta-analysis of two genome-wide association studies (GWAS) together with a replication stage including additional SSc and SLE cohorts. This increased the sample size to a total of 21,109 (6,835 cases and 14,274 controls). We selected for replication 20 SNPs from the GWAS data. We were able to validate as novel genetic susceptibility loci (for the combined SSc and SLE analysis) KIAA0319L (P = 3.31x10-11, OR = 1.49), PXK (P = 3.27x10-11, OR = 1.20), ATG5 (P = 5.30x10-7, OR = 1.14), JAZF1 (P = 1.11x10-8, OR = 1.13), SAMD9L (P = 3.17x10-7, OR = 1.19) and CSK (P = 2.59x10-7, OR = 1.13). Furthermore, we observed that KIAA0319L and SAMD9L were overexpressed in peripheral blood cells of SSc and SLE patients compared to healthy controls. With these, we add five (KIAA0319L, PXK, ATG5, JAZF1 and SAMD9L) and three (KIAA0319L, SAMD9L and CSK) new susceptibility loci for SSc and SLE, respectively, increasing significantly our knowledge of the genetic basis of autoimmunity.

O05

The lupus associated TT > A variant on 6q23 is located in an enhancer element that physically interacts with the TNFAIP3 promoter to influence TNFAIP3 expression.
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Introduction: The tumor necrosis factor alpha inducible protein 3 (TNFAIP3) gene encodes the ubiquitin-modifying enzyme A20, which negatively regulates NF-κB activity. Genetic variants in the region of TNFAIP3 are associated with multiple autoimmune diseases. We recently described a functional TT > A polymorphic dinucleotide 42kb downstream of the TNFAIP3 promoter demonstrating reduced affinity for an NF-κB nuclear protein complex, carried on a haplotype resulting in reduced TNFAIP3 expression. In this study, we investigated the mechanisms by which this polymorphism influences TNFAIP3 expression.
Materials and methods: To define how the TT > A variant influences TNFAIP3 expression we employed electrophoretic mobility shift assays (EMSA), mass spectrometry (MS), reporter assays, chromatin immunoprecipitation-PCR (ChIP-PCR) and chromosome conformation capture (3C) in the monocytoid cell line, THP1, and lymphoblastoid cell lines (LCL) carrying risk and non-risk TNFAIP3 haplotypes.

Cells were exposed to receptor specific (LPS, TNFα) and non-specific (PMA/ionomycin) stimuli to illicit genomic events in the TNFAIP3 locus.
Results: Consistent with our published results, EMSA demonstrated stimulus dependent binding of a nuclear protein complex to a probe containing the non-risk (TT) allele using nuclear extracts from either THP1 cells or LCLs. Complex formation was significantly reduced when the risk allele (A) was introduced into the probe sequence, suggesting that the risk allele alters the binding affinity of this complex. Super shift assays demonstrated that the protein complex contained NF-κB subunits in relative order of abundance: NFKB1 (p50) > cREL > RELA (p65). These findings were confirmed using ChIP-PCR in LCLs carrying risk and non-risk genotypes. To identify other proteins in this complex, we biotinylated EMSA probes and performed affinity purification followed by MS. The most abundant protein identified was SATB1, a protein known to facilitate long-range transcriptional signaling through DNA loops. SATB1 binding was independently confirmed by western blotting. To evaluate if the regulatory element containing the TT > A variant could function as an enhancer, we used a luciferase assay under the control of a minimal thymidine kinase promoter. Constructs with the non-risk sequence demonstrated significant luciferase expression following transfection into either HEK293 or THP1 cells suggesting that the regulatory element containing the TT > A variant functions as an enhancer. In contrast, constructs with the risk variant were significantly less effective in inducing luciferase expression. To determine the mechanism by which the TT > A enhancer element could influence TNFAIP3 transcript expression, we performed 3C and found that the TT > A enhancer element physically interacts with the TNFAIP3 promoter. This interaction was dependent, in part, on SATB1 as shRNA knockdown of SATB1 produced fewer promoter-enhancer interactions. Ongoing work will evaluate the TT > A risk and non-risk alleles on the efficiency of promoter-enhancer interactions using a novel allele-specific 3C assay.
Conclusions: These data demonstrate that the lupus associated TT > A variant downstream of TNFAIP3 alters a functional enhancer that interacts directly with the TNFAIP3 promoter via SATB1 mediated DNA looping. This enhancer likely delivers critical NF-κB subunits to the promoter to facilitate TNFAIP3 transcription following upstream signaling events.

19/04/13

10:40 - 11:40

Oral Presentations 2

Pacífico B

O06

SLE Cardiovascular Risk Equation
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Purpose: Accelerated atherosclerosis remains the major late cause of death in SLE. Yet, the "traditional" cardiovascular risk equations (Framingham, Reynolds, SCORE) consistently underestimate the risk. This may lead to under-recognition and under-treatment. We sought to construct a data-driven risk equation of cardiovascular risk in SLE, based on data collected in a longitudinal cohort.
Methods: To derive the score, risk factors were calculated based on variables measured in the first two years of cohort participation (mean systolic blood pressure, mean SLEDAI, etc). Cox Proportional Hazards models were constructed to determine the variables that affected the risk of a subsequent CVE. Using the results, a formula to calculate the risk of a CVE within the next 10 years was derived. There were 1342 patients, 93% female, 56% Caucasian, 38% African-American, and 6% other ethnicities. There were 109 cardiovascular events: 52 strokes, 26 MI, 18 angina/CABG, and 13 claudications.
Results: Each variable in the model is given an integer score: age=1 for each 5 years over 40; male=2; systolic blood pressure 140 or more=3; cholesterol over 160=3; smoking=3; diabetes=2; mean SLEDAI of 2 or more=3; history of lupus anticoagulant=3; and low mean C3=2.

Using this model, the risk of a CVE within 10 years is 1-0.9875(Hazard Ratio). For example, if someone is 50 years of age, male, with high systolic blood pressure, then the hazard ratio is (1.0510)x(1.74)x(2.21) = 6.26. The risk of a CVE in 10 years is then 1-0.9875(6.26) = 7.6%. In the absence of SLE risk factors, the estimated 10-year risk from our formula is higher than would be projected based on the Framingham formula. This is especially true if there are SLE-related risk factors. We then compared the risk based on the SLE equation with that of the Framingham, and found no difference in SLE patients with only traditional risk factors, and about a doubling of risk in patients with one of the SLE variables.
Conclusions: A data-driven SLE Cardiovascular Risk Score can better estimate 10-year cardiovascular risk than the Framingham equation. Its use can lead to appropriate use of imaging and intervention.

O07

Risk Factors for Non-Fatal Cardiovascular Disease in Systemic Lupus Erythematosus: Multivariate Analysis in a Cohort of 306 patients
Inanc M, Ertan-Demir S, Artim-Esen B, Ocal L
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Introduction and Background: Increased rate of cardiovascular disease (CVD) has been reported in patients with systemic lupus erythematosus (SLE). In addition to the traditional CV risk factors, disease related features may contribute to CVD in SLE. The aim of this study was to determine the prevalence and risk factors for non-fatal CVD in patients within current attenders of the SLE clinic.
Patients and Methods: Consecutive data from 306 SLE patients currently attending to the lupus clinic and fulfilling ACR classification criteria were collected with interview and from the records including demographic and clinical features, history of CVD and the presence of traditional CVD risk factors. CVD were defined as documented coronary artery disease and/or cerebrovascular disease including myocardial infarction and stroke. The association of CVD with traditional and disease related features including serology and treatment was assessed by using chi-square test. Logistic regression method were used for multivariable analysis.
Results: The mean age of the patients was 40,2± 13,4 years and 89% were female. The mean disease duration was 112,5 ±84 months, and the mean SLICC damage score was 1,05 ± 1,5. Coronary artery disease was present in 11.1% and cerebrovascular disease was in 5.4%. The prevalence of cardiovascular disease was 15.2%. Patients with CVD were older with a longer disease duration and increased SLICC damage scores. CVD events were associated with the presence of hypertension, elevated triglyceride levels, pericarditis, lymphopenia, thrombocytopenia, seizures, psychosis, IgM anticardiolipin antibodies, lupus anticoagulant, cyclophosphamide treatment and avascular necrosis. HCQ use was found protective [p= 0,003; OR: 0,34 (0,16-0,71)]. Multivariable analysis showed that pericarditis ($p < 0.001$),

lymphopenia (p=0.003), thrombocytopenia (p=0.008) and psychosis (p=0.024) were significantly associated with non fatal CVD.
Conclusions: In current attenders of the SLE clinic with a mean age of 40, the prevalance of non-fatal CVD was 15.2%. CVD was associated with particular clinical features of SLE including pericarditis, cytopenias and neurological involvement. In the univariate analysis, there was a significant protective effect of HCQ from CVD in SLE. These results indicate that CVD in SLE may be related to disease activity and/or concurrent corticosteroid usage rather than traditional risk factors.

O08

Predictive Atherosclerotic Risk Factors At Inception in a Multicentre, Multinational Cohort

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) develop premature atherosclerosis (AS). This study examines predictive factors at inception for atherosclerotic vascular events (AVE) over a maximum 10 years of followup in a multicenter, international inception cohort.
Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. At yearly visits demographic and cardiovascular risk factors are collected and vascular events (VE) are described and attributed on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, and transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria and diagnostic tests where appropriate. Attribution to AS was made by physicians on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Analysis was done using descriptive statistics and Cox proportional Hazard model.
Results: Of the inception cohort of 1844 SLE patients 93 had VE due to non-AS causes (e.g. active SLE or thrombosis) and 350 patients had only enrolment data leaving 1401 patients. 31 patients had 41subsequent AVE after enrollment. The mean time to AVE or last clinic followup was 5 years. Patients' race/ethnicity distribution was as follows: 51% Caucasian, 16% Black, 17% Asian 12% Hispanic 4% other. At enrollment risk factors for AS are shown in the table 1.

	Patients without AVE n=1370	*Patients with AVE n=31*	*P value*
Age	34.6 ± 13.1	56.0 ± 13.8	<0.0001
Sex, %	90.6	58.1	<0.0001
Diabetes, %	3.2	10.7	0.06
Framingham Risk Score Mod/High, %	1.5	25.0	0.001
Smoker Ever, %	35.7	61.3	0.004
Obese, %	29.3	53.6	0.01
Hypertension, %	32.6	60.0	0.003
Hypercholesterolemia, %	34.7	50.0	0.12
Increased LDL*, %	33.3	33.3	1.00
Increased Creatinine, %	23.5	47.8	0.01

*LDL=low density lipoprotein

Table 2. Time to Event Analysis 1 risk factor at a time

	Hazard Ratio	*95% CI*	*P value*
One Risk Factor at a Time			
Age	1.09	1.07, 1.12	<0.0001
Caucasian	3.39	1.46, 7.87	0.005
Male	6.30	3.09, 12.87	<0.0001
FRS Mod/High	13.15	3.99, 43.22	0.0001
Smoker ever	2.95	1.43, 6.09	0.003
Obesity	2.92	1.39, 6.14	0.005
Hypertension	3.10	1.49, 6.43	0.002
Hypercholesterolemia	1.85	0.90, 3.77	0.09
Stepwise Regression With All Above Variables			
Age	1.09	1.06, 1.11	<0.0001
Male	4.07	1.84, 9.04	0.0006

*FRS=Framingham Risk Score
Conclusion: Only age and male sex remain significant risk factors for AVE in a multivariate analysis of a multicentre inception cohort followed for a mean of 5 years.

O09

Renal response to a protein challenge in patients with Lupus Nephritis and variable degree of glomerular or interstitial damage after maintenance therapy

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Background: The renal response to a protein (PL) or an amino acid challenge has major diagnostic and prognosis implications in the evaluation of progressive renal diseases, a frequent finding in patients (Pts) suffering from lupus nephritis (LN) In recent years, the contribution of the tubulo-interstitial damage to the progression towards severe renal failure became increasingly aparent. Given that creatinine undergoes considerable tubular secretion, the assessment of sequential creatinine clearance (CrC) after a PL could serve as a test directed at identifying the magnitude of the functional tubular mass. The aim of this trial was to evaluate the renal response to PL in LN individuals with different degrees of chronicity index (CI).
Patients and Methods: All biopsies performed in Pts with Class III (n: 5) and Class IV (n: 12) LN between January 2011 and September 2012 were included. Individuals with LN are routinely biopsied before ending their maintenance therapy in our unit. A total of 17 LN PTs (9 with predominant glomerular sclerosis –GS- and 8 with predominant tubule-interstitial sclerosis –TIS-) underwent to a protein load test in order to assess the renal functional reserve (RFR). Briefly; after an overnight fast all the subjects received an oral water load (20 ml/kg BW) and the urinary output was then replaced orally with equal volumes of water. After two 30-min periods, a 1.5 g/kg BW PL was provided. CrC was measured every 30 min. from 1 h before and for 4 h following PL. Baseline CrC was taken as the average of two 30-min periods before PL and peak CrC as the maximal CrC recorded thereafter. The functional reserve index (FRI) was calculated as the quotient between peak and baseline CrC. All data are expressed as media ± SEM.
Results: The groups were similar with regard to demografic characteristics at baseline. Pre PL the average CrC (ml/min) was similar in GS and TIS (100.6 ± 11.4 and 99.5 ± 10.8; respectively). CrC rose after PL to a peak of 135 ± 22.0 and to 125 ± 27.5 ml/min in GS and TIS

respectively $p < 0.02$). The FRI was lower in TIS than in GS and CG (1.22 ± 0.04 and 1.42 ± 0.06 respectively ($p < 0.05$)

Conclusions: The results from this study suggest that in LN individuals the presence of tubulo-interstitial damage drastically reduces the renal response to a protein challenge assessed through the Ccr in contrast with the almost normal response obtained in subject with predominant glomerular involvement.

This decrease could be due to a fall in tubular secretion of creatinine as a consequence of a reduced functioning tubular mass or to a sub-normal glomerular hemodynamic response due to an altered tubule - glomerular feed-back mechanism.

The assessment of the RFR may help to decide whether or not to go on treatment in those pts with severe renal fibrosis.

O10

Clinical presentation, treatment and outcome of membranous nephropathy in SLE: a comparison with proliferative lupus glomerulonephritis in 141 patients

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Objectives: To study the presentation and outcome of membranous nephropathy in comparison with proliferative nephritis in SLE.

Methods: Patients with biopsy confirmed active lupus nephritis who were recruited in a RCT comparing the efficacy of mycophenolate mofetil (MMF) and tacrolimus (Tac) were studied. Participants were divided into 3 groups: group I (pure membranous lupus Gn class V); group 2 (mixed membranous and proliferative Gn: class V+III or IVS/IVG) and group 3 (proliferative lupus Gn: IVS/IVG). The clinical presentation, treatment and outcome of these patients were compared.

Results: 141 patients were studied (92% women; age 35.2+/-12.8 years; SLE duration 49.3+/-62 months). There were 25 patients (18%), 31 patients (22%) and 85 patients (60%) in group 1, 2 and 3, respectively. At presentation of renal disease, group 1/2 patients had significantly higher hemoglobin level, creatinine clearance (CrCl) (90.0+/-31 vs 69.7+/-27ml/min), C3 level but lower serum Cr (70.8+/-25 vs 91.5+/-33umol/L) and anti-dsDNA titer than that of group 3 patients ($p < 0.001$ in all). 18 (32%) patients in group 1/2 had normal range C3 or anti-dsDNA, compared to 3 (4%) patients in group 3 ($p < 0.001$). The SLE disease activity index (SLEDAI) score was significantly lower in group 1/2 than group 3 patients (13.5+/-4.9 vs 18.0+/-5.3 points; $p < 0.001$). Extra-renal activity was less common in group 1/2 than group 3 patients, but the difference was only statistically significant for arthritis. All patients were treated with high-dose prednisolone and either MMF (N=72) or Tac (N=69) for induction, followed by low-dose prednisolone and azathioprine for maintenance. Complete response to induction treatment at 6 months was less common with group 1/2 than group 3 patients (45% vs 62%; p=0.10). After a mean observation of 48.5+/-21 months, the cumulative risk of loss in 30% of CrCl compared to baseline was 4.6% at year 1, 6.3% at year 3 and 18% at year 5. Group 1/2 patients did not differ significantly from group 3 patients in terms of decline in CrCl (HR 0.46[0.15-1.46];p=0.19, adjusted for age, sex, SLE duration, initial CrCl and treatment arms). There were 4 arterial events (2 acute coronary syndrome; 2 cerebrovascular accidents) and 1 venous event (deep vein thrombosis) - all occurred in group 1/2 patients (compared with group 3; p=0.01). Infections (major and minor) were non-significantly more common in group 1/2 than group 3 patients.

Conclusions: The presence of histological membranous component in lupus nephritis is associated with more proteinuria, better renal function but less active lupus serology or extra-renal activity at presentation. Complete response to induction therapy is less likely. Renal function decline in membranous lupus nephropathy is no different from proliferative lupus nephritis, but thrombotic complications are more frequent.

19/04/13

14:30 - 15:30

Oral Presentations 3

Pacífico A

O11

Provisions of quality driven care in childhood-onset Systemic Lupus Erythematosus

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Background: Quality Indicators (QI) are retrospectively measurable elements of practice performance for which there is evidence or consensus that can be used to assess the quality of care provided. Previous QI have been developed for adult systemic lupus erythematosus. This project was the second of two Delphi surveys used to identify QI in childhood-onset systemic lupus erythematosus (cSLE) that could serve as international benchmarks to assess quality of patient care.

Methods: Based on medical literature and a previous Delphi survey, a second survey was created and distributed to 348 individuals on the member lists of EULAR, PANLAR, PRINTO, PRES, ACR and CARRA via email. 265 individuals (76%) responded via online or paper survey, with 173 (65%) participants identifying themselves as pediatric rheumatologists. The survey design included a brief summary of relevant literature for each topic prior to the question. Participants had access to the referenced articles for each question through a hyperlink in the survey. Consensus was set at 80% agreement and blank responses were excluded from the analysis.

Results: Important process QI (IF/THEN statements) addressing the following treatment domains achieved consensus: bone health, education on cardiovascular risk factors, lupus nephritis and hypertension management, medication management, ophthalmological surveillance, transfer of care, use of chronic steroids in cSLE management, and vaccinations. Of the 26 process QI for use in cSLE, 11 match those established for adults with SLE, nine required modification, and consensus was reached for an additional six QI specific to children., A substantial amount of support was noted for clinical evaluation of disease activity every 3 months (71%), while the support for safety monitoring for medications was variable. Consensus was reached around the a schedule for medication surveillance safety in cSLE

Conclusion: Delphi questionnaires are efficient instruments for reaching international consensus for minimal standards of quality care for cSLE. Additional efforts will help refine items for which there is currently not consensus. The new QI identified through this project can be used to define and standardize best practices for children and adolescents with cSLE across the world.

O12

Accuracy of Systemic Lupus International Collaborating Clinics Classiffication Criteria Applied to Juvenile Systemic Lupus Erythematosus Patients

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Background: Systemic lupus erythematosus (SLE) is a prototype autoimmune disease. The most widely used classification criteria for SLE were those developed by the American College of Rheumatology (ACR) in 1982.(1)These criteria have not been completely evaluated in pediatric patients, although Ferraz et al, describes the sensitivity and specificity in Brazilian children. (2) In 1997, ACR 1982 criteria were revised but not validated. Recently, The Systemic Lupus Collaborating Clinics (SLICC) validated new criteria in adults in order to improve clinical relevance(3).
Objectives: To assess the sensitivity and specificity of SLICC SLE criteria in a cohort of Juvenile SLE patientsTo compare sensitivity and specificity of ACR criteria vs the new SLICC criteria.
Methods: The SLICC criteria rule for SLE classification requires: 1) four criteria, with at least one clinical criterion and one immunologic criterion or 2) lupus nephritis alone in the presence of ANA or anti-DNA antibodies. Seventeen criteria were identified. Cases were JSLE patients who were attending a single tertiary center in the past 10 years. Controls were patients with rheumatic diseases other than SLE: Juvenile Idiopathic Arthritis (JIA); Juvenile Dermatomyositis (JDM), Autoimmune Hepatitis (AH) and Juvenile Systemic Sclerosis (JSS). Diagnoses were made on clinical and immunological grounds by experienced pediatric specialists. Criteria were reviewed from prospectively developed databases and medical records by pediatric rheumatologists in order to establish the number and frequency of new criteria fulfilled by each patient. Descriptive statistics were used to characterize both patients groups. Summary statistics included overall sensitivity and specificity. McNemar's test was used to assess differences between ACR 1997 criteria and SLICC criteria with respect to accuracy.
Results: Cases: 107 patients with JSLE were included (F: 89 M: 18), age at onset: 12 (3-16) yo. Controls: 102 patients with JIA (36 patients, systemic 20, polyarticular 16); JDM (28), AH (28) and JSS (10), F:76 M: 26, age at onset: 11 (2-16) yo. SLICC SLE criteria sensitivity was 100 % vs 86% ACR 1997 criteria, while specificity was 98% vs 96% (p=0.009). Six patients with a clinical diagnosis of JSLE were correctly classified by SLICC but not by ACR criteria.

Table lists the sensitivity and specificity of each criterion in SLICC SLE criteria

	Sensitivity%	*Specificity%*
Acute cutaneous lupus	61	100
Chronic cutaneous lupus	12	100
Oral ulcers	11	100
Nonscarring alopecia	14	98
Synovitis	65	68
Serositis	13	98
Renal	56	99
Neurologic	11	100
Hemolytic anemia	21	98
Leukopenia or Lymphopenia	34	95
Thrombocytopenia	31	92
ANA	100	60
Anti-DNA	63	100
Anti-Sm	30	100
Antiphospholipid antibodies	33	100
Low complement	91	90
Direct Coombs Test	29	98

Conclusion: The SLICC criteria show hight sensitivity and specificity in JSLE. The SLICC new criteria were more sensitive and specific than the ACR 1997 criteria in a cohort of patients with JSLE.

O13

Novel urine biomarkers for monitoring disease activity in juvenile lupus nephritis: A prospective longitudinal validation study

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Introduction: Systemic Lupus Erythematosus (SLE) is a severe autoimmune condition with lupus nephritis (LN) seen more frequently in juvenile disease (JSLE) where up to 80% have renal involvement [1]. The renal biopsy is crucial for diagnosis and classification but has a limited role in monitoring. Current methods of monitoring renal disease activity over time rely on a variety of standard laboratory markers and the use of disease activity tools such as the British Isles Lupus Assessment Group index score (BILAG). Improving methods of monitoring and predicting disease activity changes may allow earlier intervention and improve the long-term renal outcome.
Patients & Methods: This prospective longitudinal study aimed to identify whether standard and/or novel biomarkers are useful for monitoring and predicting LN disease activity. Using patients recruited to the UK JSLE study, urine and blood samples were collected during routine clinical reviews. The study had full ethical approval.
Results: The JSLE cohort (n=64), seen at 3 (interquartile range IQR: 2-5) clinical reviews over 364 (182-532) days were aged 14.1 (11.8-15.8) years and 80% female. Active renal episodes (23% total; renal BILAG A/B) had significantly increased concentration of; monocyte chemoattractant protein 1 (MCP1), neutrophil gelatinase associated lipocalin (NGAL), erythrocyte sedimentation rate, anti-double stranded DNA, urine albumin:creatinine ratio (UACR), creatinine, and reduced complement 3 (C3), C4 and lymphocytes.

Multivariate analysis demonstrated MCP1 and C3 as independent variables ($p < 0.001$) for active renal disease.

MCP1 was an excellent predictor of improved renal disease (area under the curve AUC: 0.81; p=0.013; concentration 343pg/ml, specificity 71%, sensitivity 70%); NGAL was a good predictor of worsened renal disease activity (AUC 0.76; p=0.04; concentration 30ng/ml, specificity 60%, sensitivity 61%). Urine MCP1 and uNGAL changed as subsequent renal disease changed (MCP1 p=0.015; NGAL p=0.038). Standard markers could not predict disease activity changes.
Conclusions: We have demonstrated that biomarkers (MCP1, C3) perform well for monitoring renal disease in JSLE, and novel biomarkers (MCP1, NGAL) out perform standard markers for predicting change. Biomarker-led monitoring may facilitate the titration of medication and allow earlier diagnosis and intervention opportunities. Collaboration with industry to develop point of care urine biomarker testing is now in progress.

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O14

Dysregulated phagocytosis in Juvenile Systemic Lupus Erythematosus

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Background: Phagocytosis is the cellular uptake of pathogens and apoptotic cells, which must be removed since inefficient clearance may provoke an inflammatory response. Evidence suggests systemic lupus erythematosus (SLE) autoimmunity could be related to impaired/delayed clearance of apoptotic cells as SLE macrophages have impaired phagocytic ability [1]. The TAM family of phagocytosis receptors, consisting of Mer, Tyro3 and Axl, may also play a role in SLE. Mice lacking Mer have deficient apoptotic cell clearance and develop lupus-like autoimmunity [2]. Soluble Mer (sMer) and Tyro3 (sTyro3) can inhibit phagocytosis and have been detected in adult-onset SLE plasma correlating with disease activity [3]. Juvenile-onset SLE (JSLE) is a more severe form of SLE and presently there are no studies into the role of phagocytosis within JSLE.
Methods: JSLE (n=15; n=30), juvenile idiopathic arthritis (JIA) (n=10; n=20) and paediatric healthy control (pHC) (n=15; n=30) plasma was analysed by ELISA for sMer and sTyro3 respectively.

Phagocytosis assay: Macrophages isolated from adult healthy control (aHC) were incubated with pHRodo stained bacteria in the presence of 10% JSLE (n=8) or aHC serum (n=7) for 30 minutes at 37°C (phagocytosis assay) or 4°C (negative control), then analysed by flow cytometry. Monocytes were isolated from JSLE (n=4) or pHC (n=5) patients and incubated with bacteria in 10% serum from JSLE, pHC and JIA patients. Results shown are mean±SEM.
Results: sMer concentration was significantly increased in JSLE plasma compared to JIA and pHC (p=0.014; $p < 0.001$). JSLE sMer concentration was inversely correlated to patient age (r=-0.72; p=0.003). sTyro3 was also significantly increased in JSLE plasma in comparison to JIA and pHC (p=0.004; p=0.021). aHC macrophages incubated with JSLE serum had significantly reduced phagocytosis compared with pHC serum (29.3±3.9% vs 46.8±4.7%, p=0.021). Incubation of pHC monocytes in JSLE serum resulted in significantly lower phagocytosis compared to pHC serum (40.8±4.1% vs 7.1±2.1%; p=0.018). However incubating JSLE monocytes in pHC serum could not always restore their phagocytic ability (33.2% vs 39.5%) suggesting that JSLE phagocytosis deficiency may be due to instrinsic cellular defects.
Conclusion: The significantly increased sMer and sTyro3 in JSLE plasma demonstrates a link between dysregulated phagocytic environment and JSLE.

Incubating aHC macrophages in JSLE serum caused significantly reduced phagocytosis suggesting that factors in the serum, such as sMer and sTyro3, may block phagocytosis. Analysis of JSLE and pHC monocyte phagocytosis demonstrated a JSLE serum and intrinsic cell effect on phagocytosis. A potential cell defect could be the ability to cleave phagocytosis receptors, forming sMer and sTyro3, therefore resulting in fewer receptors on the cell surface and subsequent decreased phagocytosis.

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O15

Hippocampal atrophy in childhood-onset Systemic Lupus Erythematosus

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Objectives: To determine the prevalence of hippocampal atrophy in childhood-onset (cSLE). To determine the possible relationships between hippocampal atrophy and disease duration, corticosteroid therapy, central nervous system (CNS) manifestations and the presence of antiphospholipid antibodies.
Methods: Neurological manifestations were analyzed according to the ACR classification criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity (SLEDAI), damage (SDI) and current drug exposures. Total dose and cumulative dose of corticosteroids and other immunosuppressant medications were evaluated. MRI scans were performed in a 3T Phillips scanner using a standardized protocol. Volumetric 1mm T1 weighted images were used for manual volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Non-parametric tests and correlation were used for statistical analysis.
Results: We included 40 cSLE patients (39 women; mean age 16.8+-3.54 years) with disease duration of 4.84+-3.67 years and 40 controls (31 women; mean age 20.32+-4.99). At study entry, right (mean volume 3.6cm3; SD+-0.41) and left (mean volume 3.49cm3; SD+-0.44) hippocampal volumes were significantly smaller in cSLE patients when compared to right (mean volume 4.4 cm3; SD+- 0.5; $p < 0.001$) and left (mean volume 4.43 cm3; SD+- 0.45; $p < 0.001$) of controls. Hippocampal atrophy was identified in the right hippocampus in 18 (45%) and in the left hippocampus in 19 (47.5%) patients and in the right hippocampus 1 (2.5%) control. Bilateral atrophy was identified in 13 (32.5%) patients and in no controls. Hippocampal volume reduction was associated with the presence of positive ACL (p=0.009), vasculitis ($p = 0.042$), disease duration (p=0.001), total dose of corticosteroids (p=0.019), cognitive impairment (p=0.005), age of disease onset ($p = 0.008$) and current age ($p = 0.013$). No relationships between hippocampal atrophy and SLEDAI, and SDI was observed.
Conclusion: Hippocampal atrophy is frequently observed in cSLE patients. The evaluation of hippocampus is an easy tool to determine patients that may have hippocampal volume loss and should be followed more closely with MRI and cognitive evaluation.

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19/04/13

14:30 - 15:30

Oral Presentations 4

Pacífico B

O16

Frequency of hematological alterations in patients with systemic lupus erythematosus (sle) and its association with vascular thrombosis - gladel registration

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Introduction: The aim of the present study is to evaluate the frequency of hematological alterations that occurred in the first thirty days after the diagnosis of SLE in patients from the GLADEL's (Grupo Latino Americano De Estudio de Lupus) longitudinal inception cohor and to explored the multiplicative interaction of such hematological alterations with the detection of Antiphospholidic Antibodies (APA), as determinants of vascular thrombosis (VT) in this patients.
Material and methods: The GLADEL provided the registration of secondary data. The associations between the detection of APA during the first thirty days after the diagnosis of SLE, with the development of VT at anytime in the follow-up after the diagnosis, as well as between the presence of hematological alterations with the development of VT during the follow-up, were estimated using descriptive statistical tests with their corresponding relative risks (RR), attributable risks (AR) and confidence intervals of 95% (IC95%).

The strength of the association between hematological alterations and APA, was assessed using the relative opportunity (OR) and their IC95%. It was estimated, through stratified analysis, the multiplicative interaction between the presence of hematological alterations and APA in the development of VT. Statistical packages used, PASW Statistics 18 and Epidat3.1. All statistical tests had two-tailed Alpha value of 0.05.
Results: Between January 1996 and December 2006, 1480 patients entered to the follow-up study of GLADEL. The frequency of women was 89.86% with a woman:man ratio: 8,9: 1. The hematological alterations found in the first thirty days after the diagnosis of SLE were: lymphopenia in 11,14%, leukopenia in 8.10%, leukopenia added lymphopenia in 5.60%, thrombocytopenia in 3.44%, IHA in 1.55%, and the Association of thrombocytopenia with IHA in 0.54%.

The distribution of positivity for APA in the first thirty days after the diagnosis of lupus, was: IgGaCL antibodies in 3.71%, IgMaCL antibodies in 2.16%, double positivity IgGaCL and IgMaCL antibodies in 1.35%, antiβ2GPI antibodies in 0.27%), Lupic Anticoagulant (LA) in 1.08%, and, falsely reactive VDRL in 0.67%.

A positive association between hematological alterations and APA was found (OR 6.17; IC95%, 3.96 to 9,62). It was estimated a RR of 2.77 (IC95%, 1.68 to 4.59) for the association between hematological alterations and TV, with FA of 64% (IC95%, 40.3% to 78.9%). Detection of APA during the first thirty days after the diagnosis of lupus, was associated to VT anytime after the diagnosis, with crude RR of 3.31 (IC95%, 1.79 to 6.11) and AF of 69.8% (IC95%, 44.1% to 83.6%), association that is modified by the presence of hematological alterations (RR stratum of interaction 3.86).
Conclusions: Although uncommon, the hematological alterations detected in the first thirty days after the diagnosis of patients with SLE, are correlated with APA of different subtypes. In addition, the concomitant presence of hematological alterations and APA determines a subgroup of patients with SLE with greater probability of developing VT.

O17

Prevalence and Clinical Significance of Severe Infection in Patients with Systemic Lupus Erythematosus: Preliminary Data From RELESSER (Registry of Lupus of the Spanish Society of Rheumatology)

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Background: Infection is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). Immunosuppression, comorbidities, and the disease itself makes patients with SLE susceptible to severe infections (SInf) but the relative contribution each of this factors are not well known.
Objectives: To retrospectively assess the prevalence of SInf and differences between patients with or without SInf in a multicentric SLE cohort.
Methods: Patients with SLE on active follow up, from the first 684 patients registered on RELESSER. Cumulative clinical data were collected. SInf was defined by the need for hospitalization. Charlson Index (ChI) was use to evaluate comorbidity, and SLICC/ACR/DI (SDI) and Severity Katz index (SKI) to assess damage and SLE severity respectively. We analyzed the impact of infection on SLE mortality in the entire cohort.
Results: 583 SLE patients (92% ≥4 ACR criteria) were included; 88% females, mean age: 45 years, median SLE duration: 111 months (IQR: 47-188). 80 patients (14.5%) suffered ≥ 1 SInf.Median SInf: 1(IQR: 1-2). First SInf localization: respiratory: 51.2%, urinary: 16.2% and bloodstream (8.7%), with a predominant bacterial aetiology (42.5%). Comparing with patients without SInf, patients with SLE and SInf were older: 50(39-61) [median (P25-75)] vs.43(34-53) years, $p < 0.0001$, had longer duration of SLE:170 (83-253) vs.103(42-174) months ($p < 0.0001$), more SKI: 4(2- 5) vs. 2(1-3), $p < 0.0001$, more SDI:1(0-3) vs. 0(0-1), $p < 0.0001$ and a higher ChI: 3(1-4) vs. 1(1-2), $p < 0.0001$. Furthermore, ≥ 2 SInf also associated with more SDI ($p = 0.003$), more SKI ($p = 0.027$) and more ChI ($p < 0.001$) comparing with only 1 SInf. Patients with SInf were more frequently hospitalized by SLE (excluding by infection): 80.0% vs. 45.0%, $p < 0.0001$ and treated with corticosteroids (CE): 98% vs. 87%, $p = 0.004$, cyclophosphamide (CPM):40% vs.17%, $p < 0.0001$, or mycophenolate m. (MPM):33% vs. 17%, $p = 0.001$(any time). At the moment of the first infection, 41 patients (77%) were treated with CE, 25(48%) with immunosupressors, 5 (20%) with CPM and 4(16.0%) with MPM, figures higher than the prevalence of these treatments in the last assessment available in RELESSER, i.e., GC: 51.8%, CPM: 1.1 % and MPM: 12%. Only 3 of 24 (12%) deceased patients, died by SInf. Excluding patients died by infection, the mortality was higher in SLE with history of SInf (9.6 vs. 1.7%, $p < 0.000$; $\chi 2$ Pearson).
Conclusions: Despite being a low-severity cohort, the cumulative incidence of serious infection is high in our SLE patients. The respiratory infection was the most common localization of SInf in SLE. An antecedent of SInf seem to be associate to more severe SLE, more mortality and comorbidity, although these associations could be related with a longer disease exposure y/or older age.

O18

Impaired Diffusion Tensor Imaging findings in the corpus callosum and cingulum may underlie impaired learning and memory abilities in Systemic Lupus Erythematosus

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Background: Memory impairment is prevalent in systemic lupus erythematosus (SLE), however the pathogenesis is unknown. In a previous functional Magnetic Resonance Imaging (MRI) study we demonstrated altered brain activity dynamics and less brain deactivation in patients with SLE as compared to healthy controls, when performing a learning and memory task. Our findings localized this impairment to the anterior medial prefrontal cortex of the default mode network (DMN). In addition altered networking of the hippocampal subsystem of the DMN was seen in patients with SLE when performing this task. These findings may reflect compensatory mechanisms to overcome memory impairment. The present study aimed to search for a structural substrate for the abnormal recruitment pattern observed in functional MRI studies by using Diffusion Tensor Imaging (DTI).
Patients and Methods: Using a DTI sequence in a 3.0T MRI scan, we characterized brain diffusivity in 10 SLE patients and 9 healthy controls matched for age and education. We examined two tracts associated with the DMN: the corpus callosum and the cingulum.
Results: In the left cingulum fibers higher apparent diffusion coefficient (ADC, $F(1,16) = 4.9$, $p < 0.05$) and radial diffusivity (Dr, $F(1,16)=4.6$, $p < 0.05$) values were seen in SLE patients as compared to controls. Similarly, in the corpus callosum, higher ADC values ($F(1,16)=13$, $p < 0.005$), radial diffusivity (Dr)($F(1,16)=7.4$, $p < 0.05$) and longitudinal diffusivity (Da) ($F(1,16)=14.4$, $p < 0.005$) were evident in SLE patients.
Conclusions: Higher diffusion coefficients in the corpus callosum and the left cingulum may indicate impaired organization/reduced integrity of these tracts which may underlie the abnormal pattern of brain activity recruitment of the DMN observed during a verbal learning and memory task. The abnormal findings in the left cingulum are in line with the central role of the left hippocampus in verbal memory and suggests that these findings may contribute to the impairment seen in patients with SLE on performance of a verbal memory task.

O19

Which Lupus Trial Endpoints Best Reflect Clinical Judgment or Biomarker Improvement?

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Background/Purpose: Outcome measures used in clinical trials of lupus are complex and difficult to interpret. With a plethora of new treatments in development and no objective gold standard to define efficacy, a better understanding of what the different endpoints signify would be helpful in designing more efficient trials and for clinicians in practice who need to interpret the results.
Methods: 91 patients from the Oklahoma Lupus Cohort (5 male, mean age 41) were identified with two visits at which SLEDAI and BILAG scoring had been performed and active disease (SLEDAI $>/=6$) at the first visit. Each was evaluated by physician judgement as same, improved or worse at the second visit based on clinical records. Serum cytokine levels were measured by xmap multiplex bead-based assay.
Results: At baseline, mean (SD) PGA, SLEDAI and BILAG were 1.75 (0.37),10.0 (4.09) and 15.1 (6.54). 68 patients were ranked as improved, 23 same or worse at the follow up visit. SRI (SLE Responder Index) and BICLA (BILAG-based Composite Lupus Assessment) were compared. Endpoints using these constructs restrict medication use. SRI and BICLA without medication criteria captured physician ranked improvement (PRI) with 85.3% vs 76.5% sensitivity and 73.9% vs 78.3% specificity. With medication limits, fewer patients were responders, but specificity increased to 82.6 and 95.6%. Similar trends were observed for modified SRI scores (SRI3 and 5). Spearman Rank correlations to PRI were: SRI3 0.605, SRI4 0.563, SRI5 0.541, BICLA 0.492 (all p values < 0.000001). All 9 patients who improved by BICLA but not SRI failed to achieve 4 point improvement in SLEDAI, which requires complete resolution of one or more disease features. However, 7 were rated as significantly improved by PRI. All 15 responders to SRI and not BICLA failed to improve in every organ, but 12 were rated as improving by PRI.

Biomarkers could provide an objective standard to compare clinical measures. Exploratory evaluation of serum cytokines allowed some preliminary modeling. In the current study IL6 was only detectable in a minority of patients (n=38) but decreased significantly in those patients who improved: PRI $p < 0.001$, SRI3 and SRI 4 p=0.003, SRI5 p=0.001, BICLA p=0.005.
Conclusion: Shortfalls of SRI and BICLA are usually due to the BICLA requiring only partial improvement but in all organs vs SRI requiring full improvement but not necessarily in all organs. SRI5 and BICLA with the addition of medication restrictions may be the most specific measures for improvement despite risking loss of sensitivity, and could provide the most meaningful proof of efficacy in an appropriately powered clinical trial. Physician's overall opinion corresponds as well as or better than formalized endpoints to improvements of IL6 in an exploratory biomarker analysis of a lupus patient subset, suggesting that it could be a reasonable standard against which to compare endpoints.

O20

Adipokines association with clinical, laboratory and medication and correlation with TNF system in SLE patients. PRELIMINARY ANALYSIS

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Introduction: The adipose tissue is the primary source of adipokines of our organism. Studies describe a clear correlation between the level of adipokines and body mass index in healthy subjects and in patients with SLE (systemic lupus erythematosus). Interestingly these adipokines may interact with the system TNF (tumor necrosis factor) and consequently modify the inflammatory response of patients with SLE. Adipokines association with clinical characteristics of the disease is still unknown.Objetive: To evaluate the association of leptin, resistin and adiponectin and clinical, laboratory and medication use in patients with SLE. And evaluate the correlation between adipokines and TNF and its soluble receptors (sTNFR1 and sTNFR2).
Methods: Concentrations of resistin, leptin, TNFα, sTNFR1 e sTNFR2 were measured in 136 patients and the concentration of adiponectin in 77 patients. They were carried out at the Clinical Hospital of Federal University of Minas Gerais (HC/UFMG) of Rheumatology Center. Clinical-laboratorial findings, socio-demographic characteristics and treatment of disease were assessed and associated with adipokine concentrations. Disease activity was measured by Systemic Lupus Erythematosus Disease score Index 2000 (SLEDAI-2K) and cumulative irreversible damage by Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC-ACR/DI). For all analysis, a significance level of 5% ($P < 0.05$) was considered.
Results: The mean (SD) age of the patients and duration of SLE was 41.6 (11.2) and 150.6 (77.3) months, respectively. The median (IQR) of SLEDAI-2K modified, ID and corticosteroids dosage were 0(1-4), 2(1-3) and 5(0-10)mg, respectively. Resistina was associated with absence of photosensitivity [with photosensitivity 1.45 (5.24)ng/ml versus without photosensitivity 2.17(0.70)ng/ml; $p < 0,01$]. Adiponectin was

associated with thrombocitopenia [with thrombocitopenia 21.18(5.57)ng/ml versus without thrombocitopenia 12.38(7.44)ng/ml; p=0.037], corticosteroids usage [with corticosteroids 14.06(7.97)ng/ml versus wihtout corticosteroids 10.51(6.29)ng/ml; p=0.034] and antimalarial usage [with antimalarial 14.50(8.09)ng/ml versus without antimalarial 8(5.82)ng/ml; p=0.006].There was a positive correlation with levels of resistin and time monitoring of the disease (rs: 0.224, p = 0.009) and a trend of correlation with resistin and age. No correlation was observed between disease activity and leptin, adiponectin and resistin concentrations. A correlation was found with leptin levels and sTNFR2 (rs: 0.265, p = 0.002). The resistin was correlated with sTNFR1 (rs: 0.489, p < 0.001) and with sTNFR2 (rs: 0.298, p < 0.001).
Conclusion: This preliminary analysis observed a correlation whit adipokines and TNF system and certain association with adipokines and manifestations of SLE. The role of adipokines in the pathogenesis of these clinical manifestations and its correlation with TNF system remain to be determined.

20/04/13

10:40 - 11:40

Oral Presentations 5

Pacífico B

O21

Blisibimod, an Emerging Subcutaneous Biologic Therapy for Patients with Active, Moderate-to-Severe Systemic Lupus Erythematosus

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Introduction: The efficacy and safety of subcutaneous blisibimod, an inhibitor of soluble and membrane-bound B–cell activating factor (BAFF), were evaluated in a phase 2b clinical trial in patients with SLE.
Patients and Methods: 547 SLE patients with anti-dsDNA or antinuclear antibodies and SELENA SLEDAI score ≥6 at baseline were randomized 1:1 to receive placebo or blisibimod administered at 1 of 3 dose levels, 100 mg weekly (QW), 200 mg QW, or 200 mg every 4 weeks. Randomization was stratified by SELENA SLEDAI score (6-9 vs ≥10) and race. The primary endpoint was a comparison at Week 24 of the percentage of subjects in the pooled blisibimod and placebo groups who achieved an SLE Responder Index-5 (SRI–5: ≥5 point improvement in SELENA–SLEDAI, no new BILAG A or ≥2B organ domain scores, and no worsening in Physician's Global Assessment).
Results: The primary endpoint was not met due to the lack of efficacy in the two lower dose groups. However, SRI-5 response was higher in subjects receiving blisibimod 200mg QW from Week 16 (ΔSRI–5=8%, p=0.14), through Week 24 (ΔSRI–5=8.2%, p=0.15), reaching statistical significance at Week 20 (ΔSRI 5=13.4%, p=0.02). When compared to regimen-matched placebo, and using analyses in which responders attained SELENA–SLEDAI improvements of ≥7 or ≥8, the treatment effect of blisibimod 200mg QW at Week 24 was greater: ΔSRI–5=8.7%; ΔSRI–7=16.3% p=0.003; ΔSRI–8=17.4% p=0.001.

Blisibimod 200mg QW was highly effective in a severe SLE subgroup with baseline SELENA–SLEDAI≥10 and receiving corticosteroids (n=278): ΔSRI–5=13.8%, p=0.18; ΔSRI–7=28.9%, p=0.002; ΔSRI–8=31.1%, p < 0.001.

In subjects with baseline urinary protein excretion equivalent to 1–6g/24hrs (n=48), treatment with blisibimod resulted in significantly greater reductions in proteinuria compared to placebo from Week 8 through Week 24. At week 24, blisibimod treatment resulted in a mean reduction in proteinuria of 35% (-0.73g/24hr, p=0.05) in the pooled blisibimod group, and 50% (-0.96g/24hr, p=0.07) in the 200mg QW group, compared with 5% (-0.24 g/24hr) in the pooled placebo group.

Further evidence of the effect of blisibimod was observed in its direct effect to reduce B cell counts and anti–dsDNA antibody levels, and its indirect effect to increase in complement C3 and C4.

Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Amongst the commonly-reported AEs, imbalance was observed only with injection site reactions (200mg QW blisibimod=15%, matched placebo=7%), which were never serious or severe.
Conclusions: These data are the first evidence that SLE disease activity may be improved with subcutaneous injections of a novel biologic therapy

O22

Efficacy and safety of rontalizumab (anti-interferon-alpha) in sle patients with restricted immunosuppressant use: results of a randomized, double-blind, placebo-controlled phase 2 study

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Background/Purpose: Dysregulation of interferon-alpha (IFNα) activity and/or signaling is implicated in systemic lupus (SLE). This randomized, double-blind, placebo-controlled Phase 2 study (ROSE) evaluated the efficacy and safety of intravenous (IV) and subcutaneous (SC) rontalizumab, a humanized IgG1 antibody against all anti-IFNα isoforms, in adults with moderate to severe extrarenal SLE.
Methods: Patients were randomized 2:1 in sequential cohorts to: 750mg IV q4wk rontalizumab or placebo (part 1) and 300mg SC q2wk rontalizumab or placebo (part 2). Immunosuppressants were not permitted at randomization, and steroids were to be tapered to ≤10mg/day by Week 8. Rescue therapy was allowed for worsening of disease but defined as treatment failure. Efficacy endpoints included reduction in disease activity by BILAG (primary), and SLE Response Index (SRI, secondary) at Week 24. Exploratory measures included the **I**nterferon **S**ignature gene expression **M**etric (ISM) at baseline. Pharmacokinetics and immunogenicity of rontalizumab were assessed.
Results: 159 patients received rontalizumab (81 IV, 78 SC) and 79 received placebo. Patients were 94% female with mean age of 39 years. At baseline, the mean SELENA-SLEDAI (SS) was 10, and the most common disease manifestations involved musculoskeletal and mucocutanenous systems. 76% of patients were ISM^{Hi}. Baseline disease activity was comparable in ISM^{Hi} and ISM^{Lo} patients except for higher likelihood of autoantibodies and low complement in ISM^{Hi} patients vs ISM^{Lo}: (anti-dsDNA 71% vs 34%, anti-ENA 73% vs 19% and low C3 43% vs 16%, respectively). Overall, BILAG and SRI response rates were similar between rontalizumab and placebo all-comer groups. However, rontalizumab vs placebo SRI response was 55% vs 31% in those on >10mg prednisone at baseline (IV and SC groups, pooled). In an exploratory, pre-specified, biomarker-defined subgroup, ISM^{Lo} patients, rontalizumab vs placebo SRI response rates were 75% vs. 18%, and 75% vs. 62% in the IV and SC groups,

respectively. The estimated treatment difference of SRI response in rontalizumab and placebo ISM^{Lo} arms was 31% (90% CI: 9-51%, p=0.0285). Exploratory results with the more stringent SRI6 response were 41% vs. 9%, and 69% vs. 31% in the IV and SC groups, respectively. A reduction in SS flare rates occurred in rontalizumab patients vs. placebo: hazard ratio 0.61 (0.46-0.81, p=0.0040), driven by ISM^{Lo} patients. A greater percentage of patients achieved prednisone reduction (≤10mg/day) by week 24 in the rontalizumab ISM^{Lo} group: 91% vs. 67% placebo. Incidence of adverse events (AE) was comparable between placebo and rontalizumab groups. The most common AEs were UTI, URI, headache, and nausea. There were more SAEs from SLE flares in the active group (n=10, 6%) vs. placebo (n=1, 1%), which occurred only in ISM^{Hi} patients. Treatment emergent anti-therapeutic antibodies were uncommon (1/159, 0.6%).

Conclusions: Moderate to severely active lupus patients administered rontalizumab without background immunosuppressants was associated with improvement in signs and symptoms of SLE, flare rates and steroid burden at week 24 in a pre-specified biomarker defined group of ISM^{Lo}.

O23

Safety, Pharmacokinetics and Pharmacodynamics of AMG 811 (anti-IFN-gamma): Results of a Phase I Single Dose Study in Subjects with Systemic Lupus Erythematosus

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Introduction: Interferon-gamma (IFN-γ) is a major pro-inflammatory cytokine that modulates the function of several important populations of immune cells including B cells, T cells, and macrophages. Several lines of evidence from animal models and humans suggest increased levels of Type I and/or Type II IFN are associated with inflammatory disorders including systemic lupus erythematosus (SLE). Although some information is available on the effect of blocking Type I IFNs from human trials in SLE, little is known about the role of Type II IFN. AMG 811 is a human IgG1 monoclonal antibody that selectively targets and neutralizes human IFN-γ. The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single dose administration of AMG 811 was assessed in SLE subjects.

Patients and Methods: Mild, stable SLE subjects were administered AMG 811 or placebo in single doses (SD) (n=26) ranging from 2 mg to 180 mg SC or 60 mg IV. Serum AMG 811 concentrations were measured using an enzyme-linked immunosorbent assay (ELISA), and anti-AMG 811 antibodies (ADA) were measured using an electrochemiluminescence (ECL) based immunoassay. Serum protein and whole blood RNA biomarkers were analyzed pre- and post-dosing with AMG 811 and placebo by ELISA and Agilent microarray, respectively. Whole blood immunophenotyping parameters were measured by flow cytometry.

Results: No deaths or withdrawals due to adverse events occurred, and few adverse events were reported by more than a single subject receiving either AMG 811 or placebo. AMG 811 displayed linear PK and properties consistent with a typical IgG1 antibody. Immunogenicity to AMG 811 was low (1 of 18 subjects had transient non-neutralizing ADA). No changes in expression of MHC I or II on circulating immune cells were observed following AMG 811 treatment. AMG 811 produced a dose dependent modulation of the expression of many genes associated with IFN-γ signaling and that are differentially expressed in lupus subjects. Levels of IL-18, CCL2 (MCP-1), and IP-10 (CXCL10) serum proteins were found to be elevated at baseline in lupus patients as compared to healthy volunteers. Treatment with AMG 811 reduced IP-10 protein in a dose/concentration dependent manner.

Conclusions: AMG 811 demonstrated acceptable safety and favorable PK profiles following single dose administration to SLE subjects. AMG 811 administration impacted IFN-associated gene expression. The identity of impacted genes and the magnitude of modulation following AMG 811 treatment in SLE subjects suggest that the lupus 'interferon signature' is not solely derived from Type I IFN. In contrast to reported studies targeting Type I IFN, AMG 811 inhibited serum protein levels of IP-10, which has been associated with increased disease activity and to correlate with future SLE flare, in a dose and concentration dependent manner. These data support further evaluation of AMG 811 as a therapeutic for SLE, including subjects with active lupus nephritis.

O24

Safety, Pharmacokinetics and Pharmacodynamics of AMG 557 (anti-B7RP-1) in Subjects with Systemic Lupus Erythematosus: Results of a Phase 1 Multicenter, Randomized, Double-blind, Placebo-controlled, Sequential Rising Single-dose Study

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Introduction: The interaction of inducible costimulator (ICOS) with its sole ligand B7-related protein-1 (B7RP-1 or ICOSL), plays a role in T cell differentiation, cytokine production and T cell dependent help for B cells. Blockade of the B7RP-1/ICOS co stimulator pathway could thus be efficacious in treating SLE and other autoimmune diseases characterized by immune dysregulation. AMG 557 is a human IgG2 monoclonal antibody that binds to B7RP-1, inhibiting its interaction with ICOS. The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single dose administration of AMG 557 were assessed in SLE subjects.

Patients and Methods: Fifty-six subjects with mild, stable SLE received a single dose of placebo or AMG 557 ranging from 1.8 mg to 210 mg SC or 18 mg IV. Each subject in the 60, 140, and 210 mg SC cohorts also received two 1-mg intradermal injections 28 days apart of keyhole limpet hemocyanin (KLH) as a neoantigen. The following were measured: serum AMG 557 concentrations by an enzyme-linked immunosorbent assay (ELISA); anti-AMG 557 binding and neutralizing antibodies by a bridging ELISA and a receptor binding assay, respectively; B7RP-1 target occupancy and immunophenotyping in whole blood specimens by flow cytometry; serum protein and whole blood RNA biomarkers by ELISA and microarray, respectively; and serum anti-KLH IgG and IgM antibodies by a flow cytometric bead array assay.

Results: Single dose administration of AMG 557 was generally well tolerated. The incidence of adverse events was similar between the AMG 557 and placebo groups. Serum AMG 557 exposure increased greater than dose proportionally across the dose range 1.8–140 mg SC. Approximately dose-proportional PK was observed for 140–210 mg

SC. Two of 36 subjects (6%) receiving AMG 557 and two of 20 subjects (10%) receiving placebo tested positive for anti-AMG 557 binding antibodies (with one subject from each group below the quantitation limit) and no neutralizing antibodies were detected. B7RP-1 target occupancy increased with increasing dose of AMG 557. At 6 mg SC 50% occupancy was achieved; occupancy reached the maximum detection limit at 140 mg SC with greater duration of occupancy at 210 mg SC. No significant difference in anti-KLH IgG or IgM responses were observed between the AMG 557 and placebo groups or between AMG 557 dose groups. There were no changes to select SLE-related disease biomarkers including immunophenotyping, RNA or serum protein analytes.

Conclusions: Single dose administration of AMG 557 up to 210 mg SC and 18 mg IV demonstrated an acceptable safety profile. AMG 557 bound to cell surface B7RP-1 in vivo and the degree of target occupancy was dose-related, reversible, and reached maximal levels at the 140 mg SC group. No functional impact of B7RP-1 blockade was observed, including on the anti-KLH antibody responses, but longer duration of AMG 557 exposure may be required to detect biological effects. These data support further evaluation of AMG 557 as a therapeutic for SLE.

O25

Final Results from an Open-Label Extension Study of Epratuzumab (SL0006): Maintained Improvements in Disease Activity and Clinically Meaningful Improvements in Quality of Life in Patients with Moderate-to-Severe Systemic Lupus Erythematosus

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Background: Epratuzumab, a monoclonal antibody targeting CD22, is in development for SLE. Two randomized, double-blind trials (ALLEVIATE 1 and 2) were terminated because of interrupted drug supply. SL0006 was an open-label extension for ALLEVIATE patients. This abstract reports final results from SL0006 over a median of 210 weeks' treatment (~4 years).

Methods: US ALLEVIATE patients were eligible. Patients received 12-week cycles of epratuzumab 360mg/m^2(infusions: days 1 and 8). Assessments were every 4 weeks from screening (Visit 1; V1). Analyses were based on observed cases for individual timepoints compared to ALLEVIATE baseline (BL) and SL0006 screening (V1).

Results: Patients (n=29) were aged 22–61 years; almost 90% women; 72% of European descent (79% Caucasian). Ten enrolled from ALLEVIATE-1 and had severe (BILAG A) SLE activity in $\geq$ 1 body/organ system; 19 enrolled from ALLEVIATE-2, with moderate (BILAG B) activity in $\geq$2 body/organ systems. Median (range) delay in epratuzumab dosing between ALLEVIATE and SL0006 entry was 52.6 weeks (11.1–93.0). Median (range) study duration was 210.4 weeks (14.1–275.4) (~4 years). Median BILAG total scores and numbers of BILAGA/B in each body/organ system were reduced between BL and V1, with most V1 BILAG A/B grades improving to C/D at least once during the study. Median (95% CI) time to new severe lupus flare (1 new A or 2 new Bs) was 0.61 years (0.38, 1.47). Median (range) of circulating B-cell counts (cells/μL) decreased from 104 (20–1478) at BL to 41 (20–1303) at V1, remaining in the range 40-55 cells/μL at most time points. After two years, median percentage change in B-cell numbers from BL remained in the range –55% to –65% at most timepoints. Median corticosteroid dose (range) decreased from 21 mg/day (10–80) at BL to 7.5mg/day (0–30) at V1, with lower doses maintained throughout SL0006. Mean scores for most SF-36 domains improved from BL to V1, and throughout four years (Table). Mean PCS and MCS scores increased throughout the study. Improvements in PCS, and in three domains (Role Physical, Bodily Pain, Social Function) exceeded MCID throughout SL0006. All patients reported at least one AE, and 14 (48.3%) at least one SAE. Four patients (13.8%) discontinued because of AEs.

Conclusions: In this open-label, single-arm extension study, continued administration of epratuzumab for ~4 years maintained or further improved SLE disease activity and corticosteroid sparing. Patients reported clinically meaningful improvements in HRQoL that were sustained throughout the study, and epratuzumab was generally well tolerated with no new safety signals.

Role of the study sponsor: SL0006 was funded by UCB Pharma. Epratuzumab was licensed from Immunomedics, Inc.

Measure...	*Physical Component Summary PCS*	*Mental Component Summary MCS*	*Physical Function PF*	*Role Physical RP*	*Bodily Pain BP*	*General Health GH*	*Vitality VT*	*Social Function SF*	*Role Emotional RE*	*Mental Health MH*
ALLEVIATE baseline (n = 29)	31.8	42.2	52.8	35.8	37.6	30.5	31.5	48.7	67.8	62.6
Threshold for mean change $\geq$ MCID from ALLEVIATE baseline	36.8	47.2	55.3	38.3	40.1	33.0	34.0	51.2	70.3	65.1
SL0006 VA (n = 29)	36.3	43.4	60.0	47.6	43.5	38.0	35.8	54.7	71.0	64.7
Threshold for mean change $\geq$ MCID from SL0006 V1	41.3	48.4	62.5	50.1	46.0	40.5	38.3	57.2	73.5	67.2
Week 12 (n = 29)	38.6	44.5	65.3	50.7	54.0	40.9	43.1	58.6	71.0	69.3
Week 24 (n = 25)	38.0	43.7	64.2	49.5	50.1	41.6	37.5	61.0	69.3	67.6
Week 48 (n = 28)	39.1	43.6	63.4	55.1	52.6	43.4	40.0	59.8	70.2	66.1
Week 72 (n = 22)	41.2	44.6	64.8	62.8	55.8	46.4	46.0	64.8	72.4	66.9
Week 96 (n = 22)	39.5	44.4	66.1	57.7	50.5	42.4	40.3	66.5	72.0	66.8
Week 120 (n = 19)	39.1	44.3	61.6	56.3	49.9	42.4	40.5	62.5	70.6	69.0
Week 144 (n = 21)	39.3	45.0	65.9	56.0	51.1	43.5	43.8	63.7	73.4	67.4
Week 168 (n = 18)	38.8	44.4	58.9	55.6	52.9	42.7	44.1	63.9	68.5	66.3
Week 192 (n = 18)	39.3	42.5	63.9	50.7	51.8	41.9	43.4	61.1	65.3	64.2
Last visit (n = 29)	38.3	44.2	62.4	55.6	48.6	41.2	39.9	62.9	68.4	68.5
Age- and gender-matched norms	50±10	50±10	85.5	84.3	71.0	69.6	54.1	81.8	85.8	70.5

20/04/13

10:40 - 11:40

Oral Presentations 6

Buen Ayre A+B+C

O26

The Granulocyte Signature and Organ Inflammation in TLR7 Responsive mice is RNA and type 1 Interferon Dependent.

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Background: Microarray expression analysis of blood taken from patients with Systemic Lupus Erythematosus (SLE) has revealed two characteristic signatures: one that reflects exposure to type 1 interferon (IFN) and the other reflective of immature circulating granulocytes. Whereas the IFN signature is thought to arise predominantly from the activation of TLR7 in plasmacytoid dendritic cells (pDC) by RNA containing nucleoprotein immune complexes (ICs), the generation of the granulocyte signature is uncertain. Mice that overexpress TLR7 (TLR7 transgenic (Tg) mice) not only develop a lupus-like syndrome, but also a myeloid expansion in the spleen.

Goals: A) To determine the relationship between the myeloid expansion and the pathology in TLR7 Tg mice. B) To determine whether the myeloid expansion and immunopathology is driven by the TLR7 ligand, RNA, and whether it is also IFN dependent.

Methods: Granulocytes (CD11bhigh Ly6Ghigh Ly6Chigh) and inflammatory monocytes (CD11bhigh Ly6Chigh Ly6Gnegative) were flow sorted from the spleen. Microarray analysis on RNA isolated from whole spleen was performed using Illumina's MouseWG-6 v2.0 Expression BeadChips. Chips were scanned on an Illumina HiScanSQ System and >2.0-fold changes in gene expression by TLR7 Tg compared with B6 were analyzed by Ingenuity software. To create TLR7 mice that either overexpressed RNase A or were deficient in the type 1 interferon receptor (IFNAR), TLR7 mice were crossed to RNase Tg or IFNAR deficient mice respectively. Parenchymal organs were examined by light microscopy, Mac2 staining and by other methods as appropriate.

Results: Transcript profiling of TLR7 Tg and B6 spleens (n=10 in each group) revealed a striking granulocyte signature in the TLR7 Tg spleen (e.g. proteinase 3, myeloperoxidase and elastase were expressed at 16 x wild type). Surprisingly, Q-PCR of flow sorted subpopulations revealed that it was the inflammatory monocytes rather than the granulocytes that expressed high levels of these genes. These myeloid populations from TLR7 Tg mice expressed 5-10-fold more TLR7 mRNA compared to B6 mice and the inflammatory monocytes from TLR7 Tg mice expressed more inflammatory cytokines in response to the TLR7 agonist gardiquimod. Pathologic studies of TLR7 Tg mice revealed only mild kidney disease whereas a striking inflammatory infiltrate predominantly of myeloid cells was observed in the liver. This infiltrate was associated with hepatic necrosis. The inflammatory infiltrate was markedly reduced in double mutant TLR7 Tg mice that either co-expressed RNase or that were deficient in IFNAR expression.

Conclusions: Our results indicate that TLR7 Tg mice express a granulocyte signature similar to that observed in humans with SLE. This signature was a consequence of high expression of neutrophil genes in inflammatory monocytes which is likely explained by increased numbers of immature cells released by the bone marrow suggestive of altered myelopoiesis. Attenuation of disease in the double mutant mice indicate that myelopoiesis and /or activation of myeloid cells is caused by exposure to RNA in an IFN dependent process. These results have important implications for therapy.

O27

Risk of nephritis among Danish patients with systemic lupus erythematosus is associated with genetically determined mannose-binding lectin deficiency

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Introduction: The innate immunity component, mannose-binding lectin (MBL), is involved in the processing of apoptotic debris in a similar way as C1q is. C1q deficiency is strongly associated with autoimmunity, including systemic lupus erythematosus (SLE) with nephritis, i.e. lupus nephritis (LN). We hypothesized that also the more commonly occurring genetically determined state of MBL-deficiency could confer an increased risk of LN in SLE.

Patients and Methods: SLE patients attending a Danish tertiary rheumatology center were genotyped in exon 1 of the *MBL2* gene at codon 52, 54, and 57 for single-base substitutions named *O* versus the wild-type allele *A*. *MBL2* genotype data were grouped into high producers (*A*/*A*), low producers (*A*/*O*), and deficient producers (*O*/*O*). The follow-up period was defined as the time from fulfillment of the ACR 1987 classification criteria for SLE until the occurrence of an event or end of follow-up. During this period patients were recorded as to the development of LN, defined as the presence of persistent proteinuria >0.5 g/d or the presence of cellular casts such as hemoglobin and red blood cells, and any further development of end-stage renal disease (ESRD), defined as performed renal transplantation or need for permanent dialysis. Cox regression analyses were controlled for gender, age, and race.

Results: Of the 171 patients included in the study, 91 percent were female and 92 percent of Caucasian descent. The median age at SLE onset was 29 years (range 11-72 years). The median follow-up from time of SLE classification to development of LN or end of follow-up was 5.7 years (range 0-34 years) with a total of 1165 patient-years. LN developed in 94 patients and among these ESRD developed in 16 patients. The prevalence of high, low and deficient MBL producers was 58, 35 and 7.0 percent, respectively.

Event and MBL stratification:	*Hazard ratio (95% CI)*	*P=*
Lupus nephritis (n=94/171)		
– MBL high producer (n=99)	1	
– MBL low producer (n=60)	1.1 (0.7 – 1.7)	0.65
– MBL deficient (n=12)	2.8 (1.3 – 6.1)	0.008
End-stage renal disease (n=16/94)		
– MBL high producer (n=49)	1	
– MBL low producer (n=35)	0.6 (0.2 – 1.8)	0.33
– MBL deficient (n=10)	1.1 (0.2 - 6.4)	0.93

Conclusion: The finding of an almost 3-fold increased risk of LN among MBL deficient SLE patients supports the notion that deficiencies in innate immunity components involved in removal of apoptotic remnants may promote immunecomplex mediated manifestations of SLE. ESRD was not associated with MBL deficiency indicating its greater importance in early events of LN.These findings enhance our understanding of the pathogenesis of SLE. Furthermore, the relatively high prevalence of MBL deficiency and the fact that 10 out of 12 such patients eventually developed LN, also indicates that MBL genotyping may have a place in clinical risk stratification of SLE patients.

O28

Sle18a, a murine 129-derived disease modifier locus on chromosome 3, regulates the expression of Ly108 isoforms in T cells

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Background: *Sle16*, a 129-derived lupus-susceptibility murine locus on chromosome 1, has been shown to induce the development of autoantibodies on the C57BL/6 background. The disease traits can be modified by co-expression of another 129-derived locus on chromosome 3, *Sle18*, demonstrating that this region carries gene(s) capable of suppressing the *Sle16*-driven autoimmunity. We have narrowed down the *Sle18* locus to a smaller region between 71.5 to 90.5Mbp (named *Sle18a*) capable of the same disease-modifying effects. Polymorphisms of the Signalling Lymphocyte Activation Molecule (SLAM) genes, especially of the Ly108, have been linked to lupus pathogenesis. Lupus-prone strains, including 129 mice, express less total amounts of Ly108 compared to C57BL/6 mice. In addition, the Ly108-H1 splice variant, reportedly unique to C57BL/6 mice, has been shown to have a T-cell mediated immune-suppressive function. Here, we assessed if the *Sle18a* locus could modulate the expression of Ly108 and of its splicing variant.
Material and Methods: B6.129-*Sle16* and B6.129-*Sle16Sle18a* congenic strains were generated. Naive T cells, purified from spleens of 2 month old mice, were stimulated with a plate-bound anti-CD3 antibody and proliferation was assessed by H^3thymidine incorporation at day 3. Th17 polarisation in medium supplemented with TGFβ and IL6 was quantified by assessing IL17 intracellular staining. RNA was extracted according to standard methods and Ly108 expression measured by real time PCR with primers specific for each isoform.
Results: *Sle16Sle18a* $CD4^+$ naive T cells can dampen the abnormal threshold for proliferation of *Sle16* $CD4^+$ naive T (H^3thymidine incorporation: *Sle16* 27320cpm, range 14050-40970cpm, *Sle16Sle18a* 10250cpm, range 8657-21460cpm; p=0.036) and are significantly less prone to differentiate into the Th17 lineage than *Sle16* cells (% of $IL17^+$ $CD4^+$ cells: *Sle16* 2.2%, range 2.1-3%, *Sle16Sle18a* 1.3%, range 1.2-1.5%; p=0.021). Analysis of Ly108 mRNA expression in naive T cells using real time PCR showed that *Sle16 mice had markedly decreased levels of Ly108 mRNA in comparison to C57BL/6 controls. In contrast, Ly108 expression level in Sle16Sle18a* $CD4^+$ *T cells was comparable to that in C57BL/6 controls. As anticipated the 'lupus-protective' Ly108-H1 isoform variant was present in C57BL/6 T cells and absent in T cells from the Sle16* lupus-prone strain. More importantly, this variant was detectable in T cells from the *Sle16Sle18a* mice suggesting that the *Sle18a* locus can modulate Ly108 expression.
Conclusions: Using congenic mice we have shown that a novel chromosome 3 locus (*Sle18a*) is capable of suppressing the lupus-related T cell abnormalities driven by *Sle16*. *Sle18a* can modulate the expression of the Ly108 gene and can induce the transcription of the 'lupus-protective' Ly108-H1 isoform. Taken together our data demonstrate an epistatic effect of the *Sle18a* locus on the expression of the SLAM gene family within the *Sle16* locus.

O29

Interferon-alpha May Impair Endothelial Repair Mechanisms in Patients With Systemic Lupus Erythematosus

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Introduction: Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD). Interferon-alpha (IFNα) may contribute to this increased risk by inhibiting endothelial repair mechanisms. Circulating angiogenic cells (CACs) enhance vascular repair in murine models and may be affected by IFNα. We aimed to characterise CACs in detail and determine the effects of IFNα on their function ex vivo to develop a model of failed vascular repair in SLE.
Methods: Peripheral blood mononuclear cells were obtained from healthy controls (HC) and clinically stable SLE patients (n=5 each) and cultured on human fibronectin in endothelial media for 7 days. CACs were identified as dual positive for LDL-uptake and lectin binding. Cell surface marker expression was determined by RT-PCR and immunocytochemistry. CAC function was studied in terms of: migration (towards SDF-1), adhesion to TNFα-activated aortic endothelium and angiogenic capacity (augmentation of endothelial network formation). The number of LDL-positive cells was enumerated after 7 days treatment with IFNα2b (0.01-100ng/ml). To study angiogenic capacity, supernatant from day 8 CACs (+/- IFN pre-treatment) was added to human aortic endothelial cells (HAoEC) on Matrigel for 16 hours. Network parameters were calculated using a semi-automated computer algorithm. The number of polygons (PG) in the network was used as a marker of network complexity/density, normalised to media alone (NPG) for comparison of HC and SLE cells.
Results: CACs expressed markers of myeloid (CD14, CD45, CD31) but not endothelial (vWF) lineage. Cells were phagocytes with high expression of CD163 and CD206 suggesting an alternatively-activated (M2) macrophage phenotype. CACs migrated towards developing endothelial cell tubules in Matrigel but were not able to form networks alone. CACs migrated towards SDF-1 (0.1-100ng/ml, r2=0.87, $p < 0.001$) with increased adhesion to TNFα-activated HAoECs, compared to unstimulated endothelial cells (p= 0.02).

HC CAC supernatant was pro-angiogenic compared to growth media alone (PG 21.9 vs 38.3, $p < 0.01$). Although there was no difference in the number of CACs at day 8 between HC and SLE patients, there was a trend towards a reduced angiogenic capacity of SLE CACs (NPG 1.69 vs 1.47, p=0.26).

IFNα dramatically reduced HC CAC survival (r2=0.77, $p < 0.001$) at day 8. This was associated with loss of angiogenic capacity with 10ng/ml IFNα (PG 38.1 vs 24.1, p=0.01) but not 0.1ng/ml (37.4 vs 36.8, p=0.90). IFNα (0.1ng/ml) did not significantly affect CAC migration or adhesion (relative no. cells 2.05 vs. 1.72, p=0.40, and 2.09 vs 2.21, p=0.67 respectively).
Conclusions: We have characterised CACs as M2 macrophages with angiogenic capacity and demonstrated that survival ex vivo is reduced by IFNα. CACs may be dysfunctional in stable lupus patients, and further inhibited by IFNα in active disease. Restoration of CAC function is a novel therapeutic target to reduce CVD in SLE.

O30

The effect of the antiphospholipid syndrome (APS) on survival in Chinese patients with SLE: a prospective study of 679 patients

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Objectives: To study the effect of the antiphospholipid syndrome (APS) on survival in Chinese patients with SLE
Methods: A cohort of 679 southern Chinese patients who fulfill at least 4 of the ACR criteria for SLE from 1995 to 2011 was studied. The status of the patients at last clinical visits (alive or death) was evaluated. The cumulative survival rate over time was studied by Kaplan-Miere's plot. For those who died during the course of their disease, data were censored at the time of their deaths whereas data of other patients were censored at the time of last clinic visits. APS was defined by the modified Sydney criteria in 2006, ie. The presence of arterial or venous thrombosis, or miscarrages (recurrent abortion or intra-uterine death) plus any one of the following positive twice at least 12 weeks

part: (1) lupus anticoagulant; (2) moderate to high titers of anticardiolipin antibodies (IgG or IgM); or (3) beta-2-glycoprotein-I. Comparison of the survival of patients with and without APS was made.
Results: 679 SLE patients (92% women; age of disease onset 32.5+/-14 years) were prospectively followed for 9.7+/-7.3 years. Sixty-eight (10%) patients died and 33 (4.9%) patients were lost to follow-up. The main contributing causes of death in these patients were: infection (53%), cardiovascular events (6%), cerebrovascular events (15%), and cancer (9%). Forty-four (6.5%) patients qualified the criteria for APS, manifested as: ischemic stroke (55%), deep venous thrombosis (32%), obstetric morbidity (14%), cardiovascular events (9%) and peripheral vascular disease (9%). Twenty-three (52%) patients developed APS after the diagnosis of SLE, 16 (36%) patients had concomitant APS diagnosed at the same time as SLE and 5 (11%) patients had APS preceding SLE diagnosis. Nine (20%) APS patients died, which was significantly more frequent than the non-APS SLE patients (59/635[9%]; p=0.02). Patients with the APS died at an older age than those without APS (54.0+/-11.4 vs 45.1+/-18.2; p=0.07). The duration of SLE at the time of death was also longer in patients with the APS than those without (13.9+/-10.4 vs 7.47+/-7.4 years; p=0.11). The cumulative mortality of patients with APS was 4.6% at 5 years, 7.8% at 10 years and 22.2% at 15 years, which was not significantly higher than that of non-APS patients (5.4% at 5 years, 9.2% at 10 years and 11.3% at 15 years; p=0.14). However, if only patients with APS caused by arterial thrombosis were considered, the presence of APS was significantly associated with mortality (HR 2.29 [1.13-4.64]; p=0.02).
Conclusions: The presence of APS increases the mortality risk of patients with SLE, which is mainly contributed by arterial thrombotic events that occur late in the disease course.

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Oral Presentations 7

Pacífico A

O31

Long-Term Outcomes of Children Born to Women with Systemic Lupus Erythematosus

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Background/objectives: SLE can cause considerable morbidity during pregnancy. Although several studies have evaluated foetal outcome in lupus pregnancy, few have examined the long-term outcome of children born to mothers with SLE. We aimed to determine if children born to women with SLE have an increased risk of major congenital anomalies, serious infections, and cardiac conduction disturbances compared to children born to women without SLE.
Methods: We identified all women who had ≥1 hospitalization for delivery after SLE diagnosis using Quebec's administrative databases (1989-2009). Women were defined as SLE cases if they had: 1) ≥1 hospitalization with a diagnosis of SLE prior to the delivery, 2) a diagnosis of SLE recorded at the time of their hospitalization for delivery, or 3) ≥2 physician visits with a diagnosis of SLE, occurring 2-24 months apart, prior to the delivery. We randomly selected a general population control group, composed of women matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery.

We identified children born live to SLE cases and their matched controls and obtained information on all physician visits and hospitalizations incurred by these children. We ascertained major congenital anomalies (i.e.≥1 hospitalization or physician visit for a major congenital anomaly <12 months of life), serious infections (i.e.≥1 hospitalization with a primary diagnosis of infection), and cardiac conduction disturbances (i.e.≥1 hospitalization or 2 physician visits within 2-24 months) through to end of database follow-up.

We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, major maternal co-morbidities and/or obstetrical complications, and relevant maternal medication.
Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Compared to controls, children born to women with SLE experienced slightly more major congenital anomalies [13.5% (95% CI 11.1, 16.2) vs 10.4% (95% CI 9.8, 11.1)], serious infections [23.9% (95% CI 17.6, 31.5) vs 16.3% (95% CI 14.6, 18.1)], and cardiac conduction disturbances [3.1% (95%CI 2.0, 4.7) vs 1.2% (95% CI 1.0, 1.4)].

In multivariate analyses, children born to women with SLE had substantially increased risks of major congenital anomalies (OR 1.35, 95% CI 1.07, 1.70). serious infections (HR 1.88, 95% CI 1.17, 3.03) and cardiac conduction disturbances (HR 4.52, 95% CI 1.23, 16.59) compared to controls.
Conclusions: Compared to children from the general population, children born to women with SLE have an increased risk of major congenital anomalies, serious infections, and cardiac conduction disturbances.

O32

Lupus Anticoagulant at First Pregnancy Visit is Predictive of Pregnancy Loss

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Introduction: Multiple factors, including proteinuria, antiphospholipid syndrome, thrombocytopenia and hypertension, are predictive of pregnancy loss in SLE. In the PROMISSE study of mediators of pregnancy loss, only a battery of lupus anticoagulant tests (Dil PT, dRVVT, PTT LA, and KCT) were predictive of adverse pregnancy outcomes (including pregnancy loss, preterm birth, pre-eclampsia, and small for gestational age). We examined the predictive value of one baseline lupus anticoagulant test (dRVVT) with pregnancy loss alone in women with SLE.
Methods: This analysis is based on pregnancies that were observed from 1987 to 2011. After excluding twin pregnancies, there were 402 pregnancies from 326 different women. We determined the percentage of women who had a pregnancy loss in groups defined by potential risk factors. Generalized Estimating Equations were used to calculate p-values, accounting for repeated pregnancies of the same woman.
Results: The age at pregnancy was <20 years (3%), 20-29 (50%), 30-39 (43%), and over 40 (3%). 59% were Caucasian and 34% African-American. Predictors of pregnancy loss are shown in the table. Lupus anticoagulant, but not anticardiolipin, at the 1st visit was highly predictive of pregnancy loss (and ever being positive was also associated, although less so). Moderately active lupus was associated with pregnancy loss (p=0.012) but not low complement or high anti-dsDNA.
Conclusion: The strongest predictor of pregnancy loss in SLE is the lupus anticoagulant in the first trimester by dRVVT testing. In contrast to the PROMISSE study, 3 lupus anticoagulant assays were not necessary. In addition, moderate disease activity by the physician global assessment was also predictive of pregnancy loss, but not low complement, anti-dsDNA, or anticardiolipin. These data suggest that

treatment of the lupus anticoagulant should be considered, even in the absence of prior history of miscarriage.

O33

French registry of 189 cases of immune congenital heart block: maternal data analysis.

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Background: Women positive for anti-SSA antibodies have a 1 to 2 % risk of having a fetus or a child affected by a congenital heart block (CHB). Few data are available regarding the risk of those mothers to develop an autoimmune disease.

Patients and Methods: The inclusion criteria in the registry of neonatal lupus are the positivity of anti-SSA and/or anti-SSB antibodies and a manifestation of neonatal lupus. In this retrospective study, we analysed the data of the mothers who had a foetus/child with CHB.

Results: 172 mothers were included: 99.4% (171) were positive for anti-SSA antibodies and 58.1% (100) had anti-SSB antibodies.

At the time of their first diagnosis of CHB, 127 mothers (73.8%) were asymptomatic. The 45 mothers (26.2%) with an auto-immune disease had a systemic lupus erythematosus (SLE, n=18, including 2 with antiphospholipid syndrome with venous thrombosis), a sjogren syndrome (n=12), an undifferentiated connective tissue disease (UCTD, n=10), a rheumatoid arthritis (n=2), a idiopathic thrombocytopenic purpura (n=1), an autoimmune hepatitis (n=1) and a systemic scleroderma (n=1). Clinical manifestations of SLE mainly included cutaneous and articular manifestations and only 6 mothers had more severe manifestations (renal, neurological, pericarditis, hematological). Only one had received cyclophosphamide.

After a median follow up period of 5.9 years [1 day-36.5 years], 65 mothers (37.8%) remained asymptomatic. The 107 mothers (62.2%) with an autoimmune disease had an SLE (n=37, including 2 with an antiphospholipid syndrome with venous thrombosis), a Sjogren syndrome (n=39), an UCTD (n=19), SLE associated with a Sjogren syndrome (n=4), a rheumatoid arthritis (n=3), a idiopathic thrombocytopenic purpura (n=2), an autoimmune hepatitis (n=1), a systemic scleroderma (n=1) and a primary obstetrical antiphospholipid syndrome (n=1).

Conclusion: At the time of the CHB diagnosis in their offspring, a third of the mothers had a diagnosis of autoimmune disease. During the follow up period, another third developed an autoimmune disease. The remaining third was still asymptomatic after a median follow up period of 5.9 years [1 day-36.5 years].

O34

Study of anti-Müllerian hormone and the relationship with subsequent probability of pregnancy in 112 systemic lupus erythematosus patients exposed or not to cyclophosphamide.

Morel N[1], Bachelot A[1], Chakhtoura Z[1], Ghillani-Dalbin P[1], Amoura Z[1], Galicier L[2], Aumaitre O[3], Piette JC[1], Pourrat J[4], Sacre K[5], Kahn JE[6], Duhaut P[7], Farge D[2], Francès C[8], Guettrot-Imbert G[3], Harlé JR[9], Lambotte O[10], Guern V Le[11], Sène D[1], Trad S[12], Vidal E[13], Sarrot-Reynauld F[14], Tanguy ML[1], Lacorte JM[1], Costedoat-Chalumeau N[1]

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Introduction: The anti-Müllerian hormone (AMH) serum level is reflective of the ovarian reserve in adult women. Cyclophosphamide is associated with a risk of ovarian failure, resulting in infertility. We analyzed AMH levels and the probability of pregnancy in systemic lupus erythematosus (SLE) patients according to cyclophosphamide exposure.

Patients and methods: AMH was measured using the serum bank of the PLUS study (ClinicalTrials.gov: NCT00413361). Serum from women below 40 years of age who had received cyclophosphamide (n=56) were compared to serum from 56 women unexposed to cyclophosphamide and matched for age within 6 months. All patients were interviewed in May 2012 regarding their obstetrical status.

Results: The mean age of the 112 patients was 31.6±5.8 years. The mean AMH level was low (1.21±1.01 ng/ml) and was significantly lower in patients exposed to cyclophosphamide ($p = 0.03$) and in patients older than 30 years ($p = 0.02$). During a median follow-up (interval between sampling and the interview) period of 4.2 [2.5-4.8] years, 38 patients wished to become pregnant and 32 succeeded (84.2%). In the univariate analysis, the risk of failure was associated with cyclophosphamide cumulative dose (p=0.007) and older age (p=0.02). In the multivariate analysis, only CYC cumulative dose (OR=1.2 [1.02-1.32], p=0.03) was significantly associated with the risk of failure.

Conclusion: We confirm that AMH levels are low in SLE patients, and decrease significantly with age and cyclophosphamide exposure. Despite this, the risk of failing to become pregnant was low (15.8%), and was predicted by prior cyclophosphamide exposure but not by AMH levels.

O35

Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: A multicentre prospective study of 1000 patients

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Introduction: The antiphospholipid syndrome (APS) is characterized by a combination of thrombosis, pregnancy morbidity and raised titres of antiphospholipid antibodies (aPL). The aim of the present study was to assess the frequency and characteristics of the main causes of morbidity and mortality in APS after a 10-year follow-up, to determine the incidence of different clinical manifestations according to duration of disease and the predictors of several outcomes.
Methods: The clinical and immunological features of a cohort of 1000 patients with APS from 13 European countries, who had been followed up from 1999 to 2009 (Euro-Phospholipid project), were analyzed.
Results: The cohort included 820 (82%) females and 180 (18%) males, with 985 (98.5%) white patients and 15 (1.5%) of other races. Mean (SD) age at inclusion was 42 (14) years (range, 0–82; median, 40). 53.1% had primary APS, 36.2% had APS associated with systemic lupus erythematosus (SLE), 5% associated with lupus-like syndrome and 5.7% associated with other diseases. 419 (41.9%) patients were lost to follow-up (mean, 4% every year). During the study, 8 patients diagnosed at entry as primary APS were reclassified as lupus-like syndrome, 3 patients were reclassified as APS associated with SLE and 9 patients developed an episode of catastrophic APS. Table 1 depicts the frequencies of the main APS clinical manifestations during the 10-year prospective study and compares cumulative manifestations at baseline with those that appeared during the initial 5 years (1999-2004) and the ensuing 5 years (2004–2009). Low dose antiaggregants were used in 41.4% and oral anticoagulants in 49.7% of patients (62% at a target international normalised ratio (INR) of 2-3 and 38% at a target INR 3-4). 61 patients developed hemorrhages (mucocutaneous in 31 patients, cerebral in 15, gastrointestinal in 10 and intra-abdominal in 5) and in 10 patients they were the cause of death. During the observational period, 93 patients died (57% in the first period and 43% in the second one). Table 2 shows the main causes of death.
Conclusions: The Euro-Phospholipid project, which covers an APS population that is representative of Europe, identified the prevalence and characteristics of major clinical and immunological manifestations at onset and during the follow-up of the disease.

Table 1. Main clinical manifestations related to the antiphospholipid syndrome (APS) that appeared during the 10-year follow-up (1999–2009) of the total cohort of 1000 patients.

*Clinical manifestations**	*0 year*† *(n=1000) No. (%)*	*0-5 year (n= 1000) No. (%)*	*5-10 year (n=796)* ‡ *No (%)*	*0-10 year (n=1000) No (%)*
Thrombocytopenia (< 100,000 /μl)	296 (29.6)	37 (3.7)	50 (6.3)	87 (8.7)
Livedo reticularis	241 (24.1)	26 (2.6)	55 (6.9)	81 (8.1)
Stroke	198 (19.8)	24 (2.4)	29 (3.6)	53 (5.3)
Transient ischaemic attacks	111 (11.1)	23 (2.3)	24 (3.0)	47 (4.7)
Deep vein thrombosis	389 (38.9)	21 (2.1)	22 (2.7)	43 (4.3)
Pulmonary embolism	141 (14.1)	21 (2.1)	14 (1.7)	35 (3.5)
Epilepsy	70 (7.0)	17 (1.7)	15 (1.9)	32 (3.2)
Skin ulcers	55 (5.5)	17 (1.7)	14 (1.7)	31 (3.1)
Valve thickening/dysfunction	116 (11.6)	17 (1.7)	29 (3.6)	46 (4.6)
Vegetations	27 (2.7)	14 (1.4)	7 (0.9)	21 (2.1)
Myocardial infarction	55 (5.5)	9 (0.9)	10 (1.2)	19 (1.9)
Superficial thrombophlebitis	117 (11.7)	9 (0.9)	8 (1.0)	17 (1.7)
Autoimmune haemolytic anaemia	97 (9.7)	9 (0.9)	31 (3.9)	40 (4.0)
Obstetric manifestations§	*(No.=1580)*	*(No.=105)*	*(No.=83)*	*(No.=188)*
Pre-eclampsia/eclampsia	82 (5.2)	8 (7.6)	4 (4.8)	12 (6.3)
Early pregnancy loss (< 10 weeks)	560 (35.4)	18 (17.1)	13 (15.7)	31 (16.5)
Late pregnancy loss (≥10 weeks)	267 (16.9)	7 (6.7)	2 (2.4)	9 (4.8)
Live birth	753 (47.6)	80 (76.2)	57 (68.7)	137 (72.9)
Live birth with prematurity¶	80 (10.6)	28 (35.0)	38 (66.7)	66 (48.2)
Live birth with intrauterine growth restriction¶	11 (1.5)	11 (13.7)	25 (43.8)	36 (26.3)

* Some patients had several associated presenting manifestations.
† Cumulative clinical manifestations at baseline (previous period: median, 6 years).

Table 2. Causes of death during the 10 year follow-up (1999–2009) of the total cohort of 1000 patients.

*Causes of death**	*0-5 year (No.=53)* † *No. (%)*	*5-10 year (No.=40)*† *No. (%)*	*0-10 year (No.=93)*† *No. (%)*
Bacterial infection	11 (20.8)	9 (22.5)	20 (21.5)
Myocardial infarction	10 (18.9)	3 (7.5)	13 (13.9)
Stroke	7 (13.2)	4 (10)	11 (11.8)
Haemorrhage	6 (11.3)	4 (10)	10 (10.7)
Malignancy	6 (11.3)	7 (17.4)	13 (13.9)
Catastrophic APS	5 (9.4)	0	5 (5.4)
Pulmonary embolism	5 (9.4)	0	5 (5.4)

(continued)

Table Continued

*Causes of death**	*0-5 year (No.=53) † No. (%)*	*5-10 year (No.=40)† No. (%)*	*0-10 year (No.=93)† No. (%)*
SLE pulmonary involvement	3 (5.7)	0	3 (3.2)
SLE renal involvement	2 (3.8)	1 (2.5)	2 (2.5)
SLE central nervous system involvement	1 (1.9)	0	1 (1.1)
SLE haematologic involvement	0	1 (2.5)	1 (1.1)
Chronic renal failure	0	2 (5)	2 (2.5)
Viral infection	0	4 (10)	4 (4.3)
Fungal infection	1 (1.9)	0	1 (1.1)
Trauma/Accident	0	3 (7.5)	3 (3.2)
Unknown	0	3 (7.5)	3 (3.2)

**Several patients had more than one cause of death.*
† Number of death (No.)
APS, antiphospholipid syndrome

20/04/13

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Oral Presentations 8

Pacífico B

O36

Outcomes Associated with Belimumab in Patients with Systemic Lupus Erythematous (SLE) in Clinical Practice Settings: Results from OBSErve Study in the United States (U.S.)

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Background: The objective of this study is to describe the clinical outcomes associated with belimumab use in U.S. clinical practice settings.
Methods: OBSErve (BLM117295) is a multicenter retrospective medical chart-review study. Ninety-two rheumatologists from U.S. non-academic centers with > 10 SLE patients annually and > 5yrs of practice experience were randomly recruited. Physicians randomly identified adult SLE patients who had received ≥8 belimumab infusions as part of usual-care. Index-date is the date of the first infusion. Physicians assessed the following in the 6months pre- and 6months post-index period: demographics/comorbidities/SLE disease characteristics, clinical outcomes, and health-resource-utilization (HRU). The primary outcome measure was the change in SLE disease manifestations between the pre- and post-index period, based on physician judgment.

Results: 501 eligible patient charts were abstracted. Key patient characteristics at baseline were mean age:41.3yrs; female:89%; caucasian:53%, black/AfricanAmerican:24%, Hispanic:18%; diagnosed with SLE≤5yrs ago:56%; 68% and 67% of patients had hypocomplementemia and high anti-dsDNA respectively; 3%/77%/20% had mild/moderate/severe disease. The top 3 reasons for initiating belimumab (10mg/kg) were to decrease steroid use, ineffective previous treatment regimen and patient condition worsening. Oral steroids, antimalarials and immunosuppressants were used in 78%, 70% and 61% of patients respectively. Mean number of clinical manifestations present at time of belimumab initiation was 4.5. After receiving 6months of therapy, 88%, 49% & 11% of patients were observed to have an overall clinical improvement of ≥20%, ≥50%, ≥80% respectively. Changes in the top 5 manifestations by organ system are shown in the table and mirrored similar degrees of improvement in manifestations including arthritis, rash, fatigue, low complements and high anti-dsDNA. Patients on steroids at belimumab-initiation had a mean reduction in steroid dose of 11.5mg/day; 77% decreased their doses and 9% discontinued steroids altogether. Mean HRU was observed to decrease in the pre- to post-index periods within the following categories: number of hospitalizations (0.6 to 0.2; p=0.02), ER visits (0.2 to 0.07; p < 0.001), unscheduled visits to treating-physician (1.0 to 0.5; p < 0.001) and visits to specialty physicians (2.0 to 1.4; p=0.001).
Conclusion: Clinicians observed improvements in SLE clinical manifestations, a reduction in steroid doses, and reduced HRU among patients who received at least 6 months of belimumab in this sample of U.S. clinical practices.

ABSTRACT DISCLOSURE STATEMENT: During the study time, SN, GD and GK were full-time employees of Human Genome Sciences (HGS). Currently, SN, GD, and GK are employees of Ipsos, UCB, and MedImmune respectively.
STUDY SPONSOR DISCLOSURE: Research funded by HGS and GlaxoSmithKline.

	Musculoskeletal	*Mucocutaneous*	*Immunologic*	*Constitutional*	*Hematologic*
# of Manifestations (patients)	429 (390)	464 (321)	411 (269)	297 (266)	211 (168)
Worsened	0%	1%	0%	0%	0%
No change	4%	5%	10%	4%	9%
% Improvement					
< 20%	9%	11%	12%	11%	12%
≥20%	86%	83%	78%	84%	78%
≥50%	46%	48%	42%	47%	44%
≥80%	13%	17%	16%	12%	21%

O37

Validation of the Lupus Impact Tracker (LIT), a Patient-Reported Outcome (PRO) tool, in a Prospective Multicenter Longitudinal Study of Systemic Lupus Erythematosus (SLE) Patients

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Introduction: This study examined longitudinal reliability and validity of the LIT, a 10-item PRO assessing the impact of SLE on patients. The acceptability and feasibility of LIT from the patient's and physician's perspectives was evaluated.

Methods: This was a prospective multicenter longitudinal study conducted at 20 North American rheumatology clinics. Patients ≥18 years old with SLE were enrolled and completed the LIT, SF-36v2 (baseline only), PHQ-9 and LupusQoL at baseline and a 3 month follow-up visit. Patients completed the LIT 7-14 days following baseline to assess test-retest reliability. Patients also self-reported change in SLE status 7-14 days post baseline and at follow-up. Rheumatologists completed disease activity assessments (SELENA-SLEDAI, BILAG), physician's global assessment (PGA) and patient's flare status at baseline and follow-up, and SLICC/ACR Damage Index at baseline only. Patients and physicians completed a questionnaire at baseline and follow-up on the feasibility/acceptability of LIT. Reliability was evaluated using internal consistency (Cronbach's alpha) and test-retest methods (intra-class correlation). Convergent validity was evaluated by correlating LIT scores with SF-36, LupusQoL and PHQ-9 scores. Construct validity was evaluated by comparing mean LIT scores across patients that differed in PGA ratings and flare status. Responsiveness was evaluated using known-groups validity, where changes in mean LIT scores between baseline and follow-up were compared across patients with changes in PGA, SELENA-SLEDAI, and patient-reported SLE status. ANOVA and Student's t-tests were used to test mean differences in LIT scores across patient groups.

Results: 325 SLE patients were enrolled; 90% were female, 53% White and 33% Black, with a mean age of 42 years. Internal consistency reliability of LIT was 0.91 at baseline and 0.92 at follow-up; test–retest reliability was 0.88. Convergent validity correlations at baseline ranged from -0.63 to -0.74 with SF-36, -0.40 to -0.76 with LupusQoL, and 0.75 with PHQ-9. Mean LIT scores differed as hypothesized across patients with different PGA ratings at baseline ($F=5.8$, $p=0.004$) and follow-up ($F=12.6$, $p<0.001$). Mean LIT scores also differed between patients with and without a recent SLE Flare at baseline ($F=4.5$, $p=0.038$) and follow-up ($F=9.2$, $p=0.003$). The LIT was highly responsive to patient-reported changes in SLE impact ($F=14.7$, $p<0.001$), however LIT scores were not as responsive to changes in PGA ($F=1.8$, $p=0.168$) or SELENA-SLEDAI ($F=1.2$, $p=0.307$). The majority (>70%) of patients and physicians found LIT to be acceptable and feasible to administer in a clinic setting.

Conclusion: The LIT is a reliable and valid instrument for assessing the impact of SLE on patients, and captures unique and important information not included in physician disease assessments. The LIT can be useful in a clinical practice setting to enable efficient incorporation of the patient's perspective in disease management.

O38

Mortality Rates among U.S. Medicaid Recipients with SLE, 2000-2006

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Background: The U.S. Centers for Disease Control (CDC) reported significant differences by age and race in mortality rates (MRs) among SLE patients, 1979-1998 (1). MRs were highest among African Americans and patients > 45 years old (1), but MRs among U.S. SLE patients with have not been reported more recently. Medicaid is the U.S. federal-state jointly run program for providing medical insurance to low income individuals.

Aim: To examine MRs among SLE patients enrolled in Medicaid in the U.S. from 2000-2006

Methods: From the Medicaid Analytic eXtract (MAX) data, containing all billing claims from 2000-2006, we identified patients aged 3-65 with prevalent SLE (>3 SLE ICD-9 codes [710.0], >30 days apart), as well as those with lupus nephritis (defined with > 2 additional ICD-9 codes for nephritis, renal insufficiency or renal failure). Demographic data included age, sex, race, ethnicity, and region of residence. MRs were calculated using annual deaths among individuals with SLE in each sociodemographic group in each year (deaths ± SD per 100,000 Medicaid patients with SLE). T-tests were used to compare differences among groups.

Results: We identified 43,351 patients with prevalent SLE. 40,417 (93%) were female, 39,283 (91%) were adults and 22% of SLE patients had lupus nephritis. Racial and ethnic breakdown was: African American (38%), White (37%),Hispanic (14%), Asian (4%), Native American (2%) and other (5%). 38% of patients lived in the South, 22% in the West, 21% in the Northeast and 19% in the Midwest. During the study period, the overall mean annual MR was 1,185 ± 387 deaths per 100,000. Annual MRs were higher among males than females (1,420 ± 416 vs. 951 ± 153 per 100,000; $p=0.02$), among those aged 45-64 compared to those aged 15-44 (1,462 ± 248 vs. 730 ± 146 per 100,000, $p<0.0001$) and higher among African Americans, Whites and Native Americans (compared to Hispanics and Asians, all $p<0.05$). Among women aged 45-65, MRs were 6.5 x higher in Native Americans (1,759 per 100,000) and 6.0 x higher in African Americans (1,686 per 100,000) than those among Asians (270 per 100,000). (Table)

Conclusions: We found marked age, sex and race-specific differences in MRs among Medicaid patients with SLE. MRs among SLE patients were highest among African and Native Americans, men vs. women and patients over age 45.

Reference

1 MMWE Morb Mortal Wkly Rep 2002;5:371-4.

Table. Mortality Rates Among Medicaid Enrollees with SLE By Sex, Age Groups and Race/Ethnicity (Deaths per 100,000)

	Sex		*Age group*			*Race/Ethnicity*				
Year	*Female*	*Male*	*3-14*	*15-44*	*45-64*	*White*	*African Amer.*	*Hispanic*	*Asian*	*Native*
2000	693	1599	167	651	1003	492	1088	253	0	840
2001	1007	1644	0	843	1517	1187	1242	335	92	1124
2002	1053	919	350	856	1432	1018	1172	450	374	1717
2003	1076	1625	431	798	1702	1113	1357	555	390	923

(continued)

Table Continued

	Sex		Age group			Race/Ethnicity				
Year	*Female*	*Male*	*3-14*	*15-44*	*45-64*	*White*	*African Amer.*	*Hispanic*	*Asian*	*Native*
2004	1117	2042	194	875	1761	1298	1362	464	466	826
2005	867	972	201	545	1441	826	1162	234	327	1400
2006	848	1140	465	547	1378	916	1091	283	211	1231

O39

Risk of myocardial infarction in patients with systemic lupus erythematosus: A population-based study.

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Background/Purpose: Previous studies have consistently shown that patients with systemic lupus erytheamtosus (SLE) have an increased risk of myocardial infarction (MI). However, as approach and management of SLE has changed in the last decade, recent studies examining the risk of MI at the population level are very limited. To fill this knowledge gap, we estimated the risk of newly recorded MI events among incident cases with SLE compared to controls from the general population using physician billing and hospitalization databases that cover the entire province of British Columbia, Canada ($\sim$ 5 million).
Patients and Methods: Our data includes all visits to health professionals and hospital admissions covered by the comprehensive provincial medical services plan from January 1, 1990 until December 31, 2007 for all individuals $\geq$ 18 years of age. We conducted a retrospective matched cohort study among patients satisfying at least one of the following criteria: a) diagnosis of SLE on at least two visits within a two-year period between January 1996 and Dec 2007 by a non-rheumatologist physician; b) diagnosis of SLE on at least one visit by a rheumatologist or from a hospital. Ten controls matched by birth year, sex and calendar year of exposure were selected from the general population for each case. For purposes of matching, the controls were considered ''exposed'' on doctor visit date and ages 100+ were treated as equivalent. The analyses were conducted using an administrative health database from the entire province of British Columbia, Canada. Outcome: newly recorded MI events from hospital or vital statistics (cause of death).
Results: Among 5,156 individuals with SLE (83% female, mean age of 49 years), 115 developed MI. Compared with non-SLE individuals (N= 51,560), the age-, sex-, and entry-time-matched RRs were significantly associated for MI. The risk was 5 times greater within the first year after disease onset. After further adjustment for obesity, alcoholism /liver disease, hypertension, sepsis, peripheral vascular disease, inflammatory bowel disease, trauma and Charlson's comorbidity index, the results remained statistically significant.
Conclusion: This large population-based study indicates an increased risk of MI in patients with SLE, especially in younger individuals and within the first year of disease onset. Our results support increased monitoring of MI complications and risk factors in those with SLE at the population level.

Table: Relative Risk of Incident MI According to SLE Status

	SLE	*Non-SLE*
Incidence Rate Ratios of MI		
Cases, N	115	522
Incidence Rate/1000 Person-Years	5.5	2.4

(continued)

Table Continued

	SLE	*Non-SLE*
Overall IRR (95% CI)	2.3 (1.9 – 2.8)	1.0
IRR < 1 year of disease duration	4.9 (3.3 – 7.3)	1.0
IRR 1-4.9 years of disease duration	2.3 (1.7 – 3.0)	1.0
IRR 5+ years of disease duration	1.2 (0.7 – 1.9)	1.0
Multivariable RR		
Overall (95% CI)	2.5 (2.1-3.1)	1.0
Females	2.5 (1.9 – 3.1)	1.0
Males	2.8 (1.9 – 4.0)	1.0
Age < 45	9.2 (4.4 – 19.2)	1.0
Age 45 - 59	3.1 (2.2 – 4.4)	1.0
Age 60 - 74	1.9 (1.3 – 2.8)	1.0
Age 75+	1.9 (1.2 – 2.9)	1.0

O40

Admixture Mapping in Lupus Identifies Multiple Functional Variants within IFIH1 Associated with Apoptosis, Inflammation and Autoantibody Production

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Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a strong genetic component. African-Americans (AA) are at increased risk (3 to 5 times higher that individuals with Caucasian ancestry) of SLE, but the genetic basis of this risk is largely unknown. To identify causal variants in SLE loci in AA, we performed admixture mapping followed by fine mapping in AA and European-Americans (EA). Through genome-wide admixture mapping in AA, we identified a strong SLE susceptibility locus at 2q22-24 (LOD = 6.28) and the admixture signal is associated with the European ancestry (ancestry risk ratio $\sim$1.5). Large-scale genotypic analysis on 19,726 individuals of African and European ancestry revealed three independently associated variants in the IFIH1gene: an intronic variant, rs13023380 [Pmeta = 5.20x10-14; odds ratio, 95% confidence interval = 0.82 (0.78-0.87)], and two missense variants, rs1990760 (Ala946Thr) [Pmeta = 3.08x10-7; 0.88 (0.84-0.93)] and rs10930046 (Arg460His)

[Pdom = 1.16x10-8; 0.70 (0.62-0.79)]. Both missense variants produced dramatic phenotypic changes in apoptosis and inflammation-related gene expression. We experimentally validated function of the intronic SNP by DNA electrophoresis, protein identification and in vitro protein binding assays. DNA carrying the intronic risk allele rs13023380 showed reduced binding efficiency to a cellular protein complex including nucleolin and lupus autoantigen Ku70/80, and showed reduced transcriptional activity in vivo. Thus in SLE patients, genetic susceptibility could create a biochemical imbalance that dysregulates nucleolin, Ku70/80, or other nucleic acid regulatory proteins. This could promote antibody hypermutation and auto-antibody generation, further destabilizing the cellular network. In summary, to our knowledge this is the first study to use a whole-genome admixture mapping design to identify SLE susceptibility loci, confirm case-control association analysis in AA and EA, and identify novel variants within IFIH1 associated with SLE susceptibility. We report three independently associated IFIH1 variants with significant ethnic variation, providing a possible basis for differences in SLE risk between ethnically diverse populations.In addition, we show allele-specific differential cellular signaling and predict an in vivo role of Ku70/80 and NCL autoantibodies that could impair function of IFIH1 by disrupting DNA binding. Together with molecular modeling, our results establish a distinct role for IFIH1 in apoptosis, inflammation and autoantibody production, and explain the molecular basis of these three risk alleles for SLE pathogenesis.

Poster Presentations

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 1 Lupus & Genetics"

Atlantico A+B+C

P001

LXR alpha Gene Polymorphisms in Korean patients with Systemic Lupus Erythematosus

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Introduction: Liver X receptors (LXR) are established sensors of lipid and cholesterol homeostasis. The recent studies have reported that LXRs are involved in regulation of inflammation and immune responses. We attempted to identify single nucleotide polymorphisms (SNPs) of the LXR genes.
Patients and Methods: Blood samples were collected from Korean SLE patients (n=300) and normal controls (NC, n=217). Also, replication samples were collected from Korean SLE patients (n=160) and NC (n=143). SNPs were genotyped using SNaPSHOT assay. The promoter activity was analyzed by luciferase reporter assay in Hep3B cells and COS-7 cells. Also, we tested a functional assay of transcriptional activity and B cell proliferation assay. To investigate whether the genetic polymorphism changed a transcription factor binding, we performed an electrophoretic mobility shift assay.
Results: We have identified five polymorphisms (-1851 T > C and -1830 T > C in the promoter region, -1003 G > A, -840 C > A and -115 G > A in the intron 1 region) including one novel SNPs (-1003 G > A) in the NR1H3 gene. Two SNPs in the NR1H3 gene, -840 C > A and -115 G > A, showed the complete linkage disequilibrium. There was significant difference in the -1830 T > C polymorphism (co: p=0.001), -1003 G > A polymorphism (co: p=0.002), -115 G > A polymorphism (co: p < 0.001) between SLE and NC. These results were consistent with those of replication samples. Three common haplotypes for four polymorphisms were constructed: HT1 [TTGG], HT2 [CTGG] and HT3 [TCAA]. There was significant difference between SLE and NC in the observed haplotype HT1 [TTGG] (co: p=0.033) and HT3 [TCAA] (co: p=0.008). In the -1830 T > C polymorphism, arthritis was significantly more common in the SLE patients with the -1830 C allele (p=0.005). The -1003 G > A polymorphism was significantly associated with oral ulcer (p=0.039), arthritis (p=0.006), anti-dsDNA (p=0.041) and elevated triglyceride (p=0.007). The -115 G > A polymorphism was significantly associated with oral ulcer (p=0.024), arthritis (p= < 0.001) and elevated triglyceride (p=0.011). Luciferase activity of the constructs containing -1830 C and -1003 A was lower than that of the constructs containing -1830 T and -1003 G (p=0.009 and p=0.030, respectively). Moreover, promoter activity of the -1830 C and -1003 A was less enhanced when compared to that of the -1830 T and -1003 G in GW3965 and T0901317 treated cells (p=0.034 and p < 0.001, respectively). Proliferation of -1830 TC type was increased when compared to that of -1830 TT type in basal, GW3965 and T0901317 treated B cells from SLE patients (p=0.011, p= 0.040 and p=0.017, respectively). We found that transcription factor GATA-binding protein 3 (GATA3) protein preferentially bound the -1830 T promoter.
Conclusion: These results suggest that the NR1H3 gene genetic polymorphisms may be associated with disease susceptibility and clinical manifestations of SLE in Korean population. Specially, -1830 T > C polymorphism within NR1H3 promoter region may be involved in regulation of NR1H3 expression.

P002

The BLK allele encoding an Ala71Thr lupus associated variant is phosphorylated and renders a protein with higher degradation rate

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The B lymphocyte kinase (BLK) gene is associated genetically with several human autoimmune diseases including systemic lupus erythematosus. We recently described that risk is given by two haplotypes: one covering several strongly correlated SNPs within the promoter of the gene where the risk allele correlates with low transcript levels of BLK mRNA, and a second, rare (heterozygosity= 0.016) haplotype that includes a rare non-synonymous variant (Ala71Thr). We have proposed that the 71Thr leads to increased degradation of the BLK protein. Here we show that indeed, this variant is a major determinant of BLK protein levels. In vitro analysis showed that the rare isoform is constitutively phosphorylated and the variation confers a lower protein half-life. We also determined the differential level of expression between the risk and the non-risk allele in heterozygous primary cells and immortalized cell lines from healthy individuals. We found imbalances in allelic transcription that give raise to different proportions of BLK isoforms, and interestingly, explain variation in the global amount of protein between heterozygotes.

Because the Ala71Thr substitution is located in a protein interaction domain we sought for differences in trafficking or subcellular location between the two isoforms. We could not detect significant differences. Our data suggests that the abundance of BLK is determined by both, polymorphisms in the promoter affecting mRNA level and the Ala71Thr variation affecting the quality of the protein, as well as by allelic gene expression mRNA imbalances.

Grant support: Swedish Research Council, Instituto de Salud Carlos III partially supported by FEDER funds, Sara Borrell program.

References

1 Delgado-Vega, A.M., et al. Fine Mapping and Conditional Analysis Identify a New Mutation in the Autoimmunity Susceptibility Gene BLK that Leads to Reduced Half-Life of the BLK Protein. Ann Rheum Dis 71(7):1219-26, 2012.

P003

KIM-1 gene expression and tubular damage in Lupus Nephitis.

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Introduction: The extent of tubular lesions and recruitment of inflammatory cells is belived to be and important predictor of renal function in Lupus Nephritis (LN). The response of the renal tubules to proteinuria is implicated in progression of renal disease. KIM-1, a transmembrane tubular protein, is markedly induced in acute kidney injury and chronic kidney disease.

The role of KIM-1 in LN remains elusive. We studied the correlation between gene expression of KIM-1 in urine and biopsy of patients with LN diagnosis, and the relationship between KIM-1 expression and urine Protein/Creatinine ratio (P/C).

Patients and Methods: Twenty two kidney biopsies and 37 urine samples from 20 LN patients (17 F/5 M, age 33,5 range: 15-72) were evaluated. Urine samples were divided according P/C ratio as follows: patients with active LN, Group 1 (P/C < 1, n=12) and Group 2 (P/C > 1, n= 16). SLE patients without LN, Group 3 (n=9) and urine samples from healthy individuals Group 4, (n=17).

Levels of gene expression of KIM-1 were measured using Quantitative Real Time PCR (QPCR). All amplifications were carried out in duplicate and threshold cycle (Ct) scores were averaged for calculations of relative expression values. The Ct scores were normalized by subtracting the corresponding β2Microglobuline (β2M) control, or ΔCt=Ct,gene- Ct,B2M. To test for differential gene expression between groups a variance analysis (ANOVA) was performed. A Spearman's rank-order correlations (r) were used to test associations between gene expression levels in biopsy and urine pair's samples.

Results: ΔCt is inversely proportional to the gene expression level. There were a statistically significant difference in the expression of KIM-1 between groups (p= 0,0110). Results from ANOVA analysis showed that KIM-1 expression was: Group 2 > Group 1 > Group 4 > Group 3. We observed a significant correlation between biopsy and urine, where Spearman r= 0,6838 (p=0.0005).

Conclusion: Urinary KIM-1 gene expression correlates with high urine P/C ratio (Group 2, P/C >1). In LN, urinary KIM-1 gene expression is closely related to tissue KIM-1 and correlates with the severity of tubular interstitial injury. Quantitation of urinary KIM-1 is likely to be a useful noninvasive and sensitive method for the evaluation of kidney injury in LN.

P004

Impact of low copy number of C4A and C4B in the development and progression of systemic lupus erythematosus

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Background/Purpose: C4 is an important component of the Complement System. Complete C4 deficiency is among the strongest genetic risk factors for systemic lupus erythematosus (SLE). There are two C4 circulating isoforms (C4A and C4B) encoded by C4A and C4B genes, respectively, that differ by only five nucleotides. C4A protein is involved in the clearance of immune complex and apoptotic debris while C4B protein is relevant in the opsonization of microbes. C4A and C4B genes are located at a gene cassette within the MHC class III region and depict gene copy-number variation (CNV). The number of C4A copies may be related to the susceptibility to SLE. This study aimed to investigate the impact of the C4A and C4B gene CNV on susceptibility and progression of systemic lupus erythematosus.

Methods: We evaluated the number of C4A and C4B genes by real-time PCR in 427 SLE patients (meeting SLE ACR criteria) sequentially retrieved from the rheumatology outpatient clinic and 301 healthy individuals (HI) without evidence of autoimmune diseases were retrieved among blood bank donors. Peripheral blood leukocyte DNA was amplified by quantitative real-time PCR with primers for C4 gene and sequence specific TaqMan® probes for C4A (5' FAM-ACCCCTGTCCAGTGTTAG-MGB 3') and C4B (5' FAM-ACCTCTCTCCAGTGATAC-MGB 3'). Gene copy number (GCN) was determined by the delta-delta cycle threshold (DDCT) method.

Results: The risk of developing the disease was 2.625 times higher in individuals with low total C4 (< 4 copies, OR = 2.625, CI = 1.778 to 3.876, p < 0.001) and 3.595 times higher in individuals with low C4A (< 2 copies; OR = 3.595, CI = 2.157 to 5.993, p < 0.001), compared to individuals with normal or high copy number of total C4 (≥ 4) and C4A (≥ 2). The same was observed in relation to C4B, although at a lower intensity (OR = 1.468, CI = 1.031 to 2.088, p = 0.033). Furthermore, we found an association between low copy number of C4A and progression with more permanent damage assessed by the SLICC-DI damage index in patients with disease duration between 8 and 15 years (p = 0.007). Moreover, low C4A copy number was associated with lower chance of serositis development (p = 0.020) and low C4B number was a protective factor for articular damage (p = 0.022).

Conclusion: This study showed that low C4, C4A and C4B copy number increases the susceptibility to SLE and demonstrated an association between the number of C4A copies and the damage progression of this disease.

P005

Low gene copy number for C4, C4A and C4B is a strong risk factor for developing systemic lupus erythematosus in childhood

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Background: C4 is an important component of the Complement System. Complete C4 deficiency is among the strongest genetic risk factors for systemic lupus erythematosus (SLE). There are two C4 circulating isoforms (C4A and C4B) encoded by C4A and C4B genes, respectively, that differ by only five nucleotides. C4A protein is involved in the clearance of immune complex and apoptotic debris while C4B protein is relevant in the opsonization of microbes. C4A and C4B genes are located at a gene cassette within the MHC class III region and depict gene copy-number variation (CNV). The number of C4A copies may be related to the susceptibility to SLE. This study aimed to investigate the impact of the C4A and C4B gene CNV on juvenile SLE.

Methods: We evaluated 90 children and 170 adults with SLE (meeting SLE ACR criteria) sequentially retrieved from the rheumatology outpatient clinic. Two hundred healthy individuals (HI) without evidence of autoimmune diseases were retrieved among blood bank donors. Peripheral blood leukocyte DNA was amplified by quantitative real-time PCR with primers for C4 gene and sequence specific TaqMan® probes for C4A and C4B. Gene copy number (GCN) was determined by the delta-delta cycle threshold (DDCT) method.

Results: Children with SLE had lower GCN of total C4 (mean total C4=3.1; 95% CI=2.8-3.4), C4A (mean C4A=1.7; 95% CI=1.5-1.9) and C4B (mean C4B=1.5; 95% CI=1.3-1.6) than HI (C4=4.3 with 95% CI=4.1-4.5, p < 0.001; C4A=2.3 with 95% CI=2.2-2.5, p < 0.001; C4B=2.0 with 95% CI=1.8-2.1; p < 0.001). The frequency of SLE children with total C4 low GCN (< 4 copies) was significantly higher than in HI (SLE=59% versus HI=28%; OR=3.68; 95% CI=2.19-6.20; p < 0.001). The same was observed for C4A low GCN (< 2 copies) (SLE=52% versus HI=18%; OR=4.98; 95%

CI=2.88-8.62; p < 0.001) and C4B low GCN (SLE=60% versus HI=31%; OR=3.26; CI=1.95-5.47; p < 0.001). The association between adult SLE and low GCN for total C4 (OR=2.03; 95% CI=1.32-3.13; p=0.001), C4A (OR=2.36; 95% CI=1.46-3.81; p < 0.001) and C4B (OR=1.13; CI=0.73-1.74; p=0.593) was less pronounced than observed in juvenile SLE. Moreover, there was an association between cardiovascular damage and low GCN for C4A. 81% of those with cardiovascular damage had < 2 C4A against 44% of those with no heart involvement (OR=5.54; CI 95%= 1.37-22.32; p=0.016).
Conclusion: Low GCN for total C4, C4A and C4B is a strongest risk for developing systemic lupus erythematosus in childhood than in adults. Furthermore, low GCN for C4 and C4A seems to be a risk factor of cardiovascular damage in juvenile SLE.

P006

CCR5 Promoter Polymorphisms in Systemic Lupus Erythematosus
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Background: CCR5 is a CC chemokine receptor containing seven-transmembrane domain, that belongs to the G protein-coupled receptors family. This receptor is mainly expressed on the surface of cells, such as lymphocytes, monocytes, macrophages, dendritic cells and neutrophils, that participate in inflammatory processes. There are several polymorphisms described for the CCR5 gene, and CCR5 promoter region haplotypes (extending from the CCR2 open reading frame-ORF to the CCR5 ORF) have been associated with different inflammatory diseases, including Systemic Lupus Erythematosus (SLE). Given the importance of chemokine receptors in the immune response, this study aims to analyze potential implications of variations in the genes of the chemokine receptors CCR5 and CCR2 in patients with SLE. In the promoter region of the CCR5 we analyzed the CCR5-59353 C > T (rs1799988), CCR5-59356 C > T (rs41469351), CCR5-59402 A > G (rs1800023) and CCR5-59653 C > T (rs1800024) polymorphisms and in the CCR2 we analyzed the CCR2-V64I (rs1799864) polymorphism.
Patients and methods: Patients and controls samples were provided by the Hospital de Clínicas de Porto Alegre (HCPA) and this study was approved by the Ethics Committee of this hospital. Concerning the CCR5 promoter region polymorphisms we analyzed 349 patients (266 European-derived and 83 African-derived) e 287 controls (229 European-derived and 58 African-derived) by direct sequencing. Haplotypes were inferred from the sequences. For the polymorphism CCR2-V64I (rs1799864) we analyzed 372 patients (282 European-derived and 90 African-derived) e 230 controls (143 European-derived and 87 African-derived) through PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) with the BsaBI endonuclease.
Results: The analyses were performed stratifying patient and control groups by ethnic origin. All patients and control groups were in Hardy Weinberg equilibrium, exception made for the European-derived control group concerning the CCR2-V64I and the CCR5-59653 polymorphisms. For the CCR5-59402 polymorphism, the G allele frequency was higher in African-derived patients compared to the control group (30.5% vs. 18.1%, p=0.027, OR 1.98 CI 95% 1.12 – 3.58). According to the literature, this variant is typical of the HHC haplotype which is associated to a higher CCR5 expression. For the CCR5-59356 and CCR5-59402 polymorphisms and the haplotypes generated with the CCR5 promoter polymorphisms we observed that the allelic frequencies were different between the control groups (p=1.1E-6, p=8.6E-4 and p=1.1E-7, respectively), reflecting differences due the ethnic origin of such individuals.
Conclusions: Our preliminary results indicate a possible association of the CCR5-59402 polymorphism with LES susceptibility in African-derived patients, probably due to a higher expression of this receptor.

P007

Genetic Variation near IRF8 is Associated with Serologic and Cytokine Profiles in Systemic Lupus Erythematosus and Multiple Sclerosis
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Objective: Alleles of IRF8 have been associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). While type I interferon (IFN) is thought to be causal in SLE, type I IFN is used as a therapy in MS. We investigated whether the IRF8 alleles were associated with differences in serum IFN in SLE or MS.
Methods: The rs12444486 and rs17445836 single nucleotide polymorphisms (SNPs) in IRF8 (associated with SLE and MS respectively) were genotyped with Taqman primer-probe sets in more than 600 SLE patients of African-American, European-American, and Cretan ancestry and matched controls. Serum type I IFN was measured using a functional reporter cell assay.
Results: The MS-associated rs17445836 G allele was associated with the presence of anti-dsDNA autoantibodies in SLE patients across all ancestral backgrounds (meta-analysis OR=1.92). The same allele was associated with decreased serum IFN activity in SLE patients with anti-dsDNA antibodies, and low IFN levels in the subgroup of MS patients with secondary progressive MS. This allele was also associated with decreased type I IFN-induced gene expression in PBMC from SLE patients who lacked anti-dsDNA antibodies. No associations were observed with the rs12444486 allele.
Conclusions: The rs17445836 G allele was associated with decreased type I IFN responses in both SLE and MS patients. The association of this allele with MS, a condition characterized by low circulating type I IFN levels, and with low IFN in SLE patients suggests that this allele is associated with autoimmunity in the setting of low type I IFN levels. The association of this allele with anti-dsDNA antibodies suggests a role in humoral autoimmune responses.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 2 Immunology & Pathogenesis"

Atlantico A+B+C

P008

Altered Circulating Follicular Helper T Cell Phenotype And Subset Composition Are Associated With Disease Activity In Patients With Systemic Lupus Erythematosus
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Paulo, São Paulo, Brazil. [3]*Division of Immunology, Faculty of Medicine, University of São Paulo, São Paulo, Brazil.* [4]*Department of Immunobiology, Yale School of Medicine, New Haven, Connecticut, United States of America.*

Background: Autoreactive B cells in SLE undergo autoantigen selection, suggesting a requirement for germinal center follicular helper T (Tfh) cells in their maturation. However, evidence for dysregulation of Tfh cells in SLE and their potential contribution to disease remains unclear. Recently, blood CXCR5+ CD4 T cells, a heterogeneous pool consisting of functionally distinct Th1-, Th2-, and Th17-like subsets, have been proposed to be the circulating counterpart of Tfh (cTfh-like) cells. We now ask if changes in cTfh-like markers or subset composition within blood CXCR5+ cells are found in SLE patients, and the extent to which such alterations are associated with B cell and disease activity.
Methods: Blood samples from 49 clinically well-characterized SLE patients, 28 Behçet's disease (BD) patients, and 16 healthy controls were included. Expression of Tfh surface markers (CXCR5; ICOS, inducible T-cell costimulator; PD-1, programmed cell death protein-1), composition of blood CXCR5+ subsets, and frequency of plasmablasts were enumerated by flow cytometry. The phenotype of blood CXCR5+ subsets was correlated with disease activity, clinical history, and plasmablast expansion.
Results: SLE patients had significant expansion of CXCR5+ ICOS+PD-1+ CD4 T cells compared to controls ($p < 0.001$). PD-1, but not ICOS or CXCR5, expression was markedly elevated in CD4 T cells of SLE patients compared to BD patients and healthy controls ($p < 0.001$). PD-1 MFI in CXCR5+ cells correlated with SLE disease activity index (SLEDAI; Spearman $r = 0.43$, $p = 0.03$). PD-1 MFI also correlated with expansion of plasmablasts (Spearman $r = 0.34$, $p = 0.02$). In SLE patients with high anti-dsDNA antibody titers, PD-1 expression in CXCR5+ cells was also significantly elevated compared to patients with no detectable titers ($p = 0.004$). Enhanced PD-1 expression was neither a function of disease duration nor past activity; rather, it reflected current disease activity. cTfh-like cells also robustly expressed IL-21, but not Bcl6; the former indicates functional activity of these cells, with the lack of the latter indicative an origin likely prior to GC formation.
Conclusion: Our results demonstrate that dysregulation of cTfh-like cells is strongly correlated with disease activity in SLE, supporting a potential causal relationship. The altered composition of blood CXCR5+ cells also appeared to be a fundamental cellular defect in SLE, with our results revealing a novel dimension of Tfh dysregulation that may be central to disease pathogenesis.

Disclosure statement: None.

P009

ITGAM R77H: Genotype/Phenotype Relationships in Toll-like Receptor 7 Stimulated Macrophages

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Introduction: This study explored the role of a novel CR3 agonist to attenuate pro-inflammatory signaling in subjects with common and variant ITGAM polymorphism, rs1143679. The mechanism underlying initiation and perpetuation of inflammation – with eventual end organ injury – in Systemic Lupus Erythemasosus (SLE) is not yet defined. Equally unclear are mechanisms to attenuate such inflammation. An important candidate for initiation and perpetuation of the inflammatory response may be the chronic stimulation of resident leukocytes through toll like receptors (TLR). Complement Receptor 3 (CR3), a heterodimeric receptor on the surface of various types of leucocytes, is known to decrease proinflammatory signals by dendritic cells when ligated to iC3b. The goal of this study was to evaluate whether a TLR-mediated pro-inflammatory stimulus is attenuated by a novel iC3b mimetic specific for CR3 - known as LA1 – on macrophages expressing CR3. ITGAM polymorphism rs1143679, encoding for a non-conserved R77H substitution CD11b alpha chain of CR3, is known to be associated with SLE across various ethnic groups. While the polymorphism is theorized to affect ligand binding to CR3, the functional significance of the polymorphism is unknown. A sub-goal was to evaluate if rs1143679 carrier status attenuated the effect of LA1.
Patients and Methods: The effect of LA1 on basal and stimulated responses by macrophages of human subjects (twenty healthy donors) was evaluated. Rs1143679 carrier status of subjects was determined by allelic discrimination. Macrophages derived from CD14+ monocytes of healthy human donors were treated with R848 (a specific TLR7 ligand, 1 uM) and hY3 (2.5 ug), with and without LA1 (a recently described CR3 agonist, 15 uM). Quantification of TNFα secretion, the readout of TLR7 activation, was assessed by ELISA.
Results: Treatment of macrophages with R848 significantly stimulated TNFα release compared with macrophages alone (1265 ± 297 pg/ml versus 26 ± 30 pg/ml, respectively, $p = 0.006$, $n = 7$). Preexposure to LA1 followed by treatment with R848 impaired TNFα secretion from macrophages (R848 + LA1: 700 ± 249 pg/ml, $p=0.015$). Exposure of macrophages to LA1 in absence of R848 had no effect on cellular morphology, and did not induce TNFα over 24 hrs. This inhibition was accompanied by profound degradation of the adaptor protein MyD88, an effect not observed with direct inhibition of TLR ligation by an antagonist oligonucleotide. In contrast, the addition of LA1 after incubation with the TLR agonists did not result in MyD88 degration and subsequent attenuation of TNFα secretion. In TLR 7/8 stimulated macrophages isolated from donors heterozygous for the CD11b variant, pretreatment with LA1 did not downregulate TNFα release.
Conclusions: As previously shown in dendritic cells, inflammatory responses in macrophages are able to be attenuated in a CR3-specific fashion by the novel agonist LA1. These results also suggest significant cross-talk between CR3 and other pro-inflammatory pathways, such as TLR7. A novel functional difference in immune response to iC3b mimetic LA1, based on carrier-status of the rs1143679 polymorphism, is suggested.

P010

A Novel Murine Model of B Cell-Mediated Glomerular Injury is Mediated by Cytokines

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Purpose: Lupus nephritis (LN) remains the leading cause of mortality for SLE patients, and is associated with proteinuria and foot process effacement. In certain subsets of LN patients, B cell depletion therapies have been efficacious in lowering disease activity including glomerulopathy. The contributions of B cells to proteinuria and foot process effacement remain unknown. The development of a murine model of B-cell induced proteinuria and identification of pathogenic factors would enhance our understanding of immune-based glomerular diseases.
Methods: The B cell model antigen model hen egg lysozyme (HEL) was biotinylated and complexed to avidin. Following intravenous (IV) injection in mice, purified naïve HEL-specific B cells were adoptively transferred and proteinuria assessed. Kidneys were processed for immunofluorescence, H&E staining, and scanning electron microscopy (SEM). Cultured podocyte membrane ruffling was assessed with DIC videomicroscopy. IL-4 expression in mice was achieved by cloning

murine IL-4 into the piggyBac vector system and delivering these vectors to mice via hydrodynamic immunization.
Results: HEL embedded within the glomerular basement membrane (GBM) following IV injection. Proteinuria occurred after the transfer of naive HEL-specific B cells and associated with foot process effacement. No antibody or complement deposition was observed in the GBM. Intravital two-photon microscopy of live mice demonstrated that HEL-specific B cells arrested trafficking within glomeruli only in the presence of glomerular-localized HEL. This demonstrated the proof-of-concept that B cells were specifically capable of inducing glomerular injury and proteinuria.

The rapid kinetics of proteinuria suggested cytokines secreted by activated intraglomerular B cells may be responsible. B cells can elaborate numerous cytokines including IL-4, IL-13, IFN-γ and TNF-α, and podocytes express receptors for these cytokines. Since foot process effacement is the histologic correlate of actin cytoskeletal rearrangement, we hypothesized that pathogenic cytokines mediate podocyte injury through alterations in the actin cytoskeleton. The small Rho family G proteins, such as Cdc42, Rac, and Rho regulate the actin cytoskeleton. Rac induces lamallipodia formation, which is associated with foot process instability. Using cultured podocytes, we measured membrane ruffling in the presence of cytokines as a surrogate for Rac activation. IL-4 significantly increased cultured podocyte membrane ruffling and induced foot process retractions on ex vivo fragments of renal cortex. Hydrodynamic DNA immunization of wild-type mice with plasmid encoding IL-4 lead to proteinuria, which was reversed by JAK1/3 inhibition.
Conclusion: We developed a novel model of B cell-induced proteinuria with foot process effacement. B cell derived cytokines such as IL-4 induced alterations in foot process morphology, leading to proteinuria. Several reports suggested in mouse models IL-4 associated with renal injury, and the glomerulosclerosis seen in transgenic IL-4 mice was independent of autoantibody production. Furthermore, patients with membraneous LN possess glomerular lymphocytes expressing IL-4. We believe that IL-4 plays a direct role in LN by inducing podocyte injury through disruptions in the actin cytoskeletal changes. This has important implications in developing therapies to preserve podocyte function, limiting glomerular injury.

P011

Dysfunction of natural killer cell differentiation in SLE

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Objective: To elucidate the defective mechanism of natural killer (NK) activity in systemic lupus erythematosus (SLE), we have investigated whether ineffective differentiation of NK cells from hematopoietic stem cells (HSCs) is an underlying cause of the impaired NK cytotoxicity in SLE.
Methods: Patients with SLE (n=108), rheumatoid arthritis (RA; n=90), and healthy controls (n=173) were included in the experiments. Frequency of NK cells and the cytotoxicity against K562 cells were measured by flow cytometry. Changes of NK cell population and NK cytotoxicities were examined by flow cytometric analysis, and NK cell number was compared with the clinical parameters of SLE. For the measurement of lymphokine-activated killer (LAK) activity, IL-2 was added to the cytotoxic assay. The expression of NK-specific receptors and NK-associated genes was assessed by flow cytometry or reverse transcription-polymerase chain reaction (RT-PCR), respectively. NK cells were in vitro differentiated from peripheral blood CD34+ HSCs in the presence of stem cell factor (SCF), FMS-like tyrosine kinase 3 ligand (FLT3L), IL-7 and IL-15.
Results: Percentage and absolute number of NK cells in peripheral blood mononuclear cells (PBMCs) were significantly lower in patients with SLE and RA compared with age- and sex- adjusted healthy controls. NK cytotoxicity and LAK activity were also markedly suppressed in patients with SLE and RA. In particular, the patients with SLE, but not with RA, had decreased NK cytotoxicity and LAK activity for purified NK cells, suggesting a functional defect of NK cell itself. The defect was related to down-regulated expression of IL-2Rβ (CD122), perforin and granzyme. NK cell deficiency was more prominent with patients with lupus nephritis or thrombocytopenia, but it was independent of disease duration, disease activity, and laboratory data. Proliferative capacity of HSCs, proportion of NK cells in the differentiated HSCs and their cytotoxic activity were significantly decreased in patients with SLE, and the expression of c-KIT, as known as receptor for SCS, was down-regulated in HSCs with patients with SLE.
Conclusions: The results suggest that a defect in differentiation of HSCs to NK cells is an underlying cause for the numeric deficiency and functional defect of NK cells in SLE and it may cause regulation defects of immunity in SLE.

P012

Serum soluble interleukin-7R is strongly associated with lupus nephritis in SLE patients

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Introduction: The soluble form of the interleukin-7 receptor (sIL7R) is produced by fibroblasts after stimulation with pro-inflammatory cytokines. Increased sIL7R serum and synovial fluid levels were recently demonstrated in rheumatoid arthritis patients. Here, we investigated whether sIL7R production is dysregulated in systemic lupus erythematosus (SLE), and whether this correlates with disease activity.
Methods: Serum and urine sIL7R concentrations were measured by ELISA, and sIL7R qPCR studies were performed in PBMC. IL7R, TNFα, IL1β and IL17 immunostainings were performed on kidney sections.
Results: First, serum sIL7R concentrations in sera from patients with active SLE were measured. SLE patients from two different populations were characterized by significantly higher sIL7R serum concentrations, as compared to controls ($p < 0.001$ in both groups). Patients with active arthritis at the time of serum sampling did not display higher serum sIL7R levels compared to patients without arthritis. By contrast, serum sIL7R levels were significantly higher in patients with nephritis (LN), compared to patients without nephritis. Serum IL7R concentrations correlated significantly with disease activity (measured by SLEDAI) in all patients and also in the subgroup of patients with LN. In the LN group, there was no correlation between serum sIL7R and other markers of disease activity: serum creatinine, proteinuria, serum C3 or anti-dsDNA antibody titers. In 9 LN patients followed-up in a prospective trial, a strong decrease in serum sIL7R levels was observed upon immunosuppressive therapy, associated with a decrease in SLEDAI scores.

No significant differences in urine sIL7R concentrations between nephritis patients and controls were observed.Taken together, these data indicate that serum sIL7R could be a sensitive and specific marker of renal involvement in SLE patients.

Next, the cellular source of sIL7R production was investigated. qPCR experiments indicated that sIL-7R gene expression is not significantly higher in LN PBMC compared to controls. This suggested that other cell types, possibly at the site of inflammation, could contribute to the production of sIL7R protein. In our previous work, we demonstrated that sIL7R can be produced mainly by activated fibroblasts, after stimulation with pro-inflammatory cytokines such as TNFα, IL1β, IL17. Therefore IL7R, TNFα, IL1β and IL17 immunostainings were performed in kidney biopsies from controls (n=3) and untreated patients with LN (n=6). No signal was detected in any of the control biopsies. By contrast, strong IL7R expression was observed in perivascular fibroblast-like cells in all LN samples. In the surrounding tissue, expression of TNFα but not IL1β nor IL17 was observed.

Conclusions: Our data indicate that sIL7R is a marker of SLE disease activity, especially nephritis. In contrast to conventional disease activity markers, sIL7R is not produced by immune cells, but could instead reflect activation of tissue cells in the target organ.

P013

Blockade of CXCR4-CXCL12 interaction reduces homing and survival of plasma cells in NZB/W mice

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Introduction: Previously, we demonstrated that long-lived plasma cells resistant to glucocorticoids, immunosuppressive/cytotoxic drugs and B cell targeting therapies contribute to the pathogenesis of antibody-mediated diseases and should therefore be considered as a promising therapeutic target in systemic lupus erythematous (SLE). In bone marrow, the plasma cells reside in niches consisting of several cells, cytokines and adhesion molecules. Stromal cells expressing the chemokine CXCL12 organize these niches that provide for the plasma cell survival. CXCL12 is the ligand of CXCR4 expressed on plasma cells. In this study we investigated the contribution of CXCL12-CXCR4 interaction to the longevity of plasma cells in the murine model of lupus.

Material and methods: Plasmablasts and plasma cells purified from spleens of NZB/W mice were incubated with the CXCR4 blocker AMD3100 (500μg/ml) for 30 minutes and then adoptively transferred to immunodeficient $Rag1^{-/-}$ mice. After 14 days we analyzed the number of plasma cells in bone marrow. Furthermore, OVA immunized NZB/W mice were treated intraperitoneally with AMD3100 (20mg/kg) 7 times with one day interval after boost and OVA specific plasma cells in bone marrow were checked on day 3 and 15 after boost. The effect of plasma cell depletion was investigated in NZB/W mice with AMD3100 (5mg/kg s.c. 3 times per week) alone or combined with bortebomib (0.5mg/kg i.p. 2 times per week) for two weeks.

Results: Two weeks after adoptive transfer of splenic plasma cells from NZB/W to $Rag1^{-/-}$ mice the number of plasma cells treated with AMD3100 was 60% lower in bone marrow compared to a control group. After secondary immunization with OVA the AMD3100 treatment resulted in a significant reduction of anti-OVA secreting plasma cells in bone marrow by 33% on day 3 and 23% on day 15 comparing with control group. After 15 days the number of MHC class II negative OVA specific plasma cells in bone marrow significantly decreased in treated mice by 42% reduction comparing with untreated mice. In comparison with untreated mice, AMD3100 efficiently depleted plasma cells including long-lived plasma cells. After two weeks treatment, total plasma cells number was decreased 69% in spleen and 61% in bone marrow, for long-lived plasma cells 67% were depleted in spleen and 64% in bone marrow. The combination of bortezomib with AMD3100 in NZB/W significantly enhanced the depletion of long-lived plasma cells compared to monotherapy with bortezomib or AMD3100.

Conclusions: CXCR4 blockade with AMD3100 can reduce the homing of plasma cells to the bone marrow and the survival of long-lived plasma cells. The combination of bortezomib with AMD3100 shows synergistic effects on plasma cell depletion.

P014

Interferon-alpha Dependent Regulation of C-reactive Protein in Systemic Lupus Erythematosus

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Background: The type I interferon system is considered important for the pathogenesis of systemic lupus erythematosus (SLE), and novel therapies targeting interferon alpha (IFNα) are under way. We have previously shown a distinct inhibitory effect of IFNα on interleukin 6 (IL-6)-triggered hepatocytic C-reactive protein (CRP) production *in vitro*,[1] possibly explaining the poor correlation between disease activity and circulating levels of CRP in SLE. To confirm this *in vivo*, we studied the relationship between CRP levels, IFNα, and CRP-inducing cytokines as well as CRP gene polymorphisms in SLE patients.

Patients and Methods: Serum samples were prepared from 100 healthy blood donors and 155 well-characterized SLE patients fulfilling the 1982 American College of Rheumatology (ACR) classification criteria. Disease activity (SLEDAI-2K and the physician's global assessment) and were registered. The research protocol was approved by the Regional Ethics Committee in Linköping, Sweden. CRP was detected using a highly sensitive latex-enhanced turbidimetric immunoassay, IFNα by dissociation-enhanced lanthanide fluorescent immunoassay, and IL-1β, IL-6, and tumor necrosis factor (TNF) were all measured simultaneously in a multiplex magnetic bead assay. Since genetic variation in the CRP gene may account for variation in both basal and acute-phase CRP levels, we also investigated 3 CRP single nucleotide polymorphisms (SNPs) with previously described associations with CRP levels. DNA was extracted from peripheral blood leukocytes and CRP SNPs were determined by the Immunochip Illumina array. The Mann-Whitney U test was used to assess differences in cytokine or CRP levels between different disease phenotypes. The associations between CRP and circulating cytokine levels were evaluated using multiple linear regression models. Because of known or potential confounding by age, sex, body-mass-index (BMI) and glucocorticoid medication, these items were considered as independent variables in multiple linear regression analyses.

Results: Cross-sectional analysis revealed associations between CRP and age ($p < 0.0005$) and BMI ($p=0.013$), but not between CRP and IL-6 or IFNα levels. However, in patients with CRP levels $\geq$ 3 mg/l ($n = 63$) IL-6 had a positive effect on CRP ($p=0.012$), whereas IFNα had a negative effect ($p=0.011$). Age and BMI had no significant impact on CRP levels in this group of patients. No associations were found between disease activity and CRP levels, and no effect was observed for the 3 CRP SNPs.

Conclusions: We present support for an inhibitory effect of IFNα on circulating CRP levels in SLE patients with CRP $\geq$ 3 mg/l. This strengthens the hypothesis that muted CRP responses found in conditions characterized by raised type I IFNs are due to an IFNα mediated

inhibition of IL-6 induced hepatocyte CRP production. These findings have implications not only for SLE, but also for viral infections and cardiovascular disease.

1 Enocsson H, et al. Interferon-alpha mediates suppression of C-reactive protein: Explanation for muted C-reactive protein response in lupus flares? Arthritis Rheum 2009;60:3755-60.

P015

Salivary gland plasmablast monoclonal antibody specificity reflects clinical presentation and serology in lupus patients with secondary Sjögren's syndrome

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Introduction: Sjögren's syndrome (SS) is an autoimmune exocrinopathy that occurs in about 20% of patients with systemic lupus erythematosus (SLE). The serologic hallmark of SS is the presence of IgG antibodies specific for Ro (SSA) and La (SSB). Ro and La autoantibodies are produced *in situ* within the glands by plasmablast/plasma cells. We questioned whether serologic specificities associated with SLE were associated with plasmablast specificity at the site of exocrine gland inflammation.
Methods: We produced human recombinant monoclonal autoantibodies (hrmAbs) from single-cell-sorted salivary gland and peripheral blood-derived plasmablast cells from an SLE patient with secondary SS as well as a SS patient with Raynaud's. Clonality, immunoglobulin chain usage and somatic hypermutation frequencies of hrmAbs were evaluated using IMGT/V-Quest. Specificities of autoantibodies were evaluated by indirect immunofluorescence, ELISA, INNO-LIA™, BioPlex2200™ Bead array and S35 protein immunoprecipitation. Salivary antibody levels were assessed by ELISA.
Results: We produced 24 hrmAbs from single plasmablasts purified from salivary gland biopsies, whose specificities included anti-Ro, anti-Sm, anti-RNP and anti-PL12.. There was concordance between serum autoantibody and glandular plasmablast specificities. Heavy and light chains derived from glandular plasmablasts were extensively somatically hypermutated and demonstrated preferential usage as well as clonal relatedness, indicative of antigen-driven responses. Two groups of antibodies were produced; those of high-affinity targeting single antigens including Ro, SmRNP, Sm and PL12, and those of low-affinity that were polyreactive. IgG and IgA antibodies correlating to those produced by glandular plasmablasts were detected in patient saliva.
Conclusion: We have produced high-affinity human monoclonal antibodies binding antigens typically bound by IgG from patients with SLE or SS. We conclude that glandular autoantibody production extends beyond the canonical SS specificities of Ro and La to include SLE-related specificities. The antibodies production within the salivary gland is directly related to clinical presentation.

P016

Inhibiting TWEAK (TNF-like weak inducer of apoptosis) signaling ameliorates neuropsychiatric disease in MRL/lpr mice

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Background: Neuropsychiatric disease is a common and potentially dangerous type of major organ involvement in systemic lupus erythematosus (SLE). However, the mechanisms underlying neuropsychiatric SLE (NPSLE) are not fully understood, and the optimal treatment is not known. TWEAK is a cytokine member of the TNF superfamily that has been implicated in experimental autoimmune encephalomyelitis (EAE) and stroke. In the central nervous system, the TWEAK receptor Fn14 is expressed in endothelial cells, astrocytes, microglia, and neurons. Based on the known mechanisms of action of this ligand-receptor pair, TWEAK/Fn14 interactions may promote inflammatory cytokine production, neurodegeneration, and enhanced permeability of the blood brain barrier. Furthermore, we previously reported that patients with NPSLE demonstrate high cerebrospinal fluid (CSF) TWEAK levels. Based on these studies, we hypothesized that TWEAK signaling is involved in the pathogenesis of NPSLE.
Materials and methods: To experimentally address the hypothesis that TWEAK/Fn14 interactions are involved in the pathogenesis of NPSLE, comprehensive neurobehavioral tests (forced swim, anhedonia, open field, object recognition, object placement, and social preference) were employed to evaluate neuropsychiatric disease in MRL-lpr/lpr (MRL/lpr) Fn14 wild type (WT) [a spontaneous murine model with prominent neuropsychiatric manifestations] and MRL/lpr Fn14 knockout (KO) mice.
Results: We found that MRL/lpr Fn14 KO mice had markedly attenuated NPSLE, as shown by significantly less depressive-like behavior and improved cognitive function. To determine the mechanism underlying the attenuated neuropsychiatric phenotype in Fn14 deficient MRL/lpr mice, we analyzed blood brain barrier integrity, and found that Fn14KO mice had decreased CSF albumin and IgG quotients, indicating preserved barrier function. Moreover, RANTES, C3 and IgG were reduced in brains of Fn14KO mice. No differences between MRL/lpr Fn14 WT and KO mice were found in serum autoantibody titers.
Conclusions: TWEAK/Fn14 interactions may play a central role in the pathogenesis of neuropsychiatric disease in MRL/lpr mice, suggesting a novel therapeutic approach for the treatment of NPSLE.

P017

Podocyte injury in pure membranous and proliferative lupus nephritis: distinct underlying mechanisms?

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Introduction: Proteinuria is a major feature of lupus nephritis (LN) and may reflect podocyte injury. Alteration in the expression of podocyte biomarkers has been associated with cellular dysfunction in some glomerulopathies. Analysis of podocyte-associated molecules encompassing different subcellular compartments was performed attempting to identify if podocyte phenotype is distinct in pure membranous and proliferative LN.
Patients and Methods: Expression of nuclear Wilmś tumor protein 1 (WT1), cytoplasmic synaptopodin (Synpo), membranous glomerular epithelial protein 1 (GLEPP1) and slit diaphragm nephrin was evaluated in 52 LN biopsies by immunohistochemistry. Demographic, clinical and laboratorial data at the time of biopsy were analyzed.
Results: Thirty-nine (75%) biopsies were classified as proliferative and thirteen (25%) as pure membranous LN. Normal kidney revealed global and diffuse (preserved) staining of all four podocyte biomarkers. Concomitant preserved WT1/Synpo expression was more often observed in pure membranous than in proliferative LN (69.2 vs. 2.6%, $p < 0.0001$) in spite of comparable proteinuria at biopsy in

both (4.21+3.07 vs. 4.03+3.71 g/24h, respectively, p=0.87). Likewise, preserved expression of GLEPP1 (53.8 vs. 2.9%, p=0.0002) and nephrin (60% vs. 9.4%, p=0.0025) was more frequent in the former. In the mean follow-up period of four years, a tendency to lower proteinuria levels was observed in patients with preserved WT1/Synpo expression (0.26±0.23 and 0.84±0.90 g/24h, respectively, p=0.050).
Conclusion: Our data provided novel evidence that proteinuria has distinct mechanisms in pure membranous and proliferative LN, with a predominant preserved podocyte phenotypic pattern in the former and a structural podocyte injury demonstrated in proliferative nephritis.

P018

Tartrate-Resistant Acid Phosphatase Activity on Osteopontin and Regulation of Interferon-alpha

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Background: The enzyme tartrate-resistant acid phosphatase (TRAP) is highly expressed in osteoclasts. One of the main substrates for TRAP in bone matrix is osteopontin (Opn). Biallelic mutations in the gene, ACP5, that encodes TRAP, result in an immuno-osseous disease called spondyloenchondrodysplasia (SPENCD). In addition to bone and neurological abnormalities, SPENCD patients also develop autoimmune features resembling systemic lupus erythematosus (SLE). SPENCD patients demonstrate evidence of increased interferon-alpha (IFN-α) production in their blood. Since very little is known about the function of TRAP in immune cells, the **objectives** of our study were to determine whether Opn is a substrate for TRAP and to define the consequences of TRAP deficiency in immune cells.
Methods: Co-localization of TRAP and Opn was determined by confocal microscopy and also by immunoprecipitation and western blot analysis (IP-western). TRAP overexpression or knockdown was performed by transfection with cDNA or shRNA, respectively. Expression of IFN-α and IFN signature genes (ISGs) were determined by quantitative PCR (QPCR). Phosphatase activity was quantified by Biomol Green fluorimetry.
Results: We observed that TRAP co-localized with OPN in early endosomes and the Golgi in both primary macrophages as well as in plasmacytoid dendritic cells (pDC). Co-localization was confirmed biochemically: following co-transfection of cDNAs encoding TRAP and OPN in 293 cells, we reciprocally co-immunoprecipitated TRAP and OPN as determined by western blots. Also, in macrophages, anti-TRAP antibody immunoprecipitated both TRAP and OPN, indicating that they interacted with each other in primary non-transformed cells. To confirm that Opn was indeed a substrate for TRAP, we observed that recombinant human TRAP dephosphorylated OPN by the release of free phosphate in an in vitro assay. To relate the functional significance of TRAP deficiency to IFN-α production, we knocked down the expression of TRAP in pDC. We observed that TRAP specific shRNA, but not scrambled shRNA, increased the expression of IFN-α and IFN signature genes (ISGs).
Conclusions: Taken together, these findings indicate that TRAP and OPN co-localize and that OPN is a substrate for TRAP in immune cells. Significantly, TRAP deficiency in pDC leads to increased IFN-α production providing an explanation for why TRAP mutations lead to a lupus-like disease in SPENCD patients.

P019

Increased Oxidative Burst in Neutrophils but not Monocytes in Systemic Lupus Erythematosus

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Background: The role of innate immunity in the pathogenesis of Systemic Lupus Erythematosus (SLE) has acquired increasing importance lately. Chronic Granulomatosus Disease (CGD), a hereditary inability of phagocytes in producing Reactive Oxygen Species (ROS), has been associated with increased frequency of discoid lupus erythematosus (2.7%) and with SLE (0.5%). This study aimed to evaluate the oxidative response in monocytes and neutrophils from SLE patients and healthy controls (HC) at basal state and after bacterial stimulus.
Materials and methods: 300 SLE patients and 301 age- and gender-paired HC (blood donors) were clinically examined and evaluated for quantification of the oxidative burst in phagocytes by flow cytometry based on the oxidation of 2,7-dichlorofluorescein-diacetate before and after stimuli with Staphilococcus aureus and Pseudomonas aeruginosa. There was a 7-day wash-out period for immunosuppressant drugs before sample collection.
Results: No patient or HC presented oxidative burst profile compatible with CGD, however one patient was classified as carrier of defective gene (0.33%). SLE neutrophils had higher basal oxidative activity than HC [mean fluorescence intensity (MFI)=53.77±11.38 versus 15.08±2.63, respectively; $p < 0.001$]. ROS production was also significantly higher in SLE as compared with HC after stimulation with S. aureus (MFI=355.46±58.55 versus 151.92±28.25, respectively; $p < 0.001$) or P. aeruginosa (MFI=82.53±10.1 versus 48.99±6.74, respectively, $p < 0.001$). Furthermore, the neutrophilic response after bacterial stimuli (ΔMFI = post-stimulus MFI minus basal MFI) was more intense in SLE than in HC (S aureus: 301.69±54.42 versus 118.38±26.03, respectively; $p < 0.001$; P aeruginosa: 28.76±12.3 versus 15.45±5.15, respectively; $p < 0.001$). Oxidative burst profile was not associated with disease activity (SLEDAI≥6) or severity (SLICC-DI≥2). Neutrophil basal ROS production was higher in patients with lupus nephritis (median MFI=39.43; ranging from 1.0 to 167.4) than in patients without nephritis (median MFI=27.29; ranging from 1.2 to 143.9; p=0.014). In addition neutrophils from patients with lupus nephritis (n=166) presented higher increment in ROS production after stimulus with S. aureus (median ΔMFI=320.1; ranging from 194.9 to 826.1) than neutrophils from patients without nephritis (n=133; median ΔMFI=278.5; ranging from 149.9 to 649.9; p=0.03). These differences in ROS production were not observed in monocytes from patients with lupus nephritis. There was no association of PMN oxidative burst profile and the therapeutic regimen.
Conclusion: Neutrophils from SLE patients presented increased basal ROS production and increased oxidative response to bacterial stimuli. These findings were particularly evident in patients with kidney involvement. The present findings corroborate the important role of innate immunity in SLE and implicate neutrophils in the pathophysiology of the disease.

P020

Anti-dsDNA antibody isotypes in systemic lupus erythematosus: IgA anti-dsDNA help to identify glomerulonephritis and active disease

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Aim: To evaluate the role of anti-double stranded(ds)DNA IgG, IgM and IgA isotypes in the diagnosis of systemic lupus erythematosus

(SLE), and their association with clinical features and disease activity in a large cohort of SLE patients.

Patients and methods. Sera of 200 SLE patients (174 female and 26 male, mean±SD age 34±10.3 years, median disease duration 115 months, range 7-378), and of 206 controls (19 Sjögren's syndrome, 27 rheumatoid arthritis, 26 psoriatic arthritis, 15 polymyositis/dermatomyositis, 13 systemic sclerosis, 49 infectious diseases, and 57 healthy subjects) were tested for anti-dsDNA IgG, IgM and IgA isotypes. Isotypes were measured according to manufacturer's instructions, by commercially available ELISA assays (Aesku Diagnostic, Wendelsheim, Germany), based on a human recombinant dsDNA source as antigen bound to microwells.

Associations between non-parametric unpaired data were calculated by means of Mann-Whitney U and chi-square tests. Data were adjusted using the Bonferroni's test for multiple comparisons, p values < 0.016 were considered statistically significant. Statistical analysis was performed using SPSS software. The study was approved by the local Ethical Committee. Written informed consent was obtained from each patient.

Results: The sensitivity of IgG, IgM and IgA anti-dsDNA antibodies in SLE was 55%, 30% and 49%, respectively; 12.5%, 1% and 7.5% of SLE patients had positive IgG, IgM or IgA isotype alone, respectively. Considering all three antibody classes, the sensitivity was 67%, and the specificity was 90.7%.

SLE patients with glomerulonephritis showed higher levels of IgA anti-dsDNA (p=0.0002), anti-dsDNA IgG/IgM (p=0.001) and IgA/IgM ($p < 0.0001$) ratios than patients without renal disease. We also evaluated whether the IgG/IgM and the IgA/IgM ratios could be used to assess renal involvement in SLE patients. Based on receiver operating characteristic (ROC) analysis, the optimal IgG/IgM ratio value was 2.09 (sensitivity=64.6%, 95%CI 53.3-74.9%; specificity=60.2%, 95%CI 50.7-68.1%; positive likelihood ratio [LR+]= 1.62; negative likelihood ratio [LR-]=0.59); the IgA/IgM ratio value was set at 1.74 (sensitivity=54.9%, 95%CI 43.5-65.9%; specificity=83.9%, 95%CI 76.0-90%; LR+=3.41; LR-=0.54). However, the area under the ROC curve was low for both the IgG/IgM ratio (0.633) and the IgA/IgM ratio (0.693). No significant associations have been found between anti-dsDNA isotypes and other clinical features. IgA anti-dsDNA (p=0.01) and IgG/IgM ratio (p=0.005) were higher in patients with ECLAM > 4.

Conclusions: Our study suggests that the detection of IgA anti-dsDNA antibodies can improve our ability to diagnose SLE (7.5% of SLE patients were positive only for this autoantibody class), particularly lupus nephritis. By contrast, IgM anti-dsDNA antibodies might be protective for renal involvement. Our data support the hypothesis that anti-dsDNA antibody class clustering may help to refine SLE diagnosis and prognosis.

P021

Reactive oxygen production in proliferative lupus nephritis produced by NADPH oxidase and uncoupled nitride oxide synthase is modulated by endothelial nitric oxide synthase.

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Background/Purpose: The role of reduction-oxidation (redox) regulation of cell function in the different International Society of Nephrology/Renal Pathology Society (ISN/RPS) classes of lupus nephritis (LN) is not known. Different reactive intermediate (RI) species lead to differential modifications of proteins that, in turn, lead to changes in transcriptional regulation and enzyme function. RIs are unstable species that can be measured indirectly by their ability to modify protein tyrosine (Tyr) and phenyalanine, forming nitroTyr (NTyr, via peroxynitrite), metaTyr and orthoTyr (mTyr and oTyr, via hydroxyl radicals), and chloroTyr (ClTyr, via HOCl). All of these oxidative modifications ultimately stem from superoxide (SO) and subsequent H2O2 reactive oxygen species (ROS) production. The expression of endothelial nitric oxide synthase (eNOS), required to modulate inflammation, is reduced in the glomeruli of patients with proliferative lupus nephritis. eNOS-derived NO can regulate ROS production via modulation of NADPH oxidase subunits (NOX1/2/4). NOX-driven ROS can increase transcription of IL6 and MCP1. This study was designed to address the hypothesis that proliferative and non-proliferative LN have distinct profiles of RI production with distinct enzyme sources and with different urine cytokine profiles.

Methods: Serum was collected from 34 patients with active LN who had a renal biopsy with ISN/RPS classification at the time of collection. Serum proteins were analyzed for NTyr, mTyr, oTyr and ClTyr by HPLC with electrochemical detection, normalized to Tyr and summed to represent total oxidation of serum proteins. Urine IL6 and MCP1 levels were measured in a subset of patients (n=21). Snap frozen murine renal cortical tissue lysates from MRL/lpr and MRL/lpr NOS3 -/- (eNOS) mice with active proliferative LN were analyzed for superoxide (SO) production by lucigenin assay with and without inhibitors of nitric oxide synthase (NOS), NADPH oxidase subunit NOX, cyclooxygenase, mitochondrial complexes I, II, and III, xanthine oxidase, and p450 enzymes.

Results: The summed oxidation markers were greater class III and IV LN compared to classes II and V. IL6 and MCP1 levels were increased in patients with proliferative LN, and levels of both cytokines correlated significantly within individuals. SO production was increased (to 160%) in MRL/lpr NOS3-/- kidney cortex compared to MRL/lpr NOS3+/+ mcie. This increase was reduced by both NO synthase inhibitors and DPI (a nonspecific NADPH oxidase inhibitor, 40% of control) but not the remaining inhibitors.

Conclusion: Reactive oxygen species (ROS) production is increased in proliferative LN. ROS in murine LN appears to be produced by uncoupled NOS and NOX. Higher levels of SO in MRL/lpr cortical tissue from NOS3 -/- mice suggests that eNOS-derived NO can scavenge SO or modulate SO production by preventing NOS and NOX-derived SO production. The correlation observed between IL6 and MCP1 suggests common signaling mechanisms, possibly via well described regulation of redox-sensitive transcription factors. Therefore, effective therapy for SO-mediated redox signaling in proliferative LN could target pathways that increase the modulating effect of eNOS-derived NO on NOS and NOX-mediated SO production.

P022

The ubiquitin ligase Cbl-b is a key regulator of peripheral tolerance in Systemic Lupus Erythematosus

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Background: The ubiquitin ligase Casitas B-lineage Lymphoma-b (Cbl-b) is one component of the genetic program that governs anergy, and Cbl-b deficiency in murine models is associated with increased autoimmunity and resistance to anergy. However, the role of Cbl-b in systemic lupus erythematosus (SLE) has not been fully addressed.The aim of this study was to analyze the expression and modulation of TCR signaling dependent on Cbl-b in T cells from SLE patients upon tolerogenic stimuli.

Methods: Twenty SLE patients (11 in clinical remission and 9 with active untreated disease) and 20 healthy controls were included. PBMC were isolated and CD4+ T cells were negatively selected.

Four experimental conditions were defined as follow: rest, activation (anti-CD3+anti-CD28) and anergy (ionomycin). Cbl-b expression was measured by RT-PCR and western blot in peripheral CD4+ T cells from patients and controls upon the aforementioned experimental conditions. Cell proliferation was measured by CFSE. Cytokine production was analyzed by luminometry and activation markers surface expression by flow cytometry. Transfection assays were made to overexpress Cbl-b and TCR kinases phosphorylation was evaluated.
Results: Upon anergy induction, Cbl-b normalized mRNA (0.21 vs 0.47, p= 0.015) and protein expression (0.73 vs 0.90, p=0.038) in CD4+ T cells from SLE patients was decreased in comparison to controls. The decreased expression of Cbl-b was related to decreased expression of the transcription factor Egr-3. No differences were found between active and remission patients. Also, Cbl-b deficient expression was found in naïve as well as effector memory subset in SLE. CD4+ cells from SLE patients shown multiple abnormalities regarding the proliferative response, particularly, under anergy-inducing conditions, we observed increased proliferation in SLE CD4+ T cells as compared to those from controls (293.9±117.3 vs. 16.7±6.3, p=0.031), as well as higher IL-2 production (99±38.6 vs. 11.9±4.8 pg/ml, p=0.040). The effector response shown diverse abnormalities in SLE, after ionomycin treatment, there were increased levels of IL-4 (26.1±7 vs. 8.8±2.9 pg/ml, p=0.036) and IL-17 (718.9±262.1 vs. 96±6.7 pg/ml, p=0.035) as well as decreased IL-10 (165.1±68.7 vs. 1217.7±596.9 pg/ml, p=0.030) in the supernatants of SLE CD4+ T cell cultures vs controls. These changes were accompanied by increased expression of activation (CD69, CD83) and costimulatory markers (CD40L). Upon ionomycin treatment, primary T cells showed enhanced mitogen-activated protein kinase (MAPK) activity and decreased Akt phosphorylation, which was representative of the anergic state. In T cells from lupus patients, Cbl-b overexpression led to increased p-MAPK expression, which indicates the reversibility of anergy resistance.
Conclusions: Our data suggest that abnormal peripheral tolerance in SLE is caused by Cbl-b deficiency and that this ubiquitin ligase plays a key role in regulating peripheral tolerance and TCR signalling in SLE.

P023

Serial Screening Shows that 28% of Systemic Lupus Erythematosus Adult Patients Carry an Underlying Primary Immunodeficiency

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Background: Systemic Lupus Erythematosus (SLE) is associated to deficiency of C1q, C4, and C2. There is high frequency of discoid lesions (2.7%) and SLE (0.5%) in Chronic Granulomatous Disease (CGD). Selective IgA Deficiency (SIgAD) has been associated with juvenile (5.2%) and adult (2.6%) SLE. About 25% of patients with Common Variable Immunodeficiency (CVID) develop autoimmune manifestation, including SLE. Although there are reports of individual primary immunodeficiency (PID) in SLE, there is no systematic study estimating the fraction of SLE adult patients presenting any form of PID. This study aimed to estimate the prevalence of overall PID in a cohort of SLE patients and healthy controls, and to compare the clinical characteristics of the SLE patients with and without PID.
Methods: 300 SLE patients (ACR criteria) and 301 controls (blood donors) underwent clinical examination and were evaluated for total hemolytic complement (CH50), C2, C3, C4A and C4B gene copy number, immunoglobulin isotypes and IgG subclasses, as well as quantification of the oxidative burst in neutrophils. Patients who presented any laboratory indication of PID underwent a novel examination after 60 days for confirmation. Patients with active disease and abnormal results were followed and underwent novel tests after the end of the flare or excluded if no remission was attained up to the end of the study. Cases with low C2 serum levels underwent C2 gene analysis by PCR for confirmation. Those who presented altered unexplained CH50 underwent C1q determination. Those with C4A and/or C4B low copy number had C4 serum levels determined. Diagnosis of PID was established according to "2009 International Union of Immunological Societies Expert Committee on PID".
Results: There were 84 SLE patients (28%) and 10 controls (3.33%) with established diagnosis of PID ($p < 0.001$). SLE patients had a significantly ($p < 0.01$) higher frequency of IgG2 deficiency (n=37; 12.3%), IgG3 deficiency (n=24; 8%), IgG4 deficiency (n=11; 3.6%), and IgM Deficiency (n=24; 8%) as compared to HC (0.3%, 0%, 0%, and 1.6%, respectively). One female patient presented neutrophil oxidative burst profile compatible with CGD gene carrier status (0.33%). There were no cases of C2, C3, C4 or C1q deficiency, CVID, CGD, Hyper-IgM and Hyper-IgE syndromes. Patients with IgG3 or IgG4 deficiency presented higher frequency of lupus nephropathy and those with IgM deficiency presented higher prevalence of oral ulcers. Overall PID was not associated with most SLE clinical manifestations, infection rate, immunosuppressant use, age at disease onset, disease duration, comorbidity, SLEDAI and SLICC-DI.
Conclusion: Over one quarter of SLE patients presented some form of PID, largely represented by immunoglobulin deficiency. Due to the important role of immunoglobulins in the clearance of immunocomplex, apoptotic bodies and pathogens, low levels of these components might induce a state of frequent and persistent immunological stimulation, which may foster autoimmunity development in genetically predisposed individuals. Our results suggest that an underlying immunodeficiency state may be involved in the disease pathophysiology in a substantial fraction of SLE patients.

P024

Activation of the Interferon Pathway is Dependent upon Autoantibodies in African American SLE Patients, but not in European-American SLE Patients

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Background: Gene expression studies have been instrumental in defining important aspects of the complex immunological pathogenesis in systemic lupus erythematosus (SLE). SLE is a heterogeneous disease that manifests differently by ancestry, and by the presence of autoantibodies directed at RNA binding proteins (anti-RBP). Moreover, anti-RBP antibodies are associated with high serum interferon (IFN)-α, which plays an important role in SLE pathogenesis. Our overall hypothesis was that the molecular pathogenesis of SLE differs between African-American (AA) and European-American (EA) SLE patients, and between those with anti-RBP antibodies and those who lack these antibodies. We aimed to explore this hypothesis using peripheral blood gene expression profiling.
Methods: Whole blood RNA from 33 female SLE patients and 16 matched female controls from AA and EA ancestral backgrounds were analyzed on Affymetrix Gene 1.0 ST gene expression arrays. Two-tailed t-tests were performed to compare the expression values between cases and controls in each ancestry. Differentially expressed genes with a cutoff P of 0.05 were further explored using Ingenuity Pathway Analysis (IPA) to compare the top canonical pathways amongst the sample groups. An independent replication cohort of more than 100 SLE patient samples and 30 controls was used to test the hypotheses generated by the microarray data, using qPCR to quantify gene expression.

Results: Both AA and EA patients with positive anti-RBP antibodies (RBP+) showed similar IFN-related canonical pathways such as IFN Signaling (P = 1.3 x 10-7 and 6.3 x 10-11 in AA vs. EA respectively), Antigen Presenting Pathway (P = 1.8 x 10-5 and 2.5 x 10-6) and a number of pattern recognition receptor pathways. The key pathway difference was shown between AAF and EAF patients with negative anti-RBP antibodies (RBP-) as EAF patients also showed IFN Signaling (P = 1.0 x 10-5) and Antigen Presenting Pathway (P = 1.3 x 10-1Ĩ) whereas AAF patients with RBP- did not reveal any IFN-related pathways. A replication study was performed through qPCR on 3 IFN-inducible genes, IFIT1, MX1 and PKR with, and showed similar results. All three genes were strongly up-regulated in RBP+ patients in both ancestries and PKR was up-regulated in EAF patients with RBP- but these findings were completely absent in AAF patients with RBP-.
Conclusions: Our data show that IFN-induced gene expression is completely dependent on the presence of autoantibodies in AA SLE patients but EA patients could have IFN pathway activation in the absence of these antibodies. Further studies are needed to define other novel pathways that may define the heterogeneity in SLE, especially in the RBP- AA group.

P025

Regulatory T-cells, CD25 and IL2RA genetic variation in unaffected relatives of SLE patients

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Background: FOXP3+ regulatory T-cells (Tregs) in Systemic Lupus Erythematosus (SLE) are in a functionally deficient state with a characteristic reduction or absence of surface CD25 (the IL-2 receptor alpha chain) [1]. Genetic variation in the *IL2RA* locus that encodes CD25 is associated with autoimmune disorders.
Patients and methods: We have studied Treg and Treg subset CD25 by flow cytometry and typed 24 SNPs in the *IL2RA* locus. The data evaluated until now include 54 SLE patients, 118 SLE-unaffected first-degree relatives of SLE patients, and 77 unrelated control subjects.
Results: In both SLE patients and unaffected relatives, surface CD25 was found strongly reduced not only in fully activated, but already in circulating CD4+FOXP3+CD45RO-CD31+ naive thymic emigrant Tregs. Compared with CD25 levels found on these thymic emigrants, however, unaffected relatives had upregulated surface CD25 in CD4+FOXP3highCD45RO+ activated Tregs [2] much stronger than the SLE patients, reaching intermediate levels that were higher than in the patients but still lower than in the unrelated control subjects.

Activated Treg surface CD25 of control subjects was significantly influenced by genetic variation in the *IL2RA* locus. In unaffected relatives of SLE patients, however, *IL2RA* genetic variants rather influenced surface CD25 on FOXP3+ thymic emigrants. Surprisingly, those genetic variants that were associated with increased CD25 on activated Tregs in control subjects were typically inversely associated with reduced CD25 on SLE-relatives' FOXP3+ thymic emigrants, as well as with relatively reduced frequencies of activated within all circulating FOXP3+ Tregs. This frequency was strongly correlated with Treg thymic emigrant surface CD25 both in the unaffected relatives and in the patients.
Conclusions: Our results point to an intrathymic mechanism present in an extended population that carries SLE susceptibility factors, leading to reduced Treg surface CD25 and a subsequently decreased capacity of Treg activation. The functional Treg deficiency observed in SLE patients could in part be due to such thymic conditioning.

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P026

Foxp3+ Helios+ Regulatory T Cells are expanded in active SLE

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Objectives: Recent data debate the suitability of Helios, an Ikaros family member, as a marker for thymic-derived regulatory T cells (Tregs). Nevertheless, $Foxp3^+$ $Helios^+$ Tregs may be of particular relevance in mediating immune tolerance in chronic autoimmunity, such as systemic lupus erythematosus (SLE), as they possess enhanced suppressive function, compared to $Foxp3^+$ $Helios^-$ Tregs.
Methods: Multicolour flow cytometry was performed to analyse Foxp3 and Helios expression in peripheral blood $CD4^+$ T cells from SLE patients, compared to healthy controls (HC) and systemic sclerosis (SSc) and rheumatoid arthritis (RA) patients. Cytokine production, chemokine receptor expression for CXCR3 and CCR4, basal STAT5a phosphorylation levels and T cell receptor (TCR) Vβ repertoire were analysed by flow cytometry, and the methylation status of the Foxp3 locus (Treg-specific demethylated region, TSDR) by Realtime-PCR.
Results: Frequencies of $Foxp3^+$ $Helios^+$ Tregs, unlike $Foxp3^+$ $Helios^-$ T cells, were significantly increased in SLE patients and positively correlated with disease activity, whereas they were unaltered in SSc and RA patients. Compared to HC, $Foxp3^+$ $Helios^+$ Tregs in SLE predominantly displayed a $CD45RA^-/CD31^-/FoxP3^{low}$ memory phenotype with increased Ki-67 expression, enhanced basal pSTAT5a levels and a restricted TCR repertoire. Nonetheless, similar to HC, $Foxp3^+$ $Helios^+$ Tregs in SLE lacked effector cytokine production, possessed a highly demethylated TSDR and expressed comparable levels of CXCR3 and CCR4.
Conclusions: Our data suggest that Helios-expressing $Foxp3^+$ Tregs with functional suppressive capacity and migratory potential into inflamed tissues are expanded in active SLE, presumably through gamma-chain signalling cytokines and TCR stimulation, to compensate for autoreactive effector responses.

P027

Spontaneous Aggregation of the Anti-Viral Mavs Protein: A Mechanism for Excessive Type I Interferon Production in SLE Patients

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Background/Purpose: Patients with systemic lupus (SLE) have increased type I interferon levels (IFN-I) and activation of IFN-inducible genes (IFN signature). The interferon signature activation is

thought to be an important underlying process in the pathogenesis of autoreactivity, yet its mechanism is unknown. Type I interferon production is activated by a Toll like receptor signaling pathway, and also through the more recently described RIG-I pathway. The mitochondrial adaptor protein MAVS (also known as IPS1, VISA or CARDIF) is a key intermediary in the RIG-I pathway, where viral RNA triggers a conformational change in RIG-I, leading to MAVS activation and then downstream activation of IKK and TBK1, with subsequent IFN production driven by IRF-3/7 (IRF3 for IFN-beta; IRF7 for IFN-alpha) and NFkB activation and translocation. Using in vitro methods, it has recently been observed that MAVS may form large prion-like aggregates that might stimulate IFN-I activation in a potent and prolonged fashion (Hou et. al., Cell 146:448, 2011). Remarkably, aggregated MAVS triggered the further aggregation of monomeric MAVS in a prion-like fashion. We wondered if MAVS aggregates might be detectable ex vivo in cells from SLE patients, and whether the aggregates might play a role in the sustained increased production of IFN-I.
Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 30 patients fulfilling ACR criteria for SLE, and from 12 controls. Thirty million PBMCs were lysed and supernatants loaded onto semi-denaturing 1.5% vertical agarose gels. After electrophoresis, the proteins were transferred to membranes for immunoblotting with anti-MAVS antibody or anti-beta-actin. Plasma levels of interferons alpha and beta were measured by ELISA, and phosphorylated IRF-3 was detected by western blot.
Results: Eleven of 30 SLE patients showed clear MAVS aggregation, with essentially all of their MAVS protein in a high molecular weight aggregated form. None of 12 controls had abnormal MAVS. SLEDAI scores of MAVS-aggregate positive SLE patients did not differ from patients with normal molecular weight MAVS, but the MAVS-aggregate positive patients were more likely to have nephritis. Patients with aggregated MAVS had higher levels of circulating interferons and their PBMC showed IRF-3 phosphorylation.
Conclusion: This is the first report of aggregated MAVS in human cells. The significance of this abnormality in SLE needs further investigation, but it is possible that prolonged and increased IFN-I production could result from such MAVS aggregation, and that the poorly degradable prion-like MAVS protein aggregates could signal IFN-I production for prolonged periods. Prolonged and elevated IFN-I production could be responsible for the SLE IFN signature and might drive the autoreactivity in lupus.

P028

Deficiency of the TWEAK receptor Fn14 is protective in the MRL/lpr mouse model of lupus nephritis

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Background: Inhibition of various TNF superfamily (TNFSF) ligand-receptor interactions has significant therapeutic effects in lupus. Previously we showed that renal mesangial cells, podocytes, and tubular cells express Fn14, the receptor for TWEAK (TNFSF12), and that TWEAK engagement of Fn14 promotes pathological mechanisms relevant to lupus nephritis (LN), namely inflammation, renal cell proliferation and apoptosis, vascular activation and fibrosis. Therefore, we hypothesized that TWEAK/Fn14 interactions may be efficacious in spontaneous models of lupus.
Materials and methods: We directly assessed the role of the TWEAK/Fn14 pathway in the pathogenesis of LN by evaluating the effect of Fn14 deficiency in the MRL-lpr/lpr (MRL/lpr) murine lupus model.
Results: We found that both kidney Fn14 and TWEAK expression increased with age in MRL/lpr mice, while splenic Fn14 expression actually decreased over time. At 22 and 26 weeks of age female MRL/lpr Fn14 WT mice (n=18) had significantly higher levels of proteinuria as compared to MRL/lpr Fn14 KO mice (n=11). Kidney pathology was markedly attenuated in both glomerular and tubulointerstitial compartments in MRL/lpr Fn14KO mice, with significantly decreased endocapillary hypercellularity, mesangial proliferation, interstitial inflammation, and tubular disease. Immunohistochemical staining for KIM-1, a marker of tubular injury, was significantly decreased in MRL/lpr Fn14KO mice as well. The reduced severity of nephritis was not due to a decrease in circulating antibodies; there were no differences in serum autoantibody titers between MRL/lpr Fn14 WT and KO mice over time, suggesting that TWEAK likely acts by modulating events locally in the kidney.
Conclusions: TWEAK/Fn14 interactions are instrumental in the pathogenesis of LN in the MRL/lpr mouse model. Our results suggest that blocking the effects of TWEAK may be a novel therapeutic approach to the treatment of the kidney disease associated with SLE without inducing systemic immunosuppression.

P029

B Cell Stimulating Cytokines BAFF, IL-21 and IL-33 mRNA Expression Are Elevated Coordinately in Active RNP Autoantibody+ SLE

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We examined a cohort of 79 consecutive patients classified as anti-ribonuclear protein (anti-RNP)+ systemic lupus erythematosus (SLE). All patients provided RNA samples obtained after providing informed consent. There were 73 female and 6 male subjects. Disease duration ranged from 0 to 453 months with a median of 37.5 months. SLE Disease Activity Index (SLEDAI) ranged from 0 to 31 with a median of 6. The goal of this study was to characterize gene expression profiles in active and inactive RNP autoantibody+ SLE versus healthy blood donors.
Methods: Gene expression profiling was performed using Affymetrix microarrays on 79 patients and 30 healthy blood donors. mRNA from the 109 samples passed quality control and were analyzed using Affymetrix U133 Plus 2.0 expression arrays to determine gene expression, and data were compared after normalization using Robust Multichip Average algorithm. Statistical analyses were performed using two-sample t-test or univariate regression analysis.
Results: BAFF, IL-21, IL-33, and CXCL13 mRNA expression was significantly higher in patients versus healthy controls ($p < 2E-8$) while ICOS and CXCR5 were lower in patients ($p < 3.7E-18$). There were strong correlations between expression of these genes, especially in patients with more active disease as defined by SLEDAI of 6 or greater. BAFF, IL-21, IL-33, and CXCL13 were high in patients with active disease. In addition, several of these were coordinately regulated. We found correlation for BAFF vs ICOS ($p < 0.02$); BAFF vs CXCR5 ($p < 0.02$); IL-21 vs ICOS ($p < 0.0001$); IL-21 vs CXCR5 ($p < 0.0001$) and IL-33 vs ICOS ($p < 0.02$).
Conclusions: There was elevation of mRNA expression for the B cell stimulatory cytokines BAFF, IL-21 and IL-33 in active RNP+ SLE supporting the concept that these are potentially important therapeutic targets for treatment of SLE in the presence of autoantibodies. In addition, the observed differences in mRNA expression of factors influencing B cell migration and trafficking, ICOS and CXCL13-CXCR5, and the apparent coordinate change of these with other B

cell stimulator cytokines (BAFF, IL-21 and IL-33) in active SLE suggests that these may also be of importance in disease pathogenesis.

P030

The deficiency of natural killer T cells in systemic lupus erythematosus is related to disease activity

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Objective: This study was designed to examine the frequency of natural killer T (NKT) cells and the response to α-galactosylceramide (α-GalCer) in systemic lupus erythematosus (SLE) patients and to investigate the clinical relevance of NKT cell levels.
Methods: Patients with SLE (n = 120) and age- and sex-matched healthy controls (HCs) (n = 90) were enrolled in the study. NKT cell and CD1d levels were measured by flow cytometry. Gene expression was determined by reverse transcription-polymerase chain reaction, and cytokine secretion by multiple cytokine assay. Peripheral blood mononuclear cells (PBMCs) were cultured in vitro with α-GalCer. Proliferation indices of NKT cells were estimated by flow cytometry.
Results: Percentages and absolute numbers of NKT cells were significantly lower in the peripheral blood of SLE patients than in that of HCs, whereas CD1d levels in PBMCs were comparable between these two groups. Notably, this NKT cell deficiency was found to be correlated with SLE Disease Activity Index. NKT cell proliferation was found to be impaired in SLE patients, and cytokine production by NKT cells in response to α-GalCer was diminished. This poor responsiveness to α-GalCer was found to be due to a NKT cell dysfunction rather than to an abnormality in CD1d-expressing cells.
Conclusions: Our data show that NKT cell levels and functions are defective in SLE patients. Furthermore, these deficiencies were found to reflect disease activity. It would appear that these NKT cell abnormalities could contribute to immune system dysregulation in SLE.

P031

Increased proportion of naturally occurring CD4+ Foxp3+ regulatory T cells in circulation of patients with systemic lupus erythematosus

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Introduction: Foxp3 is a typical transcription factor that is specifically expressed by $CD4^+$ regulatory T cells (Tregs), and plays a critical role in immunosuppressive function of Tregs. Recently, several studies have shown plasticity and heterogeneity within $CD4^+Foxp3^+$ cells, which include naturally occurring Tregs (nTregs), adaptive Tregs, and a subpopulation of activated effecter T cells. It has been described that the number and function of $Foxp3^+$ Tregs are altered in patients with systemic lupus erythematosus (SLE), although data reported are somewhat conflicting. In this study, we examined roles of $CD4^+Foxp3^+$ cells in pathophysiology of SLE by focusing on the heterogeneity of $CD4^+Foxp3^+$ cells.
Methods: We enrolled 47 patients with SLE who fulfilled the American Rheumatism Association revised criteria and 19 healthy subjects. Frequencies of $Foxp3^+$ cells in $CD4^+$ cells were determined by flow cytometry. Clinical characteristics were retrospectively collected by review of clinical chart records. $CD4^+$ or $CD4^+Foxp3^+$ cells were isolated from peripheral blood mononuclear cells using magnetic bead-based cell sorting or fluorescent-activated cell sorting, respectively, and were subjected to genomic DNA extraction. The proportions of cells with Treg specific demethylated region (TSDR) of the *FOXP3* gene, which is specifically demethylated in nTregs, were quantified using TSDR-specific quantitative polymerase-chain reaction systems.
Results: Frequencies of $Foxp3^+$ cells in $CD4^+$ cells were significantly increased in SLE patients, compared to those in healthy subjects (mean ± standard deviation: 15.4 ± 7.3% versus 8.9 ± 2.3%, $P < 0.01$). Frequencies of $CD4^+Foxp3^+$ cells were correlated positively with anti-double-strand DNA antibody titer ($r = 0.52$, $P < 0.01$) and SLE disease activity index (SLEDAI) ($r = 0.57$, $P < 0.01$), and negatively with CH50 ($r = -0.52$, $P < 0.01$). Serial analysis revealed that $CD4^+Foxp3^+$ cell frequencies were decreased after improvement of SLEDAI by immunosuppressive treatment. In addition, proportions of cells with demethylated TSDR in $CD4^+$ cells were also increased in SLE patients, compared to those in healthy subjects (11.5 ± 6.7% versus 4.5 ± 3.5%, $P < 0.01$), and were correlated with frequencies of $CD4^+Foxp3^+$ cells ($r = 0.52$, $P < 0.01$). Interestingly, TSDR in $CD4^+Foxp3^+$ cells was completely demethylated in SLE patients as well as in healthy subjects.
Conclusions: In SLE patients, circulating nTregs were increased and involved in pathophysiology of SLE.

P032

The blood brain barrier is breached in murine neuropsychiatric Systemic Lupus Erythematosus (SLE)

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Background: Neuropsychiatric involvement is one of the earliest manifestations of human SLE, and a major cause of morbidity and mortality in this disease. While the pathways underlying neuropsychiatric SLE (NPSLE) are not fully understood, blood brain barrier disruption and altered brain perfusion have been postulated to contribute to the pathogenesis. The purpose of this study was to non-invasively evaluate blood brain barrier (BBB) integrity, macromolecule content, and other indicators of neurological damage in MRL-lpr/lpr mice which spontaneously develop NPSLE, compared to the background control strain MRL/+.
Materials and methods: Female MRL-lpr/lpr (MRL/lpr) and MRL/+ mice were imaged by magnetic resonance imaging (MRI) at 9-10 weeks of age, at which time major neuropsychiatric symptoms including depression and cognitive dysfunction were already manifest.
Results: Dynamic contrast enhancement MRI indicated increased gadolinium uptake in MRL/lpr mice in all regions of the brain, with the largest differences visualized in the hypothalamus where these changes were significant. Furthermore, MRL/lpr mice displayed significantly higher concentrations of albumin, total immunoglobulin, and antibodies to double stranded DNA in their cerebrospinal fluid. In contrast, whole brain analysis of magnetic transfer contrast and quantitative T2 imaging indicated no significant differences between the MRL-lpr/lpr and MRL/+ mice.
Conclusions: By non-invasive brain imaging, we determined that lupus prone MRL/lpr mice display abnormal blood brain barrier permeability at the time they exhibit neuropsychiatric manifestations. Thus, a compromised blood brain barrier (particularly in specific regions) in lupus prone MRL/lpr mice may allow for the passage of circulating autoantibodies and/or other inflammatory mediators such as cytokines from the systemic circulation into the brain, and induction of some of the neuropsychiatric abnormalities observed in this mouse strain. Preventing the regional breakdown in barrier integrity may be a novel approach to the treatment of neuropsychiatric involvement in SLE.

P033

Over-expression of CXCR4 on B cells in peripheral blood may play a pathogenic role in SLE

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Introduction: It is increasingly appreciated that circulating B cells are functionally altered and are involved in pathogenic process in patients with systemic lupus erythematosus (SLE). We previously reported that anti-dsDNA antibody-secreting B cells and plasma cells were recruited into circulation in active disease phase in SLE patients. In this study, we further evaluated mechanisms contributing to emergence of antibody-secreting cells into circulation by focusing on roles of chemokines.
Patients and Methods: We studied peripheral blood samples from 13 patients with SLE and 7 healthy donors. We recorded the disease activity index (SLEDAI) at blood sampling by a retrospective chart review. According to the previous report, active disease was defined as SLEDAI $\geq$ 5. Peripheral blood mononuclear cells (PBMCs) were obtained by density gradient centrifugation and analyzed by flow cytometry for expression or mean fluorescence intensity of CXCR4, CXCR5 and CCR7 on CD19+ B cells. The concentration of serum CXCL12, which is a ligand for CXCR4, was measured by ELISA. Chemotaxis assay was conducted to test the chemotactic responsiveness of B cells toward the CXCL12. CD19+ B cells were enriched from PBMCs by magnetic activated cell sorting (MACS) system. B cells were added to the upper chamber of transwell inserts and the lower transwell was filled with CXCL12 solution containing 0 or 384 ng/ml. After incubation for 1.5 hours (at 37°, 5% CO2), the number of moved to the lower chamber were counted, and migration rates were calculated in comparison with the number of cells originally applied to the upper chamber.
Results: Seven active and 6 inactive patients with SLE were enrolled. Flow cytometric analysis revealed that expression of CXCR4 was higher in patients with SLE than normal healthy controls ($p = 0.03$). In patients with SLE, the expression of CXCR4 was higher in those with active disease than in those with inactive ($p < 0.05$). The expression levels of CXCR5 and CCR7 were not different between patients with SLE and normal healthy controls. Serial analysis in 2 patients with active disease showed that expression of CXCR4 on CD19+ B cells decreased after improvement of SLEDAI by immunosuppressive treatment. In contrast, there was no difference in circulating concentration of CXCL12 between patients with active and inactive disease (2413 vs 2471 pg/ml, $p = 0.8$). Migration ability of B cells toward CXCL12 was enhanced in SLE patients compared with normal healthy controls (33.9 vs 19.4 %, $p < 0.05$). Moreover, SLE patients with active disease represented more prominent chemotaxis towards CXCL12 than did those with inactive disease (52.9 vs 27.6 %, $p < 0.05$).
Conclusions: In SLE patients with active disease, up-regulated expression of CXCR4 on circulating B cells contributes to enhanced chemotaxitic responsiveness towards CXCL12.

P034

Increased PD-1 expression in CD4+ regulatory T cells in patients with systemic lupus erythematosus.

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Background: Programmed death-1 (PD-1) has been regarded as a negative regulatory signal in T cells. Previously, we have demonstrated in the NZB/NZWF1 mouse model of lupus that reduced expression of PD-1 is necessary for full suppressive function of CD4+CD25+Foxp3+ regulatory T cells (Treg). In fact, inhibiting high expression of PD-1 in the mice delayed onset of nephritis and improved survival. In particular, Fas was one of the candidate molecules in the apoptotic pathways that was downregulated in splenic CD4+Treg upon blockade of PD-1. Hence, we believe that PD-1 plays an important role in T cell regulation in autoimmunity.
Objectives: We hypothesized that patients with systemic lupus erythematosus (SLE) have increased PD-1 expression compared to healthy individuals, which may contribute to the compromised CD4+Treg function in these patients via Fas-induced apoptosis.
Methods: Thirty-five female SLE patients and fifteen healthy female controls have been enrolled to date. Medical chart review was done to assess SLE disease activity index (Selena SLEDAI) score. PD-1, PD-L1, Fas and FasL expression, and cell cycle arrest on CD4+Treg (defined as CD4+CD25hiFoxp3+) from the PBMC collected on the same day of the chart note was analyzed by flow cytometry, as were samples from healthy donors. Statistical analysis was performed to assess the relationship between PD-1 expression and SLEDAI.
Results: SLE patients had fewer CD4+CD25hiFoxp3+ Treg in their PBMC compared to healthy controls ($p < 0.03$). These cells had significantly increased PD-1 and PD-L1 expression ($p < 0.02$). There was a trend that patients with SLEDAI $\geq$4 had more CD4+Treg with PD-1 expression than patients with SLEDAI <4 ($p < 0.07$). These CD4+Treg had increased Fas expression, and were prone to spontaneous apoptosis at the G1 phase when compared to controls. A bigger sample size is being acquired to assess the correlation of PD-1 expression with disease duration, use of medications, and specific clinical manifestations.
Conclusions: These preliminary data suggest that SLE patients have aberrant, increased PD-1 expression on their circulating CD4+Treg that may reduce the regulatory function of CD4+CD25hiFoxp3+ T cells, which are important in the suppression of autoimmunity. One mechanism by which PD-1 sustains these Treg is by reducing their susceptibility to apoptosis via the Fas/FasL expression. We will continue this prospective study to determine the role of PD-1 in regulating peripheral T cell tolerance in SLE patients.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 3 Autoantibodies & Biormarkers"

Atlantico A+B+C

P035

HUMAN MODEL FOR AUTOANTIBODY GENERATION: The development of anti-IMPDH2 autoantibodies that exhibit "Rods and Rings" immunofluorescence pattern during treatment of HCV

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Background: Certain viruses and drugs are known to break immunological tolerance and induce autoantibody production. In the last few years, a unique immunofluorescence (IIF) staining pattern called Rods and Rings (RR) using HEp-2 cell slide has been shown in HCV patients under IFN-α+ribavirin treatment. One of the targets of anti-RR was identified as IMPDH2, a target enzyme of ribavirin.

In this work, we examined Isotype serum levels and protein targets of anti-RR antibodies in HCV patients in a longitudinal view along treatment.

Methods: 80 samples from 15 HCV patients collected before, during, and after treatment with IFN-α+ribavirin were tested by IIF (HEp-2 cells), immunoprecipitation (IP) against soluble radiolabeled K562 cells extract, anti-IMPDH2 capture ELISA using rabbit anti-IMPDH2 antibodies, and anti-HCV antibody ELISA. IIF-HEp-2 with specific IgG, IgA and IgM secondary antibodies was used to Isotype levels determination. Clinical information of patients was obtained from a structured data bank.

Results: In IIF-HEp-2 analysis, all 15 patients showed anti-RR reactivity at various periods after initiation of treatment. IP showed reactivity to a 55kDa protein compatible with IMPDH2 in 12/15 patients (80%). The 55kDa band was positive only in samples that showed RR reactivity by IIF-HEp-2 test. The intensity of the precipitated 55kDa band peaked in samples at the 6th, 9th and 12th months after treatment beginning ($p < 0.0001$) and decreased in 3-6 month post-treatment samples ($p=0.0198$), similarly to peaks in IIF-HEp-2 titers of anti-RR reactivity. 70% of anti-RR positive samples were above cut-off in anti-IMPDH2 ELISA and 11 patients (73%) became positive in anti-IMPDH2 ELISA during treatment. Levels of anti-IMPDH2 peaked at the 12th month of treatment ($p < 0.005$) and decreased in post-treatment samples. Anti-RR antibodies are mostly IgG and IgM. IgG and IgM isotype titers increase similarly until 6 month of treatment ($p=0.793$). While IgM anti-RR keep the titer, IgG levels increase with a highest pick in 12 month of treat ($p=0.023$). Both decreased in 3-6 month post-treatment samples. While anti-IMPDH2 autoantibodies appeared after ≈3 to 6 month of IFN-α+ribavirin treatment, and disappeared after finishing treatment in ≈50% of the patients, anti-HCV antibodies did not show noticeable variation before, during and after treatment.

Conclusion: Autoantibodies that elicit RR IIF-HEp-2 pattern recognized predominantly the IMPDH2 enzyme, involved in de novo biosynthesis of guanine nucleotides. The anti-RR and anti-IMPDH2 autoantibodies were induced at ≈3 to 6 months of IFN-α+ribavirin treatment in HCV patients and decreased/disappeared after treatment conclusion, which contrasts with the stable production of antibodies anti-HCV to over time. Autoimmune response of anti-RR Isotype levels and peaks show similar behavior to a "late immune response to infection", but with slow progression (≈1 year in anti-RR autoimmune response versus ≈2 month in "late immune response to infection").

P036

Association of Urinary and Serum Soluble Fn14 levels and TWEAK Levels with Lupus Nephritis Disease Activity

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Background: We have shown that the cytokine TWEAK is a biomarker for lupus nephritis (LN). Soluble receptors for key immune pathways are also potential biomarkers of disease, including SLE. We hypothesize that a soluble form of TWEAK receptor, Fn14, is present in human serum or urine and could be a biomarker for LN.

Methods: Serum and urine from 67 patients from the Einstein Lupus Cohort were included in this study. 34 had active LN (renal SLEDAI≥4) and 33 had inactive, non-LN SLE (general SLEDAI≤2). Healthy normals (n=39), age and race matched, were also evaluated. ELISAs were performed on serum and urine samples to determine soluble Fn14 and TWEAK levels.

Results: Of the 106 patients, 47% were Black, 47% were Hispanic and 6% were of another race/ethnicity. 79% were female with a median age of 43y. Median SLE disease duration was 6y. As expected LN patients had higher median protein to creatinine ratios as compared to both inactive SLE patients and normals (1.22 v 0.11 v 0.09, $p < 0.001$). Although the normal group had a higher median GFRs overall, all groups had normal median values (90 v 89 v 115, $p=0.02$)

Serum Fn14 (sFn14) levels were significantly higher in LN compared to normals ($p=0.002$) and trended toward significance when comparing LN to the inactive SLE group ($p=0.06$). Median urine Fn14 levels tended to be higher in the LN group as compared the inactive SLE ($p=0.06$) and normals ($p=0.05$) but did not achieve significance with normalization to urine creatinine ($p=0.06$ and 0.12 for comparison to inactive SLE and normal, respectively). There was no significant difference between the groups with regard to serum TWEAK. As previously shown, median urinary TWEAK levels were significantly elevated in the LN group compared to controls when normalized to urine creatinine concentration (LN v inactive SLE ($p=0.002$) and LN v normal ($p=0.002$).

We performed an ROC analysis to determine the capability of sFn14 to distinguish between LN and inactive SLE as well as LN and normals. The AUC for sFn14 by itself was fair (LN v inactive SLE, AUC: 0.63; LN v normals, AUC: 0.70) while that of normalized uTWEAK was good (LN v inactive SLE, AUC: 0.77; LN v normals, AUC: 0.72). However, when the AUC for sFn14 and uTWEAK were combined the AUC was increased (LN v inactive SLE, AUC: 0.80; LN v normals, AUC: 0.76).

Conclusions: sFn14 levels are significantly elevated in patients with LN. This novel finding contributes to our previous observations that urinary TWEAK is elevated in this patient population. Adding sFN14 levels to urinary TWEAK levels as a combined biomarker has a higher capacity than each alone to distinguish between LN and inactive SLE as well as LN and normals. sFn14 is a promising novel biomarker in LN, further underscoring the TWEAK/Fn14 pathway as a potential therapeutic target.

P037

Deep-Sequencing Reveals WHO Class-Specific Urinary microRNAs in Human Lupus Nephritis

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Lupus nephritis (LN), particularly, WHO class IV LN, is associated with significant morbidity and mortality. microRNAs (miRs) are small, non-coding RNAs that regulate translation. Previous studies report changes in miR expression in kidney tissue, urine and PBMCs that correlate with LN disease activity. However, LN WHO class-specific miRs have not been previously described.

Using deep-sequencing, we aimed to identify WHO class-specific miRs in urine from adult and pediatric patients with biopsy-proven LN.

Cell-free urine from adult (n=25) and pediatric (n=8) female patients with WHO class IV and class V LN were obtained at time of active disease and during remission. Total RNA was used to prepare small RNA cDNA libraries for sequencing. Multiplexing through

sample-specific 3' adapters was applied to limit batch effects and cost. Sequence reads were mapped to the human genome and small RNA databases. miRs were quantified by relative read abundance. qRT-PCR was used for quantitative validation.

We obtained reproducible profiles of miRs from cell-free urine. In a paired-sample analysis comparing miR abundance in urine of adult and pediatric patients with active class IV versus class V LN, we found significant changes in 6 miRs, including up-regulation of miR-193a-5p, -423, 501-3p, and -874 by 400-1,000-fold in WHO class IV LN.

In conclusion, we detected miRs with significantly higher presence in the urine of adult and pediatric patients with LN class IV, versus class V. Given that the prognosis of class IV LN is significantly worse than that of class V, identifying miRs that are associated with class IV LN is an important step in biomarker discovery of this particulary aggressive disease. Identification of target genes of these miRs may open a venue for the discovery of new pathogenic pathways in this devastating disease.

P038

Role of a neuronal surface antigen recognized by anti-ribosomal p autoantibodies (NSPA)

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Background: Autoantibodies against neuronal cell surface components can eventually provoke dysfunctions of the central nervous system (CNS). Systemic lupus erythematosus (SLE), the prototypic autoimmune disease, provides particularly interesting and challenging examples of neuropathogenic autoantibodies. Here we studied anti-ribosomal P protein autoantibodies (anti-P) largely associated with psychosis and depression in SLE patients. These antibodies cross-react with a novel protein of unknown function called NSPA (Neuronal Surface P Antigen) expressed by neurons involved in cognition, memory and emotion (Matus et al. J Exp Med, 2007). To approach the normal and pathogenic role of NSPA we analyzed the synaptic function and memory function, as well as the effect of anti-P antibodies in NSPA knock-in mice.
Methods: NSPA-null/LacZ knock-in mice in which beta-galactosidase enzyme is under the promoter of NSPA was used to assess: (i) the expression pattern of NSPA in the brain; (ii) the effects of anti-P antibodies on intracellular calcium levels in hippocampal neurons in primary culture; (iii) electrophysiological assays for field excitatory postsynaptic potential in the absence or presence of anti-P antibodies, and long term potentiation, in ex vivo hippocampus slices; (iv) memory function using the Morris water maze assay
Results: Anti-P autoantibodies enhanced cytosolic calcium levels in hippocampal neurons in primary culture leading to apoptosis and increased neurotransmission in hippocampus slices, but only in wild type mice, not in preparations from NSPA-null mice. In addition, NSPA-null mice displayed defects in long-term potentiation and memory tests, seemingly involving NMDAR.
Conclusions: NSPA is a novel neuronal surface protein involved in memory and mediates deleterious effects of anti-P antibodies, which can vary depending on the brain area where neurons express NSPA
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P039

Role of membrane-associated estrogen receptor alpha in systemic lupus erithematosus pathogenesis.

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Introduction: Autoimmune diseases are a prototypical class of illness that displays high female-to-male (F/M) ratio. Although the reason of the gender bias in autoimmune disease is still a matter of research, there is evidence for the influence of estrogens. In fact, estrogen has a profound influence on immunity and autoimmunity. Their activity is mediated by intracellular and membrane-associated estrogen receptors (ER), expressed on most immune cells, which impact distinct signaling pathways. Estrogens seem to contribute to the pathogenesis of Systemic Lupus Erythematosus (SLE) although their role and mechanism of action in this disease are not yet fully understood.

Aim of the study has been to evaluate the expression levels of ER subtypes (ERα and ERβ in T lymphocytes from SLE patients and healthy subjects and their correlation with serum estrogen, anti-ER autoantibodies and clinical features of SLE.
Patients and Methods: 41 patients (40F, 1M) with a diagnosis of SLE according to 1997 ACR criteria and 41 sex and age matched healthy subjects have been enrolled. Pregnant and post-menopausal women, and patients taking estroprogestinic have been excluded. Demographic, clinical and serological data and SLE disease activity (SLEDAI) have been recorded for each patient. Total T lymphocytes, CD4 and CD8 subpopulation have been isolates from peripheral blood mononuclear cells. Membrane and intracytoplasmic ERα expression have been evaluated by flow cytometry. Anti- ERα autoantibodies and serum estrogen (17-beta estradiol) have been tested by ELISA.
Results: In T lymphocytes from SLE patients, we observed a significant higher expression of mERα than in those from healthy donors ($p = 0.001$). In particular, increased expression of mERα was observed in CD4+ but not in CD8+ T cells. Metabolic stress, commonly observed in SLE, seems to be responsible for this increased expression that amplifies the estrogen effect on immune system. No significant difference between patients and healthy controls was observed for intracellular ER expression. Anti-ERα autoantibodies were present in 45% of patients with SLE whereas anti ERβ Abs were undetectable. Membrane-associated ERα expression in T cells was not correlated with the level of serum estrogens and serum anti-ERα Abs. A significant association between anti-ERα autoantibodies values and SLEDAI was found ($p = 0.005$).
Conclusion: Information generated by our study addressed clinical relevant issues, such as the possible value as prognostic markers of estrogen-related parameters and the therapeutic potential of targeting estrogen and its receptors to identify more specific, effective, and less toxic therapeutic treatments.

P040

Early Phosphoprotein Changes Induced with Epratuzumab, an Antibody Targeting CD22 on B Cells

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Background: Epratuzumab is a monoclonal antibody targeting CD22 currently in phase III clinical trials in SLE patients. CD22 is found almost exclusively on B cells and in vitro culture with epratuzumab downregulates B-cell receptor (BCR)-dependent cell signaling and B-cell activation events. This study aimed to construct a B-cell phosphopeptide library using LC-MS/MS methodology (TIQUASTM or Targeted Quantification of Cell Signalling), and to investigate epratuzumab-dependent changes in phosphoprotein signals in activated B cells.
Methods: B cells >90% purity were isolated from human donors undergoing routine tonsillectomy (n=8) by mechanical homogenisation followed by Ficoll-Hypaque gradient centrifugations and T cell depletion by E-rosetting using 2-aminoethylisothiouronium bromide (AET)-treated sheep red blood cells. B cells were stimulated through the BCR using anti-IgM for 2 minutes after pre-incubation with either epratuzumab or an IgG1 isotype control for 1 hour. Immediately following stimulation the cells were pelleted by centrifugation and lysed in a urea based lysis buffer containing phosphatase inhibitors. The cell lysates were sonicated on ice and quantitated by BCA protein assay. Cell lysates were analysed by Western blot for confirmatory B cell activation markers, ERK1/2. 500μg of cell extracts were subject to protease digestion and TiO2 phosphopeptide enrichment. LC-MS/MS phosphoproteomic analysis was performed using a label-free quantification strategy (TIQUASTM). A linear mixed effects statistical model was applied to a library of 3825 distinct quantifiable phosphorylation sites. Significantly regulated phosphorylated sites were imported into MetaCore and mapped to canonical pathways for further analysis.
Results: This study explored the pathways differentially modulated by epratuzumab of which the BCR pathway was the most highly regulated. This analysis was able to identify statistically significantly regulated phosphorylation sites in response to pre-incubation with epratuzumab using adjusted p-value threshold of <0.05, although the most significant changes generally showed no more than a 2-fold difference from signals induced by BCR stimulation alone. Many of the phosphorylation changes modulated by epratuzumab are novel and warrant further study; of potential interest is the observed increase in ERK. Among the other changes observed were BCR-specific downstream signals on a broad range of protein family types: adaptor proteins (SHC-1), kinases (ERK1/2,), phosphatases (SHP-1, SHIP-1), histones (H1) and transcription factors (NFAT). Additionally, there was down-modulation of the phosphorylation of S717 on CD22 itself.
Conclusion: Pre-incubation of human tonsil-derived B cells with epratuzumab induced discrete but statistically significant changes in phosphoprotein signals after BCR activation. Such observations may enable a better understanding of how epratuzumab modulates B-cell functions in vitro and possibly in patients with SLE.
Role of the Study Sponsor: This study was funded and supported by UCB.

Table. Key phosphorylation changes identified for components of the B cell signalling pathway

Protein/class	*Fold change (log2)*	*p-value*	*P-site/implications*
CD22/receptor	−0.242	1.0×10^{-4}	S717/novel site unknown role
SHIP-1/phosphatase	−0.216	1.9×10^{-2}	S243/unknown role
SHIP-1/phosphatase	0.206	$< 1.0 \times 10^{-4}$	T1108/potential MAPK p-site
SHIP-1/phosphatase	0.219	1.0×10^{-2}	Y865/unknown role
SHIP-1/phosphatase	0.226	8.0×10^{-4}	S10/unknown role
SHIP-1/phosphatase	0.209	2.6×10^{-2}	S557/unknown role
SHC1 /adaptor	0.378	7.8×10^{-3}	Y427/GRB2 binding site
SHC1 /adaptor	0.229	2.4×10^{-2}	S139/unknown role
SHC1 /adaptor	0.428	1.4×10^{-3}	S426/unknown role
PTN7/MAPK phosphatase	−0.253	2.0×10^{-3}	S44/interaction, regulation
BLNK/adaptor	0.147	1.8×10^{-2}	S129/unknown role
PPP3CB/ phosphatase	0.101	2.9×10^{-3}	S471/potential AKT p-site
PRKCD/kinase	−0.179	1.6×10^{-2}	S645/autophosphorylation site
PRKCD/kinase	0.297	$< 1.0 \times 10^{-4}$	S304/autophosphorylation site
MAPK1/ERK2 kinase	0.414	$< 1.0 \times 10^{-4}$	Y187/activation site, regulation
MAPK3/ERK1 kinase	0.315	$< 1.0 \times 10^{-4}$	T207/autophosphorylation site
GSK3A/kinase	0.177	9.0×10^{-3}	S21/enzyme activity inhibition
IPMK/kinase	0.182	1.1×10^{-4}	S7/unknown role

P041

Anti-ribosomal p protein antibodies from neuropsychiatric lupus impair hippocampal function in vitro and in vivo

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Introduction: Systemic lupus erythematous (SLE) is the prototypic autoimmune disease characterized by the production of a variety of autoantibodies and multi-systemic compromise. Among the most devastating manifestations of the disease are neuropsychiatric symptoms. Manifestations of diffuse brain compromise such as psychosis has been associated with anti-ribosomal P protein autoantibodies. We have identified a novel target of anti-P antibodies, which we called neuronal surface P antigen (NSPA) that is expressed by neurons of specific regions in the brain, including areas involved in cognition, memory and emotion (Matus et al. J. Exp. Med. 204:3221-3234, 2007). The high levels of expression of NSPA in hippocampal neurons prompt us to study the effect of anti-P and anti-NSPA antibodies in hippocampal neurons in primary culture and in recent memory in mice.
Methods: Human and rabbit anti-P and rabbit anti-NSPA antibodies that recognize a different epitope were affinity purified and tested upon: (i) intracellular calcium levels (Fura2) and apoptosis (caspase-3 activation) in hippocampal neurons in primary culture; (ii) memory flexibility in mice, applying a modified version of the classic Morris water maze protocol and using LPS injection to open the blood brain barrier (BBB). This assay was performed 24 h after i.v. injection of anti-P or anti-NSPA antibodies.
Results: Anti-P and anti-NSPA antibodies induced calcium influx and apoptosis in hippocampal neurons in primary culture. Both antibodies impaired flexible memory, reflected in the increased trials-to-criteria, only when the BBB was open by LPS, while vision and locomotor activity were not affected.
Conclusions: These results provide definitive evidence for a pathogenic potential of circulating anti-P autoantibodies upon diffuse brain dysfunctions, demonstrating for the first time properties for hippocampal interference. Autoimmunity against NSPA can contribute to cognitive

dysfunction in patients with SLE, while the requirement of BBB disruption might eventually explain either lack of or variable neuropsychiatric outcomes depending on regional permeation. Anti-P and anti-NSPA antibodies have neuropatogenic potential when present in peripheral blood, as both can provoke CNS neuron dysfunction, likely inducing cytotoxic calcium influx, when the BBB is open. Furthermore, these results suggest that anti-P antibodies might contribute to the frequent cognitive dysfunctions displayed by SLE patients.

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P042

Renal resistive index as marker of severity in patients with lupus nephritis: a monocentric cross-sectional study

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Background: Resistive Index (RI) is a simple parameter used to calculate the resistance of the artery walls calculated in color-Doppler ultrasonography (US). Recent studies suggested the association between the renal artery RI and the presence of tubule-interstitial and vascular lesions. Few data are available concerning modifications of RI in SLE nephritis. Aim of the present study was to analyze the association between intrarenal arterial RI, evaluated with color-Doppler US, and histological features of SLE nephritis.
Patients and Methods: Patients affected by SLE, according with 1987 ACR criteria, candidate to kidney biopsy were enrolled. The functional renal assessment was performed (serum creatinine, blood urea nitrogen [BUN] levels, urinary protein excretion in 24 hours, estimated glomerular filtration rate [eGFR]). Kidney biopsy was performed and the class of nephritis was assessed according to the WHO classification. The evaluation of intrarenal arterial RI was performed on the same day of biopsy. RI > 0.7 was considered above normal. As control group, we enrolled 10 SLE patients without signs of renal involvement.
Results: Fourty-two were enrolled (M:F 1:41, mean age 34.2±10.6 years; mean disease duration 122.4±85.8 months; mean creatinine levels 1.4±1.2 mg/dl; BUN 41.4±39.9 mg/dl; urinary protein extraction 2.1±2 gr/24h; eGFR 78.4±42.3 mL/min). Seven patients (16.6%) had class II nephritis, 13 (30.9%) class III, 18 (42.8%) class IV, and 4 (9.5%) class V. Mean RI was 0.64±0.08, five (11.9%) patients had RI > 0.7.

Patients with RI > 0.7 showed significant higher mean values of serum creatinine and BUN and significant lower mean values of eGFR. A higher prevalence of patients with RI > 0.7 in class IV nephritis (4/5, 80%), compared with class II, III and V nephritis ($P < 0.0001$, $P=0.009$ and $P < 0.0001$, respectively) was observed. Indeed, patients with class IV nephritis showed a trend to higher mean RI levels (0.65±0.1) than other classes (class II: 0.62±0.005; class III 0.62±0.07; class V 0.61±0.02, P=NS). When considering the specific histopathologic features of the biopsies, RI > 0.7 was more frequent in the presence of global sclerosis (15.4% vs 6.2%, P=NS), interstitial fibrosis (14.3% vs 7.1%, P=NS), tubular atrophy (13.3% vs 8.3%, P=NS). As expected, the RI showed a significant correlation with mean age (P=0.01, R=0.37), creatinine levels (P=0.01; R=0.37), BUN levels (P=0.04; r=0.32) and eGFR (P=0.007; r=0.42).

In the control group (10 patients, M/F 1/9; mean age 30.2±6.9 years; mean disease duration 7.2±5.8 years) no patients showed modifications of RI.

Conclusions: These results suggested the possibility to consider RI as a marker of severity in lupus nephritis. Larger longitudinal study are needed to confirm these results.

P043

Study of the association of autoimmune markers of thyroid disease in lupus patients with MHC class II system and the C1858T polymorphism (rs2476601) of PTPN22 genetic system

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Introduction: Systemic lupus erythematosus (SLE) is a chronic inflammatory, multisystem unknown etiology and autoimmune in nature, characterized by the presence of autoantibodies. In autoimmune thyroid disease (ETA) there are two major diseases, Graves' disease and Hashimoto's thyroiditis. Both characterized by the infiltration of lymphocytes and the production of autoantibodies against thyroid antigens specific determinants of the clinical expression. Advances in genetic methods in the past 15 years allowed significant progress in the identification of genes of complex diseases such as SLE and ETA. Thus genetic systems MHC class II and PTPN22 (C1858T), are linked to the development and/or protection of SLE and ETA. For this reason and considering that the host gene interaction is load dependent gene especially in multi-ethnic groups like the Colombian Caribbean population and the population of Cundinamarca, immunogenetic study was performed in patients suffering from SLE with autoimmune markers thyroid disease.
Material and methods: In this descriptive study, a case-control component, a nested cohort of 300 patients suffering from SLE, linked to the research institution Genetics of lupus, was performed to determine the anti-thyroglobulin and anti- thyroid peroxidase antibodies. After this, we selected two groups, one of 58 seropositive to thyroid autoantibodies (SLE/Auto-Ac), and 116 randomly selected seronegative subjects. To each study subjects underwent typing of HLA-DRB1 and HLA-DQB and SNP genotyping of PTPN22 rs2476601.
Results: The 88.6% of patients were female and 11.7% were male. Being 19.3% seropositive and 80.7% seronegative the autoantibodies. It was found that the system in MHC class II HLA-DRB1 * 0701, HLA-DQB * 0202, HLA-DQB* 0603 behave as predisposing factors to the development of SLE/Auto-Ab. Moreover HLA-DRB1 * 1503, HLA-DQB * 0309, HLA-DQB * 0602 acts as a protective factor. Similarly it was found that the haplotypes HLA-DRB1 * 0701/HLA-DQB*0202 and HLA-DRB1* 1503 */ HLA-DQB* 0602 behaves as predisposing factors and protective, respectively. Also in the PTPN22 system, the presence of allele A is associated as a predisposing factor. Similarly GG and AG genotypes in the population behave as protective factors and predisposing, respectively.
Conclusions: In this study, is met as described in the literature regarding the relationship between gender and disease, like autoantibodies in the study group, as evidenced by the group Kundan Kumar et al, in a review of 2012. In reviewing the literature, in two different studies of autoimmune thyroiditis cases and healthy controls, made in the UK Caucasian population, the researchers found that HLA-DRB1 * 03/04/08 and HLA -DQB*04/03, behave as predisposing factors, with HLA-DRB1 * 07/ 13 as protective factors. Moreover, in a study of Korean children in 2011, found that the most common allele is HLA-DRB1 * 08. Making a big difference with our study. In a meta-analysis of PTPN22 polymorphism C1858T, in four Asian population studies and seven studies with Caucasians, found a significantly increased risk for development of autoimmune thyroid disease in all populations. Like as demonstrated in our study.

P044

The effect of acute physical exercise on cytokines levels in patients with systemic lupus erythematosus.

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Introduction: Acute physical exercise increases IL-6, IL-10 and TNF-α serum levels in healthy subjects. Some studies showed acute exercise can worse inflammatory response in patients with type I Diabetes Mellitus, cystic fibrosis and obstructive pulmonary disease. Studies also showed resting SLE patients have higher levels of IL-6 and IL-10 compared to healthy controls. Although being established in the literature that SLE patients have benefits with the aerobic training, mainly related to cardiovascular risk factors, no study evaluated the effect of acute exercise on cytokines levels in SLE patients, mainly those that could cause some concern about the risk of worsening inflammatory cytokines.
Objective: To assess serum levels of IL-6, IL-10 and TNF-α at baseline and after acute exercise in SLE patients.
Methods: Twenty-seven female SLE patients (≥ 4 ACR classification criteria) followed at University Hospital with inactive or mild active disease, and 30 age-matched healthy women were evaluated. At baseline and soon after the ergospirometric test, 10 ml of peripheral blood were collected for IL-10, IL-6 and TNF-α measurement by ELISA technique (R&D Systems, Inc. Minneapolis, USA). Disease activity was evaluated by SLEDAI. Student's t-tests and Mann-Whitney test were used for intra and inter-group comparisons. P values < 0.05 were considered significant. All participants signed the consent form approved by the University Ethic Committee.
Results: The table 1 shows the demographic characteristic, ergospirometric variables and cytokine levels of SLE and control groups at baseline. The mean disease duration was 05.5±85.5 months and the mean SLEDAI score was 1.96±2.32. Regarding espirometric variables SLE patients presented worst parameters and concerging to interkeukin levels, patients presented higher levels of IL6 and IL10 when compared to controls. Acute exercise did not significantly alter the levels of IL-6, IL-10 and TNF-αin SLE patients. On the other hand, in the control group, acute exercise increased IL-6 level [1.71±0.29 vs 2.01±0.27 pg/ml, p=0.003] without significant change on IL-10 and TNF-α levels.
Conclusion: SLE patients presented worst physical performance. At rest they also presented higher level of IL-6 and IL-10 than healthy controls. Acute physical exercise increased IL-6 levels in control women, but did not alter IL6, IL10 and TNF-α level in SLE patients. We concluded that acute exercise did not increase inflammatory cytokines level in SLE patients and seem be safe for patients with controlled disease.

Table 1. Demographic, Ergospirometric variables and Cytokines levels of 27 SLE patients and 30 controls at baseline

Variables	Patients	Controls	P
Age (y.o)	32.5±7.4	30.4±7.7	0.275
BMI	24,4±3,8	23,4±0,8	P=0,129
VO2 Max(ml/kg/min)	25.78±5.511	32.74±5.85	P < 0.001
HR Max (bpm)	74.18±12.36	185.15±2.07	P=0.001
VE Max(l/min)	65.51±15.87	80.48±18.98	P=0.001
Veloc Max(Km/h)	7.68 ± 1.24	9.4 ± 1.22	P < 0.001
IL-6 (pg/ml)	2,38±1,70	1,71±0,29	P=0,035
IL-10 (pg/ml)	1,09±1,55	0,30±0,11	P=0,037
TNF-α(pg/ml)	4,88±7,82	4,19±1,44	P=0,867

P045

Anti-Ribosomal P Antibodies In Large Cohort Of Autoimmune Hepatitis With No Evidence Of Lupus: A Common Underlying Mechanism Targeting Liver?

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Background: Anti-ribosomal P proteins antibody (anti-rib P) is a highly specific marker for systemic lupus erythematosus (SLE) and it is associated with liver involvement in this disease. Similarities between autoimmune hepatitis (AIH) and SLE-associated hepatitis raise the possibility that anti-rib P antibodies may also have relevance in AIH. This study was therefore undertaken to evaluate the frequency and clinical significance of anti-rib P antibodies in a large AIH cohort before treatment.
Methods: We screened sera from 93 consecutive patients that fulfilled the international criteria for AIH. Charts were extensively reviewed for demographic, clinical, treatment and laboratorial parameters. Frozen sera samples obtained at diagnosis were tested for anti-ribosomal P protein performed by ELISA kit employing synthetic 22 amino acid C-terminal peptide and compared to 82 healthy controls.
Results: Nine AIH patients (9%) were moderate or high titer anti-rib P ($>$ 40U) with a mean level of 93.6 ± 33.1 units and none of the controls were positive (p=0.003). AIH patients with and without anti-rib P antibodies had similar demographic/clinical features, including the frequency of cirrhosis (44% vs. 28%, p=0.44), laboratorial findings and frequencies of therapy used at their initial evaluation. The follow up period was long and comparable in those with and without anti-rib P antibodies (10.7± 5.1 vs. 10.3 ± 5.2 years, p=0.68). At the final observation AIH patients with anti-rib P had a significantly higher frequency of cirrhosis compared to negative group (100% vs. 60%, p=0.04) despite no difference in the frequency of drugs used after diagnosis ($p > 0.05$).
Conclusions: The novel demonstration of anti-rib P in AIH patients without clinical and laboratorial evidence of SLE suggests a common underlying mechanism targeting liver in these two diseases. In addition, this antibody seems to predict a group of patients with worse AIH prognosis.

P046

Evaluation of High-throughput Platforms for Digital Antinuclear Antibody (ANA) Indirect Immunofluorescence (IFA) Screening

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Introduction: ANA IFA screening is a gateway test in clinical and laboratory evaluation of autoimmunity. High-throughput enzyme immunoassays (EIAs) that replaced IFA methods on HEp-2 cells raised concern about limited number of antigen specificities on immunobeads and about batch variation of antigen content in cell lysate based EIAs. Return to traditional ANA IFA is impeded by labor intensity, lack of standardization, interobserver variation, and the need for highly-trained technical staff. A high-throughput, cost-efficient IFA method with observer consistency and ease of quality control and monitoring is desirable. We evaluated commercial platforms for digital ANA IFA image acquisition and analysis.
Methods: Three commercial platforms for digital ANA IFA screening, image capture, and analysis were tested. Each employed proprietary HEp-2 slides and antihuman IgG fluorescein conjugates. Results were compared to previous manual IFA testing on a fourth proprietary

HEp-2 cell substrate using antihuman polyvalent immunoglobulin conjugate. Results were interpreted by a single senior laboratory scientist.
Results: Normal donors (n=120) and at least 153 patient samples submitted for testing were evaluated by manual ANA IFA and on each platform. Initial platform screening using the original factory settings indicated the need to adjust instrument positivity threshold to approximate the performance of the manual method used as the gold standard (Table 1).

Table 1. Optimization of Threshold for Positivity: Platform 1 vs Manual Method

Fluorescence Intensity Positive Threshold Value (Units)					
	66	147	180	219	280
Sensitivity	98%	90%	90%	86%	83%
Specificity	33%	71%	78%	86%	92%

After optimization of platform threshold of detection, all 3 platforms were evaluated against the antecedent manual method (Table 2).

Table 2. Agreement Between Digital and Manual Methods

Platform:	*1*		*2*		*3*	
Manual:	*Positive*	*Negative*	*Positive*	*Negative*	*Positive*	*Negative*
Agree	92(90%)	40(78%)	88(85%)	27(53%)	67(68%)	67(93%)
Disagree	10(10%)	11(22%)	8(8%)	19(37%)	32(32%)	5(7%)
Unrecognized			5(5%)	4(8%)		
No Image			3(3%)	1(2%)		

Conclusions: Before adjusting the positivity threshold, digital platform specificity was low, giving an unacceptable number of false positives when compared with the manual method gold standard. Aligning the platform threshold for positivity with that of the manual method improved specificity without sacrificing sensitivity. Discordant samples tended to have low titer by digital or manual methods. Digital method negative but manual method positive samples tended to have nucleolar ANA patterns, several with moderate titers. Thresholds based on total field intensity units may fail to recognize more discrete patterns such as nucleolar or nuclear dots. Technologists should review all images generated on digital platforms to confirm positivity versus negativity and identify patterns that may be overlooked by digital analysis algorithms. Further, technologists should be alert to the potential for image enhancement through image capture and enlargement that may increase false positive results.

P047

Stratification of sle patients for improved diagnosis and treatment

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Background: Systemic autoimmune diseases (SAIDs) affect about 2 % of the population in Western countries. Sufficient diagnostic criteria are lacking due to the heterogeneity within diagnostic categories and apparent overlap regarding symptoms and patterns of autoantibodies between different diagnoses. Systemic lupus erythematosus (SLE) is regarded as a prototype for SAIDs and we hypothesize that subgroups of patients with SLE may have different pathogenesis and should consequently be subject to different treatment strategies.
Objectives: Our goal is to find new biomarkers to be used for the identification of more homogenous patient populations for clinical trials and to identify sub-groups of patients with high risk of for example cardiovascular events.
Methods: In this study we have utilized 320 SLE patients from the Karolinska lupus cohort and 320 age and gender matched controls. The SLE cohort was characterized based on clinical, genetic and serological data and combined by multivariate data analysis in a systems biology approach to study possible subgroups. A pilot study was designed to verify and investigate suggested subgroups of SLE. Two main subgroups were defined: One group was defined as having SSA and SSB antibodies and a negative lupus anticoagulant test (LAC), i.e., a ''Sjögren-like'' group. The other group was defined as being negative for SSA and SSB antibodies but positive in the LAC test..e. an ''APS-like'' group. EDTA-plasma from selected patients in these two groups and controls were analysed using a mass spectrometry (MS) based proteomic and metabolomic approach. Pathway analysis was then performed on the obtained data.
Results: Our pilot study showed that differences in levels of proteins and metabolites could separate disease groups from population controls. The profile/pattern of involved factors in the complement system supported a division of SLE in two major subgroups, although each individual factor was not significantly different between subgroups. Complement factor 2 (C2) and membrane attack complex (MAC) were analyzed in the entire cohort with complementary methods and C2 verifies our results while the levels of MAC did not differ between SLE subgroups. The generated metabolomics data clearly separated SLE patients from controls in both gas chromatography (GC)-MS and liquid chromatography (LC)-MS data. We found for example that tryptophan was lower in the SLE patients compared to controls.
Conclusions: Our systems biology approach may lead to a better understanding of the disease and its pathogenesis, and assigning patients into subgroups will result in improved diagnosis and better outcome measures of SLE.

P048

Unique Protein Signature of Circulating Microparticles in Systemic Lupus Erythematosus

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Background: Impaired removal of subcellular material is thought to contribute to the pathogenesis of systemic lupus erythematosus (SLE). We here present global protein expression profiles of circulating subcellular particles (microparticles, MPs) from patients diagnosed with SLE, systemic sclerosis (SSc), rheumatoid arthritis (RA) and from healthy controls (HCs).
Patients and Methods: Microparticles from a total of 36 different patients and controls were analyzed. This included SLE (n=12), SSc (n=6), RA (n=6), and HCs (n=12). Proteins were quantified after tryptic digestion using nano-LC coupled tandem mass spectrometry. Main outcomes were protein identities and quantities and correlations with disease severity.
Results: SLE MPs have higher protein loads and among 530 identified individual proteins there were highly significant differences between HCs and SLE regarding the abundance of a large number of proteins (268 at a false-discovery rate of $q < 0.05$). Almost half of the 191 more than twice up-regulated proteins were complement proteins, immunoglobulins, and immunoglobulin fragments. MP immunoglobulin and complement loads also distinguished SLE from SSc and RA cases and correlated strongly with clinical SLE severity. Additional up-regulation at highly significant levels were observed for subsets of microtubule

proteins, fibronectin, 14-3-3 protein η isoform, and desmosomal proteins. Innate immunity molecules including ficolin-2 and galectin-3 binding protein were increased 5-10 fold on SLE MPs. Proteins decreased in abundance on SLE MPs represented cytoskeletal, mitochondrial, and intracelular organellar proteins including lysosome-associated membrane glycoprotein 1 (Lamp-1) and transforming growth factor β1.

Conclusions: The data distinguish SLE from other systemic autoimmune diseases and strenghten the notion that circulating MPs in SLE are grossly atypical and constitute a heterogeneous yet important reservoir of autoantigens and diagnostic and disease activity markers.

P049

Looking for protein biomarkers in cerebrospinal fluid in patients with neuropsychiatric lupus

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Background: Systemic lupus erythematosus (SLE) affects almost all organs with clinical manifestations such as neuropsychiatric (NP) compromise, with a prevalence that varies between 12-95%.

NP manifestations have been associated with morbidity and mortality of the disease. To date, the diagnosis of NP-SLE is performed using the nomenclature and description of case, American College of Rheumatology (ACR) 1999, however, the use of this nomenclature has not been effective for diagnosis because the complex pathogenesis, heterogeneity of clinical presentations, an unpredictable course of the disease. Additionally, the laboratory tests and imaging used are not conclusive.

This study aims identifying the molecules in the protein profiles of the cerebrospinal fluid (CSF) of patients with NP-SLE, compared with the profiles of patients with other clinical conditions and control individuals (CI), with the purpose of finding potential biomarkers to facilitate diagnosis of NP-SLE.

Patients and Methods: samples of 25 CSF of patients classified in five groups: 5 with NP-SLE, 5 no neuropsychiatric SLE (SLE no-NP), 5 neuropsychiatric no SLE (NP no SLE), 5 with other autoimmune diseases (OADs) and 5 CI was evaluated.

Proteins were extracted by precipitation with acetone. The protein profiles were obtained using two-dimensional electrophoresis. The comparative analysis to determine differentially expressed proteins was done using the ImageMaster 2D Platinum 7.0 software. These proteins will be identified by mass spectrometry (MALDI-TOF).

Results: Several spots with differential expression (presence/absence) were observed comparing patients with NP-SLE with individuals of other groups, particularly eight spots were found only in individuals with NP-SLE (table 1), they will be identified by MALDI-TOF.

Tabla 1. spots present in NP-SLE patients. The table shows: the intensity value, isoelectric point and molecular weight for each spot.

Spot	*intensity value*	*IP*	*MW*
300	0.931859	5.8	31
302	0.598395	5.8	41
303	1.38159	6.3	46
304	1.10895	5.3	50
306	1.16117	5.31	50
307	0.475146	5.2	54
308	0.787401	5.1	55
309	0.882547	5.0	56

Conclusions: The eight proteins found in NP-SLE patients and absent in the other groups, allow considering the idea of a specific bio-profile expressed in patients with the disease.

The identification of differentially expressed proteins allow the characterization of specific biomarkers for NP-SLE, which will be useful in diagnosis and monitoring of these patients, and perhaps can be correlated with the manifestations clinics.

P050

Utility of anti single and double stranded DNA antibodies as markers of disease activity in systemic lupus erythematosus.

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Introduction: Anti DNA antibodies are considered a hallmark of systemic lupus erythematosus (SLE). Anti double stranded DNA antibody (dsDNA) is part of the SLE classification and activity criteria due to its high specificity. However its sensitivity is moderate. On the other hand, the role of single stranded DNA antibodies (ssDNA) has not been fully addressed. The objective of this study is to correlate the presence of anti ssDNA and dsDNA antibodies with SLE activity, measured by ECLAM (European Consensus Lupus Activity Measurement).

Materials and Methods: We reviewed the charts of our SLE patients who had both anti ssDNA and dsDNA antibodies measured simultaneously between 2001 and 2011. Anti dsDNA was determined by *Crithidia lucillae* immunofluorescence assay and anti ssDNA was determined by a home-made ELISA. In each serologic determination, disease activity was established by ECLAM according to chart information from the previous 30 days. Disease activity by ECLAM was stratified in low, moderate and high activity and the anti ssDNA and dsDNA levels were stratified in low ($\leq$ 54 and $\leq$1/80) and high ($\geq$ 55 and $\geq$1/160) titres respectively.

Results: Ninety patients were evaluated (80 female), with a median age (range) of 39 (23-77) years. There were 328 simultaneous serologic determinations of anti ssDNA and dsDNA. According to the ECLAM, activity was found in 269 (82%) determinations and inactivity was found in 59 (18%) determinations.

	Sensitivity % (95% CI)	*Specificity % (95% CI)*	*Positive predictive value % (95% CI)*	*Negative predictive value % (95% CI)*
Anti ssDNA	78 (73-82)	44 (39-49)	86 (83-90)	30 (25-35)
Anti dsDNA	28 (23-32)	92 (88-94)	94 (91-96)	22 (17-26)

Secondly, patients were classified in 4 serologic groups for analysis: Group 1 (negative ssDNA and dsDNA), Group 2 (positive ssDNA and negative dsDNA), Group 3 (positive ssDNA and dsDNA) and Group 4 (negative ssDNA and positive dsDNA).

	Sensitivity % (95% CI)	*Specificity % (95% CI)*	*Positive predictive value % (95% CI)*	*Negative predictive value % (95% CI)*
Group 1 (n: 83)	21 (17-27)	56 (42-69)	69 (57-78)	14 (10-18)
Group 2 (n: 165)	52 (45-58)	53 (39-65)	83 (76-88)	19 (14-26)
Group 3 (n: 77)	27 (22-33)	92 (80-97)	94 (85-98)	22 (17-28)
Group 4 (n: 3)	–	–	–	–

Finally, the seropositive determinations were correlated with ECLAM variables:

	Group 2		*Group 3*	
	Relative Risk	p	*Relative Risk*	p
< 50 years	2,65	***0,001***	19,18	***0,0001***
Joints	1,31	0,607	3,79	***0,026***
Skin	0,93	0,902	1,79	0,370
Neuropsychiatric	1,45	1,000	5846,53	0,992
Renal	4,17	***0,035***	6,35	***0,008***
Hematologic	0,74	0,323	1,03	0,939
Eritrosedimentation rate	1,43	0,304	1,66	0,238
Hypocomplementemia	4,13	***0,0001***	6,31	***0,0001***

Conclusion: Anti ssDNA antibody shows a higher sensitivity and lower specificity than anti dsDNA antibody for SLE activity.

The presence of anti ssDNA with or without anti dsDNA antibody, was associated with younger age, hypocomplementemia, renal and joint involvement.

P051

Anti-Fibronectin autoantibodies and SLE

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SLE is a nonorgan-specific autoimmune disease, the hallmark of which is a vast array of antiself antibodies (autoAbs). Matrix protein such as laminine and fibronectin (Fn) are also frequently targeted by autoAbs. Nephritis is not only a common complaint in SLE, but it is also the most life-threatening complication of the disease. In a previous work we demonstrated association of ANCA, a-Fn and a-Histone (a-His) with renal disease. The proposal of the present work was 1) analize if one, two or all of them individually or associated, allow to distinguish between SLE patients with or without renal compromise; 2) characterize a-Fn autoAbs in Lupus nephritis. 1) Serum samples from 54 SLE patients, 20 with renal complications (R) and 34 without evidence of renal disease (NR), were analized for ANCA by indirect immunefluorescence and for a-Fn and a-His by *made in house* ELISAs. The association of each of them with R and NR groups was studied employing Chi-squared test, concluding that in lupic patients exist a significant association between a-Fn and renal compromise (p=0.0272); odds ratio=3.6, CI 95%: (1.1; 11.8) means 3.6 times higher chance of getting renal complications when a-Fn is positive than when it is negative. Analysis of continuous variable with Mann-Whitney Test lead to conclude that mean a-Fn titles in R is significantly higher than in NR (p=0.0345). Association between a-Fn and a-His was studied considering both variables as categorical (Mc-Nemar Test) or continous (Spearman's rank correlation coefficient). In the first case, there was no significative association in no group (NR p=0.99 and R 0.18). By contrast, in the second case the Spearman's rank correlation coefficient were 0.33 for NR (p=0.04) and 0.8309 for R (p=0.0000) indicating strong positive association between antibodies against Fn and histones which are autoantigens particularly sensible to conformational changes. 2) A group of 10 serums from Lupus nephritc patients were evaluated to quantitate the relative affinity of the a-Fn antibody population. Fn purified in our laboratory by gelatin affinity chromatography was coated onto Costar microtiter plates (1μg/well). Next blocking with 3% BSA, serial dilutions of patients serums were incubated 30 min at 37°C. Bound human a-Fn was detected with peroxidase-labeled goat anti-human IgG and visualized with TMB-H2O2 substrate by reading absorbance at 450 nm. The apparent equilibrium dissociation constants (Kd) were calculated by fitting data to a one site binding model. The a-Fn antibodies were shown to be of high affinity, with Kd ranging from of 8.4×10^{-8} M to 10.2×10^{-8} M. Taken toghether our results strongly suggest that a-Fn would be usefull not only to predict renal complication in SLE but also an excellent tool for further studies on the role of auto Abs and its process of affinity maturation in the pathogenesis of SLE.

P052

Comparison of three assays to assess antibodies against double-stranded DNA in systemic lupus erythematosus

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Introduction: Analysis of antibodies against double-stranded DNA (anti-dsDNA) is important as a diagnostic and prognostic tool in systemic lupus erythematosus (SLE). Anti-dsDNA analysis by the Farr radio-immunoassay or the *Crithidia luciliae immunofluorescence test (CLIFT) are regarded as reference methods. CLIFT has the advantage of offering IgG-specific antibody analysis, although the quantitative estimate by titration is rough compared to the Farr assay. Generally, anti-dsDNA analyses by conventional enzyme-immunoassays have lower diagnostic accuracy than CLIFT and Farr. Herein, CLIFT was used as reference to compare two more recent anti-dsDNA assays, i.e.* the PhaDia enzyme immunoassay and the fluorescent microspehere immunodetection system (FIDIS).

Subjects and methods: 192 patients with SLE (93% Caucasians; 92% female; mean age 50.5 years/range 18-80; mean duration 11 years/range 0-45) participating in the KLURING study (Swedish acronym for 'Clinical lupus register in southeast Gothia'). 81% of the patients met the 1982 ACR criteria, and the remainder fulfilled the Fries' criteria, *e.g.* 2 typical organ manifestations at diagnosis and positive IgG antinuclear antibody (ANA/HEp-2) above the 95th percentile among 150 healthy female blood donors. For CLIFT and PhaDia, the following disease controls were included: 100 blood donors (50 women, 50 men), 97 with rheumatoid artritis and 54 patients with Sjögren's syndrome. Sera were analyzed for the presence of IgG anti-dsDNA by CLIFT (cut-off >99th percentile among 100 healthy female blood donors) and by PhaDia (Thermo Fisher Scientific/Phadia AB) and FIDIS (Theradiag) with the cut-off limits suggested by the manufacturers.

Results: When comparing anti-dsDNA results in relation to fulfillment of the ACR-82 criteria, Fisher's exact test revealed that all three anti-dsDNA tests showed significant positive associations to criterion 7 (renal disease) and 10 (immunologic disorder). CLIFT and FIDIS, but not PhaDia, showed significant negative associations to criterion 3 (photosensitivity), whereas PhaDia alone showed a significant negative association to criterion 4 (oral ulcers). The proportions of positive anti-dsDNA tests in SLE, healthy subjects and disease controls are shown in Table 1.

Table 1. Positive anti-dsDNA tests obtained with CLIFT, Phadia and FIDIS.

	SLE (n=192)	***RA (n=97)***	***Sjögren (n=54)***	***Healthy (n=100)***
CLIFT	25 %	2 %	6 %	0 %
PhaDia	34 %	6 %	13 %	1 %
FIDIS	32 %	nt	nt	nt

Spearman's rho correlation revealed that anti-dsDNA levels measured by CLIFT correlated more strongly to FIDIS (rho 0.631, $p < 0.0005$) than to PhaDia (rho 0.475, $p < 0.0005$). The correlation between PhaDia and FIDIS was 0.607 ($p < 0.0005$).

Discussion: When CLIFT is chosen as 'the gold standard' for anti-dsDNA measurement in SLE, the present study indicates that FIDIS performs better than PhaDia. This applies both to the associations of positivie/negative tests in relation to disease manifestations, and to the serum levels of anti-dsDNA. As regards diagnostic specificities of the tests, we found that a positivie CLIFT was more SLE-specific than PhaDia. The corresponding results for FIDIS, however, remain to be elucidated.

P053

Urinary neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 are associated with lupus nephritis in Chilean patients.

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Introduction: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of autoantibodies and a variety of clinical manifestations in different organ systems; SLE results from the interaction of genetic, hormonal and environmental factors. Renal involvement affects up to 60 % of SLE patients; 5-22 % of them will progress to end-stage renal disease (ESRD). These rates are probably related to the difficulty in diagnosing lupus nephritis (LN) or recognizing early that a flare is occurring, before permanent damage ensues. Biomarkers have been used for the diagnosis of SLE but there is a paucity of them available for the identification of patients at high risk of LN or of flares of LN. There is some evidence that suggests that urinary gelatinase-associated lipocalin (uNGAL) and Kidney Injury Molecule-1 (KIM-1) could be associated with LN in other populations. The objective of this study was to evaluate if there is association of uNGAL and uKIM-1 levels with the presence of renal activity and renal damage of LN in Chilean SLE patients.

Patients and Methods: Patients attending the Rheumatology clinics of the P. Universidad Catolica de Chile were invited. For the study, 26 patients with LN (24 female and 2 male), 16 patients with SLE without LN (15 female and 1 male) and 10 healthy controls were included. The urinary levels of NGAL and KIM-1 were quantified by enzyme linked immunosorbent assay (ELISA). Clinical, serological and other markers of disease activity (C3, C4 and anti-dsDNA) were measured by standard laboratory procedures.

Results: Urinary NGAL was significantly higher in patients with active LN ($p < 0.002$). In 5 patients with active LN, urinary NGAL levels were evaluated during a LN flare and after 3 months of treatment. We observed a significant decrease in NGAL after remission induction. Also, urinary KIM-1 levels were higher in the active LN group ($p < 0.006$) than patients with inactive LN and SLE patients without LN.

Conclusions: Urine NGAL and KIM-1 are elevated in Chilean SLE patients with active LN. These data may have practical applicability to the management of patients with SLE.

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P054

Disappearance and reappearance of immune complexes and IgG, IgA and IgM autoantibodies in rituximab-treated SLE patients

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Introduction and background: We have earlier shown that circulating immune complex (IC) levels in SLE are associated with anti-SSA/SSB (Mathsson et al, Clin Exp Immunol 2007), and that IgG antibodies against RNA-associated autoantigens accumulate more in SLE IC than IgG antibodies against DNA-associated autoantigens (Åhlin et al Lupus 2012). To further investigate the relation between IC and specific autoantibodies we developed a line blot technique for the quantification also of non-classical (IgA and IgM) SLE autoantibody isotypes. IgG autoantibody levels drop after institution of rituximab therapy. The objective was to investigate parallel changes IgG, IgA and IgM autoantibody isotypes in parallel to IC levels. As rheumatoid factors (RF) arise as a response to IC, we also investigated RF isotypes in parallel.

Patients and Methods: Six rituximab-treated SLE patients with ANA-associated antibodies were followed with repeated samplings at baseline and after 1, 3, 6 and 12 months. All samples were investigated concerning IgG/A/M autoantibodies with line blot quantitated with densitometry and concerning IgG autoantibodies with Addressable Laser Bead ImmunoAssay (ALBIA, or Luminex) technique. Twentyfive rituximab-treated SLE patients were serially followed concerning levels of C1q-binding IC as well as quantitation of IgG, IgA and IgM RF with enzyme immunoassays. Significant changes were defined either as $\geq$33% drop or as $\geq$50% increase, compared to the lowest levels experienced during the follow-up.

Results: ALBIA measurements showed significant initial drop in anti-dsDNA in 4/6 patients but also significant drop in levels of anti-histone, anti-SSA/Ro60, anti-Sm and anti-Sm/RNP in individual patients. Late increases in antibodies against dsDNA, SSA/Ro52, SSA/Ro60, SSB, Sm, Sm/RNP ribosomal P protein and histones were associated with clinical relapse. Late increase in IgA/IgM anti-DNA, anti-histones and anti-nucleosomes was also found in one patient with persistent kidney disease treated with mycophenolate mofetil at 10 months. Non-classical autoantibody isotypes showed late increases that often were not paralleled by the corresponding IgG autoantibodies. Different isotypes showed different kinetics of appearance and disappearance.

Fifteen/25 patients had initially elevated circulating IC-levels, and 12/25 patients showed significant initial drop in IC levels whereas three patients later experienced significant rises. Increased IC levels were only found in SLE patients with ANA-associated antibodies. The IgG RF isotype snowed the greatest tendency to change: 5/25 patients decreased after therapy start whereas 7/25 patients showed a later increase sometimes associated with arthritis flare; the corresponding figures for IgA RF was 5 and 1, and for IgM RF 4 and 2. ANA-negative patients showed no significant changes in RF. There was no clear correlation between later increase in autoantibodies/IC and the re-appearance of circulating CD19 positive B cells.

Conclusions: Measurement of non-classical isotypes of RF and ANA-associated autoantibodies might yield clinically useful information when monitoring B-cell depleted SLE patients. Among RF isotypes, IgG RF show the greatest degree of re-appearance during follow-up.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 5 Epidemiology & Quality of Life"

Atlantico A+B+C

P055

Validity of a Self-administered Version of the Brief Index of Lupus Damage (BILD) in a Predominantly Black Systemic Lupus Erythematosus Population in the United States

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Introduction: The Brief Index of Lupus Damage (BILD) is an interviewer-administered measure of organ damage in systemic lupus erythematosus (SLE). It was developed for use in epidemiologic studies when completion of the SLICC Damage Index (SDI) by physicians is not feasible. Preliminary studies suggest that BILD is acceptable to responders, and has content, criterion, and construct validity. In this study we assessed the reliability and validity of the SA-BILD, a self-administered version of BILD, in an independent predominantly Black SLE population.

Patients and Methods: Reliability, criterion and construct validity of the SA-BILD were assessed using data from the 2011 annual patient-reported survey of the Georgians Organized Against Lupus (GOAL). GOAL is a prospective cohort comprised of 910 individuals with documented SLE predominantly enrolled from the Georgia Lupus Registry, a population-based lupus registry established in the metropolitan Atlanta, Georgia, United States. Among 800 respondents in 2011, 757 completed self-administered questionnaires and 43 were interviewed by phone. To test reliability, the SA-BILD was re-administered within 4 weeks to 34 patients. Construct validity was assessed among 757 participants dividing the SA-BILD scores in quartiles and examining the association with demographics and health status. Criterion validity for the SA-BILD was examined in 150 respondents for whom the SDI was also completed by trained clinicians.

Results: The mean age and educational attainment of 757 responders of the SA-GOAL were 46.3 years and 14.2 years, respectively. 93.7% were women, 77.4% Blacks and 19.7% Whites, 35.1% were employed, and 45.3% had incomes below the federal poverty level. All GOAL survey respondents completed the SA-BILD questionnaire. Among the 25 SA-BILD items examined for criterion validity, the item-by-item agreement with the SDI was very good (0.81-100) for 20 items and good (0.61-0.80) for 5 items. The overall Spearman rank correlation for SDI and SA-BILD was moderate ($r=0.59$, $p<0.0001$). The test-retest correlation score was 0.92 ($p<.0001$). SA-BILD scores showed significant associations in the expected directions with age, disease duration, self-reported disease activity, overall health, number of comorbidities, and physician visits (see Table).

Conclusion: The SA-BILD is reliable and has very good or good criterion validity compared to the SDI when tested in a predominantly Black cohort of U.S. patients with SLE. Associations of SA-BILD scores with sociodemographics and health status are consistent with previous studies on damage in SLE. These findings support the use of a self-administered version of a damage measure in SLE patients from under-represented minority groups.

Comparisons of sociodemographics and health status by quartiles of SA_BILD

Characteristics	*0 (n=198*	*1(n=160)*	*2-3(n=224)*	*> 4(n=175)*	*p-value*
Sociodemographics					
Age at survey, mean +SD years	40.7±12.4	44.8±12.9	48.1 ± 13.1	51.6 ±12.5	< .0001
Female, n (%)	191 (26.9)	148 (20.9)	211 (29.8)	159 (22.4)	0.06
Non-White, n (%)	143 (23.5)	141 (23.2)	184 (30.3)	140 (23.0)	0.12
High school or less, n (%)	61 (23.2)	47 (17.9)	88 (33.5)	67 (25.5)	0.05
Living below poverty level, n (%)	79 (24.4)	70 (21.6)	99 (30.6)	76 (23.5)	0.28
Unemployed, n (%)	93 (18.9)	95 (19.3)	153 (31.2)	150 (30.5)	< .0001
Health status					
Disease duration, mean +SD years	10.5 ± 8.2	12.6 ± 9.1	13.8 ± 8.8	17.2 ± 9.7	< .0001
SLAQ score, mean +SD years	13.2 ± 8.7	16.7 ± 9.2	18.6 ± 9.0	20.5 ± 8.9	< .0001
Fair or poor health, n (%)	66 (16.1)	78 (20.3)	122 (31.7)	119 (30.9)	< .0001
Comorbidity Index, mean +SD	1.4 ± 1.3	2.5 ± 1.6	3.2 ± 1.6	4.7 ± 1.7	< .0001
Annual doctor visits, mean +SD	7.1 ± 5.9	8.7 ± 8.5	9.3 ± 9.1	14.0 ±19.6	< .0001

P056

Mortality in Systemic Lupus Erythematosus compared to the general population

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Background: The aim of the study was to examine mortality in a well-defined Systemic Lupus Erythematosus (SLE) cohort in Oslo from 1999-2010.

Method: We identified 326 SLE patients within the city of Oslo from 1999 to 2008 using five different sources; inpatient and outpatient Hospital Discharge diagnosis registers, a local cohort from 1995, The Norwegian systemic connective tissue disease and vasculitis registry (NOSVAR), private rheumatologists and National Causes of Death Registry at Statistics Norway. Only patients fulfilling four or more of the updated 1997 American College of Rheumatology criteria were included. The patients were each randomly assigned five population controls, matched for year of birth, sex and parents ethnicity. The date and causes of death were retrieved from the data files at National Causes of Death Registry.

Results: Fifty (10/34 males and 40/292 females) SLE patients and 90 (12/170 males and 78/1460 females) controls died in the time period 1999-2010. This gives a Standard Mortality Rate (SMR) of 2.8 (males 4.2 and females 2.6.) The cumulative survival at 5, and 10 years were

97.3% and 92.0% in SLE and 99.1% and 96.5% in population controls. Four males and four females died within five years, giving 86.7% five year survival for men and 98.5% for females. 1/40 Asian and 7/274 Europeans died, giving a 96.0% five year survival for Asians and 97.3% for Europeans.

The mean age of death was 63 (median 63) years for the SLE patients and 75 (median 77) years for the control group. SLE patients exhibited a bimodal pattern distribution in age of death with the first peak at 30-39 years and the second between 50 and 80 years of age.

Autopsy was conducted in 36% of the SLE patients and 14% of the control group. 10 SLE patients (mean age of 65 years) and 4.8 controls (mean age of 68 years) died of malignancy as the underlying cause of death, SMR 2.1. The result when taking all causes into account is shown in table 1.

Conclusions: Half of the SLE patients die before they reach 63 years of age of whom the most frequent causes are cardiovascular disease and infections. There is an increased mortality from malignancy in this SLE population, especially later in life.

Table 1. SMR estimates for disease specific relative mortality in SLE patients; all causes

Causes of death (ICD10 code)	*Observed*	*Expected*	*SMR*
≥60 Years of age			
CVD	14	8.6	1.6
Infections	9	3.6	2.5
Renal	3	0.8	3.8
Malignancy	10	3.8	2.6
< 60 Years of age			
CVD	6	0.4	15.0
Infections	7	0.4	17.5
Renal	3	-	
Malignancy	2	1.8	1.1

CVD; Cardiovascular disease (I00-I99, R96), infections (A00-B99, J10-J18, N39), renal (N00-N28), malignancy (C00-C97)

P057

Lean Body Mass (LBM) Positively Impacts on Health Related Quality of Life (HRQoL) in Patients with Systemic Lupus Erythematosus (SLE)

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Background: The correlates of HRQoL in patients with SLE are not clear but disease activity and damage are only modestly correlated with it. Sarcopenia has been shown to be negatively associated with HRQoL in RA patients. We hypothesized that the same could be the case in patients with SLE and thus the higher the percentage of LBM the better the HRQoL.

Aim: To determine whether LBM is associated with HRQoL in SLE patients.

Methods: This cross-sectional study was conducted in consecutive SLE patients seen in our Rheumatology Department from January to November 2012. An interview, chart review, physical examination, laboratory tests and dual energy X-ray absorptiometry (DXA) were performed. SLE was defined using the ACR criteria; LBM was determined by DXA and it was analyzed as subtotal LBM (whole body excluding the head), trunk LBM and appendicular LBM. HRQoL was ascertained using the SF-36. Comorbidities were quantified according to the Charlson Comorbidity Index (CCI). Disease activity was ascertained using the SLEDAI and disease damage with the SLICC/ACR damage index (SDI). Use of prednisone was recorded as current dose and total time of exposure. The association between HRQoL and LBM was evaluated using Spearman's correlation. Subsequently, a linear regression model was performed to evaluate the association between the SF-36 subcategories and LBM, adjusting for age, disease duration, disease damage, disease activity, use of prednisone and the CCI.

Results: 123 patients were evaluated; their average (SD) age was 42.4 (12.9) years. Disease duration was 8.3 (7.0) years; almost all patients were mestizo. The SLEDAI was 6.0 (4.5), the SDI was 0.8 (1.2), the CCI was 1.4 (0.8), the current dose of prednisone was 8.3 (5.1) mg/d and the total time of exposure to prednisone was 8.0 (7.0) years. Percentage of subtotal LBM was 60.0 (6.7), of trunk LBM was 62.6 (7.7) and of appendicular LBM was 56.9 (6.9). Physical component summary (PCS) was 47.5 (20.8) and mental component summary (MCS) was 48.9 (20.4). In the univariate analysis, subtotal LBM was associated with higher physical function (Rho: 0.24); appendicular LBM with higher PCS (Rho: 0.22), higher physical function (Rho: 0.28), and higher role physical (Rho: 0.23); and, trunk LBM was associated with higher physical function (Rho: 0.19). In the adjusted model subtotal LBM was associated with physical function (β: 0.34), appendicular LBM with PCS (β: 0.26), physical function (β: 0.36) and role physical (β: 0.27), and trunk LBM with physical function (β: 0.29); $p < 0.05$ in all analyses.

Conclusion: There was a positive association between the percent of LBM, especially appendicular, and the physical components of HRQoL independent of age, disease activity and damage, disease duration, steroids' use and the presence of comorbidities in SLE patients. The preservation of LBM should be part of the overall goals in the management of lupus patients.

P058

Impact of Disease Activity on Work Productivity in Systemic Lupus Erythematosus Patients from the Southeast, United States

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Introduction: The decline of health in those afflicted by SLE yet still able to maintain employment may have a devastating impact on work productivity and long-term employment sustainability. US studies on the effect of SLE on work productivity have been conducted in samples with inadequate representation of high-risk patients from minority groups. This study examines the impact of SLE activity and comorbidities on work productivity in a large cohort of SLE patients comprised of a high proportion of African Americans from a broad socioeconomic spectrum.

Patients and Methods: Data was sourced from the 2011 annual patient-reported survey of the Georgians Organized Against Lupus (GOAL). GOAL is a prospective cohort of validated SLE patients primarily enrolled from the Georgia Lupus Registry, which is a population-based registry, established in the metropolitan Atlanta, Georgia, US. Among those employed, we measured the percentage of overall work productivity impairment due to health (WPI) using the Work Productivity and Activity Impairment instrument (WPAI). WPI accounts for the proportion of absenteeism and/or impairment of productivity while working in the past week. Disease activity scores (DAS) and comorbidity index (CI) were assessed using the Systemic Lupus Activity Questionnaire (SLAQ) and the Comorbidity Index questionnaire. Multifactor analyses of variance were performed separately to examine the impact of the DAS and the CI on the percentage of WPI.

Percentages of WPI were adjusted by disease duration, socio-demographics (age, gender, race, poverty level and education) and by the other main independent variable (DAS or CI).
Results: 279 (35%) of the 800 GOAL patients were employed, 252 (90%) of which completed the WPAI questions. The mean age and disease duration were 43.8 and 13 years, respectively; 96% were females, 69% Blacks and 28% Whites. The mean educational attainment was 15.3 years, and 34.8% reported an annual household income below $30,000.
Conclusion: After an average of 13 years of disease duration, only 35% of SLE patients from a predominantly Black cohort in the Southeast, US, were in the work force. Of those working, disease activity had a tremendous impact on their productivity. Patients with high disease activity, reported almost 45% of overall work productivity impaired, after adjusting for sociodemographic factors; whereas those without activity showed less than 10% impairment. Patients with severe symptoms of forgetfulness or depression, muscle pain or weakness, and articular activity reported the highest burden of work productivity (about 50% WPI). Presence of comorbidities did not impact work productivity after adjusting for disease activity and sociodemographic factors. Longitudinal studies including high-risk individuals are warranted to examine the economic burden of SLE at the individual and societal level.

Overall WPI as a Function of Comorbidity Index and Disease Activity

Variable	*Score*	*N=252*	*Adjusted WPI Mean (95%CI)*	*p-value*
Comorbidity Index				
No comorbidity (Ref)	0	41	27.0 (15.0-38.9)	
Low comorbidity	1-2	116	25.2 (14.3-36.1)	0.7
High comorbidity	> 3	92	33.1 (22.3-43.9)	0.3
Disease Activity Score				
Low activity (Ref)	0-10	86	9.9 (-1.4-21.2)	-
Moderate activity	11-16	80	31.0 (20.6-41.5)	< .0001
High activity	>17	87	44.3 (33.3-55.4)	< .0001
SLAQ Disease Activity Organ System				
Skin	0	81	14.1 (2.1-26.2)	
	1	171	34.1 (23.6-44.6)	< .0001
Lung	0	85	18.7 (6.7-30.6)	
	1	88	27.3 (15.9-38.8)	0.06
	2	53	41.8 (28.7-55.0)	< .0001
	3	23	43.3 (29.0-57.7)	0.0004
Raynaud's	0	136	25.0 (14.0-36.0)	
	1	126	37.9 (26.2-49.6)	0.001
Stroke Syndrome	0	111	23.8 (12.1-35.4)	
	1	66	33.7 (21.4-46.0)	0.04
	2	54	34.1 (20.9-47.2)	0.05
	3	21	40.8 (23.8-57.8)	0.02
Cognitive	0	60	21.6 (8.9-34.3)	
	1	83	26.9 (14.9-38.9)	0.31
	2	75	31.9 (20.4-43.5)	0.06
	3	34	51.8 (37.1-66.6)	< .0001
Muscle	0	63	17.3 (5.0-29.6)	
	1	81	24.6 (13.3-36.0)	0.15
	2	71	35.7 (23.5-47.9)	0.0007
	3	37	50.0 (36.7-63.4)	< .0001
Joint	0	40	10.6 (-2.7-23.9)	
	1	82	25.0 (13.6-36.3)	0.012
	2	91	35.1 (23.6-46.5)	< .0001
	3	39	48.2 (34.7-61.6)	< .0001

P059

Medical Costs and their predictors in Korean Patients with Systemic Lupus Erythematosus

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Background: Systemic lupus erythematosus (SLE) has very high economic burdens on society and healthcare system. The aim of this study was to estimate the annual direct costs and predictors of cost in Korean patients with SLE.
Patients and Methods: Total 749 patients with SLE were recruited in the Hanyang BAE lupus cohort in Seoul, Korea. We assessed the annual direct costs for the 12 months in 2010. Information was taken directly from the chart review and hospital database. And, the medication costs, which are not available from hospital database, were obtained by micro-costing methodology.
Results: The estimated total annual direct medical costs amounted to $3,305 (2010 US dollars), of which 60.4% was accounted for by inpatient costs and 39.6% by outpatient costs. Among the cost domains for total direct medical costs, the biggest component was the costs of medication. The mean medication costs were $1,251, which accounted for 38.4% of the total healthcare costs, followed by costs for diagnostic procedures and tests, accounting for 35.6% of the total. The annual direct medical costs increased significantly according to SLICC/American College of Rheumatology Damage Index (SDI) subgroup (total SDI=0, 1 or 2, and $\geq$3), both at enrollment and in 2010 (p=0.0049 vs. p < 0.0001). And, the presence of renal and neuropsychiatric SDI incurred higher costs (p=0.0002 vs. p=0.0007). Total reimbursement rates of patients with SLE were 66.3%, and copayment and non-reimbursement comprised 10.8% and 22.9%, respectively. Reimbursement rates have shown a tendency to increase, whereas, out-of pocket was decreasing gradually each year between 2007 and 2010. In the multivariate regression analyses, the predictors of increased direct costs were higher disease activity (as expressed by the adjusted mean SLEDAI score), higher organ damage (as expressed by the SDI score) and renal and hematologic involvement, whereas longer disease duration predicted lower direct costs.
Conclusions: We have reported on the first cost-identification study in Korean patients with SLE. This analysis indicates that persons with SLE incurred a mean annual direct cost of $3,305 in 2010 US dollars. Longer disease duration predicted lower costs, whereas higher disease activity, higher organ damage, renal and hematologic involvement predicted higher costs.
Disclosure: This study was supproted in part by GlaxoSmithKline Korea

Table. Multiple linear regression model of annual direct medical costs in 749 patients with SLE*

	coefficient	*p*	*R2*
Age (1yr increase)	-	-	0.2000
Sex (female)	-	-	
Marital status (married)	-	-	
Disease duration (1yr increase)	-0.02825	0.0007	
Lupus onset (adult onset)	-	-	
AMS (1 incerase)	0.09591	< 0.0001	
SDI (1 increase)	0.19889	< 0.0001	
Renal involvement	0.22122	0.0039	
Hematologic involvement	0.27209	0.0353	
Neuropsychiatric involvement	-	-	
Serositis	-	-	

*Due to skewness of direct cost data, the regression analysis was performed on log-transformed direct costs.
-This coefficient and p value are not statistically significant.

P060

Efficiency of Interferon-γ Release Assay for Screening for Latent Tuberculosis in Patients with Systemic Lupus Erythematosus

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Introduction: Leading causes of death in systemic lupus erythematosus (SLE) are infections, kidney failure and cardiovascular disease. Although most infections are bacterial, there is a greater prevalence of tuberculosis (TB) secondary to multiple immunological abnormalities and immunosuppression. The tuberculin skin test (TST) and chest radiography are not sufficient to detect latent TB infection (LTBI) in this group of patients. Currently interferon-γ release assay (IGRAS): Quantiferon-TB Gold In-Tube ™ (QFT-GIT) and T-SPOT.TB ™ (T-Spot), have shown greater superiority to diagnose LTBI in immunocompetent patients but efficiency is unknown in immunosuppressed patients with SLE. The objective of the present study is to evaluate the efficiency of IGRAS in screening for LTBI in patients with SLE.
Methods: We performed a cross-sectional study that included patients with SLE according to the ACR criteria, ≥ 16 years old and signed informed consent; pregnant patients were not included, nor with active TB or with antituberculosis treatment. Patients underwent a questionnaire to obtain epidemiological and clinical data of SLE and TB, and TST and IGRAS were performed. The statistical analysis included descriptive arithmetic, chi square for categorical variables, Student's t test for quantitative variables and kappa for concordance.
Results: We reviewed a total of 106 patients with SLE, with a mean age of 34.7 ± 13.2 and 95% were female. A history of BCG was found in 90% and 84% presented a scar. Only 8% reported contact with TB patients and 12% were employees or residents of health or correctional institutions. A previous PPD was reported in 8%, of which 11% had a positive result. The 4% with previous diagnosis of TB had received treatment, 75% with lung and 25% with kidney involvement. Comorbidities: 28.3% with hypertension, 2.8% diabetes mellitus and 16% with dyslipidemia.

In the present study 9% had a positive PPD, with an average of 5.53 ± 1.92 mm. The QFT-GIT test reported 14% positive, 10% negative and 76% indeterminate. The latter test average was 1.77 ± 0.68 IU/ml in general, 3.14 ± 2.85 in the group of patients with a positive test, 1.41 ± 3.04 in the indeterminate and 0.11 ± 0.11 in the negative group. The kappa correlation between PPD and QFT-GIT amongst positive results of the two tests was 0.24 (fair).
Conclusions: In our group of patients with SLE a significant number of positive tests was observed for the diagnosis of LTBI, finding a fair concordance between the two tests, but a large number of indeterminate tests were seen. Further studies are needed to determine the usefulness of these tests in SLE and the need for a lower cutoff of IGRAS in this type of patient.

P061

Brief Group Psychoanalytic Psychotherapy for Systemic Lupus Erythematosus patients: a controlled randomized trial.

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Introduction: Brief Group Psychoanalytic Psychotherapy (BGPP) is a psychoanalytic not manualized technique that has been used to complement treatment of patients with psychosomatic disease and other diseases including cancer.
OBJECTIVES: To evaluate the effectiveness of (BGPP) to improve quality of life and coping strategies, as well to decrease depression and anxiety levels in patients with Systemic Lupus Erythematosus (SLE).
Methods: Prospective, randomized study in which 80 female SLE patients were included and 76 completed the study. Patients were randomized into 2 groups: the experimental group (EG n=35) and control group (CG n=41). Both groups continued to receive medical treatment according the physician evaluation. EG were divided in 4 sub-groups for BGPP (one session a week for 20 consecutive weeks). BGPP were conducted by a psychologist specialized in this approach. The CG remains in a waiting list until the end of study. All participants were evaluated at baseline and after 20 weeks by a blinded evaluator, using the following questionnaires and scales: socio-economic status by ABIPEME scale, organ damage by SLICC, disease activity by SLEDAI, SLE symptoms by SLE Symptom Checklist (SSC), SLE Quality of Life by SLEQOL, anxiety and depression by Hospital Anxiety and Depression Scale (HAD), and coping strategies by LAZARUS and FOLKMAN Coping Strategies Inventory. Inclusion criteria: female gender; ACR SLE classification criteria; age ≥ 18 year; at least 6 months of follow-up at institution; informed consent form signature. Illiterate patients and those with comorbidities that could compromise the participation on the study were excluded. The study was approved by Institutional Ethic Committee.

Statistical Analysis: Intra and inter-group comparison on EG and CG were performed. Student-t test, Mann-Whitney or Wilcoxon tests were used for quantitative variables and Qui-Square test for categorical variables. P value < 0.05 was considered significant.
Results: EG and CG were comparable at baseline regarding all variables analysed. After 20 weeks of BGPP the EG showed improvement of symptom evaluated by SSC ($p < 0.001$). Regarding the SLEQOL the EG also showed improvement on the following domains: physical function, occupational activity, symptoms, humor, treatment, autoimage as well in the total SLEQOL score ($p < 0.001$ for all variables). We also observed improvement on anxiety and depression levels ($p < 0.001$ for both). The use of coping strategies showed significant change on 4 of 8 domains: improvement on resolution of problems ($p < 0.001$) and positive self evaluation ($p < 0.002$) and decrease in use of confront ($p=0.021$) and escape and avoidance ($p=0.002$). For the other hand on the CG we observed a reduction of self control ($p=0.030$), social support ($p=0.008$), acceptance and responsibility ($p=0.024$) and resolution of problems ($p=0.032$).
Conclusion: The study showed effectiveness of BGPP to improve quality of life and coping strategies, and to improve depression and anxiety in patients with SLE. Psychological treatment can be a useful tool for complementary medical cares in SLE patients, improving the form how patients face the disease.

P062

Measuring Physical Activity in Systemic Lupus Erythematous (SLE) Adults: The Activity in Lupus To Energize and Renew (ALTER) Study

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Background: Prior estimates of physical activity (PA) patterns in adults with SLE are predominantly based on subjective self-report measures that are prone to error. People underestimate their daily walking distance and overestimate energy expenditure, with a tendency for greater overestimation in older and more obese individuals. In this study, we investigated: 1) estimates of energy expenditure (METS) by self-reported International Physical Activity Questionnaire (IPAQ) PA

domain and 2) the correlations between objective accelerometer measurements of PA and IPAQ.
Methods: We analyzed data from the first 100 participants in the ALTER study, a cross-sectional study of PA in persons with SLE. Accelerometer measures were obtained over 7 days and included daily counts, non-sedentary minutes, minutes of light activity, minutes of moderate/vigorous physical activity (MVPA), and MVPA 10-minute bouts. Each person completed the IPAQ long form via telephone interview. Other data analyzed included demographics (age, gender) and clinical variables (body mass index [BMI], medications, and validated SLE disease activity and severity). Spearman correlations were used to assess associations between accelerometer and IPAQ results.
Results: The sample was primarily female (92%), Caucasian (52%), with mean age 45.9 (SD, 11.3). The mean BMI was 28.1 kg/m2 (8.3), the mean SELENA-SLEDAI was 2.6 (2.9), and SLICC/ACR Damage Index was 1.8 (2.2). Daily physical activity means (SD) based on accelerometer monitoring were: total counts 228,418 (108,503); non-sedentary minutes 303 (80); light activity minutes 282 (74); MVPA minutes 21 (20); and bouted MVPA minutes 9 (14). The mean, median (IQR) MET-min per day for IPAQ intensities were: total 605.3, 471.2 (238.7, 783.4); light/walk 144.1, 78.2 (0, 236.1); moderate 269.1, 151.1 (64.3, 360.0); and vigorous 133.4, 0 (0, 205.7). The mean, median (IQR) MET-min per day for IPAQ domains were: work 175.2, 0 (0, 131.1); active transportation 93.2, 30.6 (0, 99.0); domestic and garden 192.8, 93.2 (38.6, 252.9); and leisure 144.1, 78.2 (0, 236.1).

Table 1. Spearman Correlations (p value) between Accelerometer-based Measures and IPAQ (n=91)

IPAQ MET-min per day	*Accelerometer min per day*			
	Non-sedentary	*Light*	*MVPA*	*MVPA in Bouts*
Light/walk	0.18 (0.08)	0.11 (0.31)	0.34 (0.0008)	0.35 (0.0008)
Moderate	0.06 (0.59)	0.09 (0.40)	-0.02 (0.84)	-0.09 (0.42)
Vigorous	0.14 (0.20)	0.03 (0.77)	0.41 (<0.0001)	0.40 (<0.0001)
Total	0.17 (0.10)	0.12 (0.27)	0.32 (0.002)	0.28 (0.008)

Conclusions: In persons with SLE, domestic and garden activities accounted for the greatest percentage of energy expenditure (32% of the total mean MET counts) estimated by the IPAQ, with active transportation as the least common (15%). There was a moderate association between IPAQ and accelerometer PA measures of moderate/vigorous activity. Compared to the accelerometers, the gold standard objective assessment tool for PA, the IPAQ provided primarily useful descriptive PA data. The choice of IPAQ versus objective measurement for future epidemiologic studies should consider the purpose for which PA is being measured; both may be useful.

P063

Accelerometer Physical Activity Measurements, Physical Function, Fatigue, Anxiety, Depression, Pain, and Sleep In Adults with Systemic Lupus Erythematosus (SLE): The Activity in Lupus To Energize and Renew (ALTER) Study

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Background: Physical activity (PA) conveys health benefits for persons with chronic illnesses, including SLE. Given the importance of PA in quality of life, we estimated the correlations of 1) accelerometer measurements with self-reported SLE specific Fatigue Severity Scale (FSS) and validated Patient-Reported Outcomes Measurement Information System (PROMIS) measures of fatigue, anxiety, depression, pain, and sleep, and 2) accelerometer measurements with physical function (PF) measured with the 20 meter walk test (gait speed) and PROMIS-PF.
Methods: We analyzed data from the first 100 participants in the ALTER study, a cross-sectional study of PA in persons with SLE. Accelerometer measures were obtained over 7 days and included daily counts, non-sedentary minutes, minutes of light activity, minutes of moderate/vigorous physical activity (MVPA), and MVPA minutes in 10-minute bouts or more. Gait speed, PROMIS measures and FSS were assessed prior to accelerometer wear. Other data analyzed included demographics (age, gender), and clinical variables (body mass index [BMI] and measures of SLE disease activity and severity). Spearman correlations were used to assess associations between measures of PA and other covariates.
Results: The sample was primarily female (92%), Caucasian (52%), with mean age 45.9 (11.3). The mean BMI was 28.1 kg/m2 (8.3), the mean SELENA-SLEDAI was 2.6 (2.9), and SLICC/ACR Damage Index was 1.8 (2.2). Means (SD) for the PROMIS measure T-scores (mean 50, SD 10) were: PF 43.6 (8.6), fatigue 56.1 (10.0), anxiety 54.8 (8.7), depression 50.5 (9.3), pain 55.6 (10.0), sleep impairment 55.5 (9.0), and sleep disturbance 56.1 (10.8). The mean FSS was 4.3 (1.7). Daily physical activity means (SD) based on accelerometer monitoring were: total counts 228,418 (108,504); non-sedentary minutes 303 (80); light activity minutes 282 (74); MVPA minutes 21 (20); and bouted MVPA minutes 9 (14). Mean average gait speed was 1.2 (0.3) feet/second.

Table 1. Spearman Correlation Coefficients (p value) between Accelerometer-based Measures and Selected Covariates (n = 92)

	Accelerometer counts	*Accelerometer non-sedentary min*	*Accelerometer light min*	*Accelerometer MVPA min*	*Accelerometer MVPA min in Bouts*
FSS	-0.24 (0.02)	-0.17 (0.10)	-0.10 (0.36)	-0.28 (0.007)	-0.33 (0.002)
PROMIS-Fatigue	-0.17 (0.11)	-0.17 (0.10)	-0.13 (0.23)	-0.21 (0.04)	-0.25 (0.02)
PROMIS-Anxiety	-0.06 (0.55)	0.0002(>0.99)	0.05 (0.62)	-0.04 (0.70)	-0.06 (0.58)
PROMIS-Pain	-0.40 (<0.0001)	-0.27 (0.01)	-0.18 (0.08)	-0.43 (<0.0001)	-0.38 (0.0002)
PROMIS-Depression	-0.15 (0.15)	-0.09 (0.37)	-0.06 (0.60)	-0.18 (0.09)	-0.19 (0.07)
PROMIS-Sleep disturbance	-0.10 (0.34)	-0.13 (0.22)	-0.12 (0.26)	-0.15 (0.15)	-0.17 (0.11)
PROMIS-Sleep impairment	-0.08 (0.47)	-0.12 (0.25)	-0.12 (0.25)	-0.06 (0.58)	-0.10 (0.36)

Table 2. Physical Activity Measures Spearman Correlation (p value) with Physical Function using PROMIS-PF and Gait Speed (n= 92)

	Accelerometer counts	*Accelerometer non-sedentary min*	*Accelerometer light min*	*Accelerometer MVPA min*	*Accelerometer MVPA min in Bouts*
PROMIS-PF	0.39 (0.0001)	0.23 (0.03)	0.13 (0.20)	0.43 (<0.0001)	0.40 (<0.0001)
Gait speed	0.44 (<0.0001)	0.23 (0.03)	0.13 (0.22)	0.52 (<0.0001)	0.43 (<0.0001)

Conclusions: In persons with SLE, modest inverse correlations were seen between fatigue, pain and several accelerometer-based measures, while other covariates showed lower correlations. The associations between PA and PF, both by self-report and objective report, were consistent, suggesting that PROMIS-PF or gait speed could be utilized depending on the study's **objectives** and design. Future longitudinal studies are needed to determine the temporal relationship between PA and covariates.

P064

A Systematic Review of The Quality of Prognosis Studies in Systemic Lupus Erythematosus

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Background: Prognosis studies examine future outcomes and/or seek to identify predictive or associative factors associated with outcomes. Strong and consistent prognostic factors can be used to individualize management and better outcomes of patients. Many prognostic factors have been identified in Systemic Lupus Erythematosus (SLE) but few have been consistent. We hypothesize that this is due to flawed study design. We aim to systematically assess methodological quality of prognosis studies in SLE.
Methods: A systematic search of prognosis studies in SLE was performed using MEDLINE and EMBASE, from January 1990 to June 2011. Non-English literature, non-original research, non- full length reports and animal studies were excluded. Of 5419 articles subjected to a title and abstract screen, 1039 articles were found. A representative sample of 150 articles was selected using a random number generator and assessed by 2 reviewers. Studies were classified according to design and the clarity of research question was assessed. Each study was assessed by a risk-of-bias tool "QUality In Prognosis Studies" (QUIPS) comprising 6 domains: study participation, study attrition, measurement of prognostic factors, measurement of outcomes, measurement/adjustment for confounders and appropriateness of statistical analysis. Information about missing data was also collected.
Results: Of 150 articles, 15 were pediatric studies, 3 made comparisons of pediatric and adult patients and the remainder were adult studies. The majority were published in rheumatology journals (69%). Cohort design was used in 67% of studies; the remainder used cross-sectional (21%), case-control (5%) and other designs (7%). The research question clearly included study population in 92%, prognostic factor in 54% and outcome in 61% of studies. High risk of bias (QUIPS) was noted in 57% of studies for study participation, 57% for attrition, 20% for prognostic factors, 18% for outcome, 65% for confounders and 36% for statistical analyses. Confounders were named in the methods section in only 12% of studies. Some consideration for confounding was built into the design of 21% of studies. The amount of missing data could not be assessed in 39% of studies.
Conclusions: Inadequate articulation of research questions for prognostic factors, poor design addressing confounding, study participation and attrition and inadequately reported missing data limited the quality of prognosis studies in SLE. Future prognosis studies should be designed with better consideration to the above factors to improve methodological rigor.

P065

Factors associated to Metabolic Syndrome in young Brazilian Systemic Lupus Erythematosus patients

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Background: Metabolic Syndrome (MetS) predisposes to atherosclerotic disease and also plays a role on morbi/mortality of Systemic Lupus Erythematosus (SLE). However, MetS incidence and the main factors that determine this condition are not completely defined in young population with lupus. The aim of this study was to evaluate MS prevalence and its main associated factors in young female SLE patients.
Methods: This cross-sectional study analyzed 102 women with SLE (ACR criteria) that were regularly followed at our outpatient Lupus clinic. The main inclusion criteria was age >18 and <40 years. MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III). Cardiovascular risk factors, previous cardiac disease, clinical manifestations, autoantibodies and current lipid profile, treatment, disease activity (SLEDAI), and accrual damage (SLICC) were assessed.
Results: Metabolic Syndrome was identified in seventeen SLE patients (16.8%). Patients with MetS had a mean age of $31.3 + 5.5$ years and disease duration of $9.4 + 5.9$ years that were similar to those without MS. Frequencies of previous clinical SLE manifestations, cardiovascular risk factors, cardiac disease, autoantibodies profile, and mean SLICC scores were alike among groups ($p > 0.05$). SLE patients with MetS had higher levels of apolipoprotein B ($92.3 + 23.2$ vs. $78.2 + 22$ mg/dl, p=0.019), proteinuria ($1.4 + 2.3$ vs. $0.52 + 1$ mg/24hs, p= 0.01), and cumulative prednisone dose ($44.9 + 25.2$ vs. $24.4 + 19.3$ g, p=0.001) compared to those without MetS. Moreover, SLE patients with MetS had a significantly higher frequency of SLEDAI >8 (35% vs. 6%, p=0.03), renal disease (82% vs. 51%, p=0.02), previous cyclophosphamide therapy (65% vs. 35%, p=0.02) but less frequency of antimalarial use (65% vs. 87%, p=0.03). Logistic regression revealed that cumulative steroid dose, previous cyclophosphamide use, renal disease, and disease activity (SLEDAI >8) were independently associated with MetS.
Conclusion: This study demonstrated a high prevalence of MS in young SLE patients which was mainly associated to nephritis itself and its treatment and also to the continuous disease activity.

P066

Incidence Studies of Systemic Lupus Erythematosus in Southern Sweden. Have the tides turned?

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The main objective was to study the incidence of Systemic Lupus Erythematosus (SLE)within a defined area in Southern Sweden over a period of more than 25 years. By prospectively identifying all new cases within this region using validated retrieval methods. A secondary objective was to investigate whether the phenotypic expression of SLE has changed during the study period.

The health care district of Lund-Orup had a mean population during 1981-2006 of 176.460 persons (>15 yrs of age). SLE cases were identified from multiple sources including diagnosis registries and from central laboratory databases using a previously validated "capture-recapture" methodology. The patients were observed prospectively within a structured follow-up program. Diagnosis of SLE was based on the presence of two clinical manifestations typical for SLE together with immunological abnormalities. Other causes for these manifestations were excluded and the diagnosis was continuously re-evaluated during the follow-up.

175 new cases were diagnosed with SLE from 1981-2006. There were 148 women and 27 male patients diagnosed with SLE, with a mean age of 44.3 years. In the first half of the study, from 1981-1993, the incidence of SLE was 5.0/100.000 inhabitants compared to

the second half of the study, 1994-2006, where it had decreased to 2.8/100.000 inhabitants (p≤0.001). During the first half of the study period the highest incidence was among females between the ages 45-54 were it was 15.1/100.000 inhabitants whereas in the second half of the study the incidence was reduced to 3.8/100.000 in this age group (p≤0.001). Between the years 1994-2006 the highest age and sex specific incidence was amongst women between 25-34 years of age (6.6/100.000 inhabitants), unchanged from the prior period. During the whole period the age and sex specific was highest among women between the ages 45-54 (8.9/100.000 inhabitants). The point prevalence of SLE on 31st of December 1993 was 55/100.000 inhabitants compared to the 31th of December 2006 where it was 66/100.000 inhabitants. 163 of the 175 patients fulfilled 4 or more ACR classification criteria SLE giving the criteria a sensitivity of 93 % for diagnosing SLE in our cohort. The disease phenotype did not vary over time.

The incidence rate of SLE in Southern Sweden remains stable in younger females over a 26 year period from 1981-2006. However, the incidence was reduced significantly in the older patients groups in the later period of the study.

P067

Register-based Prevalence of SLE in Sweden in 2010

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Introduction: Prevalence estimates of systemic lupus erythematosus (SLE) from around the world range from 3 to 207 per 100,000 depending on the region and population studied, Although understanding the range and scope of the burden of SLE by country or region is useful, estimates in other parts of the world may not generalize to the Swedish population. Swedish population-based registers, which include nearly all Swedish residents and can be linked via their personal identification number, are well poised to calculate the prevalence of SLE.
Materials and methods: By linking the National Patient Register (inpatient and non-primary care outpatient visits), Total Population Register, Prescribed Drug Register (all pharmacy dispensations from July 2005 onwards), and Cause of Death Register we identified all possible inpatient or outpatient visits with SLE-specific discharge diagnoses among individuals alive and registered in Sweden as of January 1, 2010. A range of definitions was used ranging from lenient classification requiring only a single hospitalization or non-primary care outpatient visit to multiple visits with an SLE ''hit'', relevant specialist care, and medication dispensations. These counts were then compared to the total Swedish population on January 1, 2010 which served as the denominator. Prevalence was calculated overall as well as by sex, age, and county of residence.
Results: As expected, SLE was more common among females (78.9 SLE cases per 100,000 individuals for the strictest definition) than males (12.2/100,000) and varied both by age and county. Prevalence increased with age in females until 65-69 years old and slightly later for males at which point the prevalence dropped steeply for women. We also observed considerable variability across counties in females and males, as well as in the sex ratio that could not be explained by density of rheumatologists. These observations were true for all register-based definitions used.
Conclusions: The prevalence of SLE in Sweden on January 1, 2010 according to multiple definitions varies by county, age, and sex. Results were comparable with a number of other international population-based estimates, however future studies are needed to confirm these register-based identifications and investigate the observed geographic variability.

P068

Contemporary estimates of the risk of end-stage renal disease in the first decade of proliferative lupus nephritis

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Background: End-stage renal disease (ESRD) is a major cause of morbidity and costs in patients with systemic lupus erythematosus (SLE). Patients with proliferative lupus nephritis are at greatest risk of ESRD, but with recent treatment advances, the proportion of patients with proliferative nephritis who develop ESRD may be decreasing. We sought to learn the risk of ESRD in patients with proliferative lupus nephritis enrolled in studies since 1990.
Methods: In a systematic literature review, we searched PubMed, Embase, and the Cochrane Database of Systematic Reviews from inception to November, 2011 to identify published articles on the risk of ESRD in lupus nephritis. We also searched references of retrieved articles and reviews. We excluded articles with fewer than 10 patients, less than 1 year of follow-up, those primarily of children, and those that did not report ESRD (dialysis or renal transplantation) as a specific outcome. Of 1144 unique articles from the searches, we did a full-text review of 373 articles. 155 articles met inclusion criteria, reported relevant data and were not duplicate reports on the same cohort. 31 studies began enrollment in 1990 or later. Here we examined the 14 studies (15 arms) that reported outcomes of patients with proliferative lupus nephritis. We computed weighted averages of the proportion with ESRD at the mean follow-up. For studies with more than 1 treatment arm, we pooled estimates across arms.
Results: The 15 arms were from 1 prospective observational study, 5 retrospective observational studies, and 9 clinical trials. Samples ranged from 9 to 117 patients. All but 1 study were done at referral centers, and 9 specifically excluded patients with elevated serum creatinine at baseline. Mean serum creatinine at entry was 1.2 mg/dl and mean proteinuria was 3.0 g/d. Mean duration of lupus nephritis at entry was 1.1 years. Mean follow-up was 4.5 years.

At 1-3 years of lupus nephritis, the pooled estimate of ESRD was 4.5% (based on 5 arms); at 4-6 years, the pooled estimate was 6.9% (3 arms); at 7-9 years, the pooled estimate was also 6.9% (5 arms); and at 10-11 years, the pooled estimate of ESRD was 3.9% (2 arms).
Conclusions: In patients with proliferative lupus nephritis enrolled in studies since 1990, the risk of ESRD over the first decade of lupus nephritis is under 7%. This estimate is largely based on long-term follow-up of clinical trials and studies that excluded patients with renal insufficiency at baseline.

P069

Prevalence of reduced bone mineral density and fragility fractures in patients with Systemic Lupus Erythematosus.

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Introduction: Osteoporosis (OP) with resultant fractures represent a considerable medical and socioeconomic burden. Patients with Systemic Lupus Erythematosus (SLE) are at high risk of developing OP; chronic treatment with Glucocorticoids (GC) is significantly associated with this condition. The aim of this work is to evaluate the prevalence of OP and fragility fractures in a monocentric cohort of patients with SLE.

Patients and Methods: We retrospectively evaluated the clinical charts of SLE patients followed at our Unit, collecting data about age, sex, menopausal status, Body Mass Index (BMI), smoking, disease duration, daily dose and total amount of GC, presence and type of organ involvement of SLE, concomitant diseases and concomitant medications affecting bone metabolism. Bone mineral density (BMD) (T-score, g/cm2) and presence of fragility fractures were also evaluated.
Results: One hundred and thirty-eight patients (F127, M11, mean disease duration 18±8 years, mean follow-up 13±7,8 years, mean age 46,8±12,8 years) were included in our analysis. All had been treated with GC, at a mean daily dose of 5,4±2,3 mg, with a mean cumulative dose of 30,4±19,9g. Ninety patients had a history of arthritis, 82 of glomerulonephritis, 35 of central nervous system involvement and 98 of cutaneous involvement. Twenty-seven patients (19,6%) had been treated with anticoagulants (AC), 124 (90%) with Hydroxychloroquine and no one had been treated with GnRH. The mean BMI value was 23,4 Kg/m2 and 36 of them (26%) were smokers; 54 (39%) had a thyroid disorder and 55 women (43%) were in post-menopausal status. Thirty-six patients (26%), 30F and 6M, had a diagnosis of OP (T-score≤-2.5SD). Thirteen women (9,4% of all patients and 36% of patients with OP) had at least one fragility fracture. Four patients (31%) fractured in pre-menopausal status, 9 (69%) had a thyroid disorder (5 Hashimoto's thyroiditis and 4 multinodular goiter) and 6 (46%) had been treated wIth AC. Fractures developed at a mean age of 53,4±9,4 years, after a mean disease duration of 16±7,9 years, after a mean cumulative GC dose of 26,5±9,4g. Fractures showed a correlation with age ($p < 0{,}0001$), disease duration and total amount of GC ($p < 0{,}01$), postmenopausal status (p=0,03), therapy with AC (p=0,01) and thyroid dysfunctions (p=0,01).
Conclusions: The analysis of our cohort shows a prevalence of OP of 26% and a prevalence of fragility fractures among OP patients higher than 30%. Age, postmenopausal status and chronic therapy with GC (although at low mean daily doses) represent, as expected, relevant risk factors for their development. Interestingly, almost one third of fractured patients had at least one fracture in premenopausal status; besides, the presence of fractures was significantly associated with both thyroid disorders and therapy with AC. Thus, these results underline the importance of OP screening in patients with SLE in chronic therapy with GC, with particular attention to those treated with AC or with a thyroid dysfunction.

P070

Lupus risk and age of onset related to smoking

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Background: Environmental factors are clearly important for the development of systemic lupus erythematosus (SLE). We sought to determine the role of cigarette smoking as an etiological factor among a large cohort of SLE patients.
Methods: We studied 1519 patients with SLE, all of whom met the 1997 revised American College of Rheumatology SLE classification criteria, as well as 821 unrelated non-SLE controls, all of whom were confirmed to not meet the classification criteria. On a standardized questionnaire all patients answered the question 'Have you ever smoked cigarettes'. Age of onset of disease was determined by questionnaire, patient interview and medical record review.
Results: We assessed smoking as a risk factor for SLE. 821 SLE patients were matched to 821 controls for age, sex and ethnicity. The odds ratio for smoking among the SLE patients compared to the controls was 1.27 ($\chi 2=5.18$, p=0.02 by the McNemar test). Next, we evaluated the effect of smoking on age of onset of SLE. First, we compared smokers to non-smokers using the entire cohort of 1519 SLE patients. The average age of onset among the smokers was 37.7 years (standard deviation=12.7 years), while age of onset averaged 32.6 years (standard deviation=13.3) among the non-smokers ($p < 0.0001$ by the Student t test, 95%CI 3.75-6.38). We also matched smoking SLE patients to non-smoking SLE patients for age, sex, and ethnicity. This analysis showed an average age of onset among 611 smokers of 36.5 years (SD=12.3) and only 34.9 among the 611 matched non-smoking SLE patients ($p < 0.026$, 95%CI 0.2-3.0).
Conclusions: In this large cohort of SLE patients we found smoking was a risk factor for disease. The magnitude of this risk was similar to those for many common population polymorphisms found with genome-wide genetic association studies. However, while a risk factor, smoking was associated with a older age of onset even with matching for age, although less significantly.

P071

Systemic Lupus Erythematosus Patients on Hemodialysis Have a High Rate of vascular Access Loss

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Introduction: The loss of vascular access is among the major complications in patients with renal replacement therapy (RRT). The aim of this study was to evaluate the frequency of aertiovenous fistula loss and to determine the factors associated to this finding in our cohort of SLE patients under RRT.
Methods: We performed a retrospective analysis of the charts of all SLE (ACR 1997 criteria) patients under RRT for more than six moths at our Institution between February 1992 and December 2011. We defined the loss as primary, when the occlusion occurred before the first course of treatment; and as secondary when it occurred during RRT. Averages ± SD were used for descriptive analysis and Student's T test applied to evaluate the statistical differences among the groups.
Results: Fifty-one patients (48 females) received RRT in the period (48 hemodialysis and 3 peritoneal dialysis). The current ages and at SLE diagnosis were 42±11 and 25±10 years old, respectively. The average SLICC score was of 5±3 and 10 patients presented HCV infections. The average follow-up time was of 91±52 months, with loss to follow-up of three patients and eight deaths. A total of 109 arterio-venous fistulas were performed (103 autologous grafts and 6 synthetic; average 2±2 per patient). There were 20 patients with vascular access loss (41.7%); 36 primary and 21 secondary losses. Three patients (6.3%) also had APS (Sapporo's criteria). When the group with vascular access loss was compared to those with no vascular access loss, there was no difference in the incidence of type I diabetes (p=0.323), dyslipidemia (p=0.743) and severe hyperparathyroidism (p=0.141), but curiously, systemic arterial hypertension was more common in the group with no loss (p=0.007).
Conclusion: SLE patients on RRT of our cohort have a higher prevalence of vascular access loss when compared to patients with essential hypertension, that have 60-80% patency in five years of follow-up. It is possible that in addition to the classic features related to vascular access loss (early utilization, hypotension and deep vein catheter), the persistent inflammatory state of the vessel wall, may have contributed to the worse outcome seen in our SLE patients.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 6 Clinical Aspects"

Atlantico A+B+C

P072

Adjusted Framingham Risk Factor Scoring for Systemic Lupus Erythematosus: Results from an Inception Cohort Followed for Eight Years

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Background/Purpose: There is a high prevalence of premature atherosclerosis among patients with SLE, with a risk 7-9 times that of the general population. The traditional Framingham risk factor underestimates the risk for coronary artery disease (CAD) in patients with SLE. It has been suggested that a modified Framingham risk score (FRS) where each item is multiplied by 2 more accurately identifies patient at Moderate/High risk of CAD, and more accurately predicted subsequent CAD. The aim of this study was to determine whether the modified FRS (mFRS) more accurately reflected the prevalence of CAD(MI, angina, pacemaker) among patients in an inception cohort.
Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. Only patients with all variables necessary to calculate the FRS at enrolment and who did not have diabetes mellitus were included in this analysis. Patients are followed at yearly intervals according to a standard protocol which included demographics, disease characteristics and classic risk factors for CAD as well as CAD events. Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate Sensitivity and Specificity (95% CI) of FRS and MFRS were evaluated in their prediction of future CAD.
Results: At enrolment 853 patients had sufficient data to calculate FRS. Of these, 140 patients had 8 years of follow-up available. 85% female, 50% Caucasian, 11.4% Black, 20.7% Asian 16.4% Hispanic and 1.4% other. 13.6% were current smokers, 22.2% past smokers. Age at diagnosis was 34.2 yrs and disease duration at enrolment was 5.0 mos. BMI was 24.4, and 25.7% were obese. 35%, were hypertensive and 42% had hypercholesterolemia. The 140 patients did not differ from those not followed for 8 years in either demographic features, disease characteristic, atherosclerotic risk factors. Table shows the calculated classic FRS and mFRS for the 140 patients.

Risk Category	*Classic FRS Number*	*Classic FRS %*	*Modified FRS Number*	*Modified FRS %*
Very low risk	133	95	112	80
Low risk	2	1.4	6	4.3
Moderate risk	2	1.4	6	4.3
High Risk	3	2.1	16	11.4
Moderate + High	5	3.5	22	15.7

Of the 140 patients 14 subsequently developed CAD, 8 of which are attributed to AS. The sensitivity of the FRS for CAD due to AS was 25.0 (3.2, 65.1) and specificity 97.7 (93.5, 99.5), whereas for the mFRS the sensitivity rose to 50.0 (15.7, 84.3) while the specificity decrease slightly to 86.4 (79.3, 91.7)
Conclusion: The mFRS, where each item is multiplied by 2, more accurately identifies patients at Moderate/High Risk of CAD. It provides higher sensitivity with little loss in specificity. Therefore the mFRS could be used to identify SLE patients for more intensive risk factor modification.

P073

Suppression of inflammation reduces endothelial microparticles in active systemic lupus erythematosus.

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Background: Systemic Lupus Erythematosus (SLE) is associated with endothelial dysfunction and an increased cardiovascular risk, in part due to inflammatory disease activity. Endothelial microparticles (EMPs) are membrane-bound subcellular particles produced by endothelial cells in response to activation triggers. EMPs reflect endothelial damage and may correlate with measures of endothelial function. In a prospective observational study, we investigated whether patients with active SLE had higher indices of endothelial damage and dysfunction compared to healthy controls, and whether improved disease control was associated with improvement in these indices.
Methods: Twenty-seven patients (mean (SD) age 41.5 (14.1) yrs) with active SLE (≥4 ACR criteria) and 22 age-matched controls (mean age (SD) 38.5 (9.3) yrs) were assessed. EMPs were quantified (number/ml) using flow cytometry after incubating platelet-poor-plasma with the cell surface markers CD31, CD42b and Annexin-V. Events positive for annexin-V and CD31, and negative for CD42b, were classified as EMPs. Brachial artery flow-mediated dilatation (FMD) was measured using 2D ultrasound and automated edge-tracking software. Twenty-two patients were re-assessed after initiating new immunosuppressive therapy (median (IQR) interval 20 (16, 22) weeks) and disease activity (BILAG 2004 and SLEDAI 2K) was recorded at each visit. Continuous data were compared using Mann-Whitney test, and Spearman's Rank was used to correlate EMP levels with FMD (%).
Results: At baseline, median (IQR) global BILAG 2004 score was 14 (12, 22) and SLEDAI-2K was 6 (5, 13) in SLE patients. EMPs (n/ml) were significantly elevated in the SLE cohort (median (IQR) 157,548/ml (59,906, 272,643) vs. 41,025 (30,179, 98,082); $p = 0.003$). Endothelial-dependent FMD was also significantly reduced in SLE patients (median (IQR) FMD 1.63% (-1.22, 5.32) vs. 5.40% (3.02, 8.57); $p = 0.05$). EMPs were negatively correlated with FMD (%) (r2 -0.42; $p = 0.008$). In a multiple regression model including SLE, age, blood pressure, total cholesterol, plasma glucose and renal function, SLE was independently associated with EMP levels (n/ml) (B coefficient 145 (29, 260), $p = 0.02$). In the 22 SLE patients who were re-assessed, disease activity improved significantly (median (IQR) change in global BILAG-2004 score -11 (-18, -3)). EMP levels were reduced (166,982/ml (59906, 278,775 vs. 55,655 (29475, 188,659; $p = 0.02$) and FMD improved (0.33% (-2.31, 4.1) vs. 3.19% (0.98, 5.09); $p = 0.1$) over time. There was a moderate correlation between change over time in EMP count (%) and change in global BILAG 2004 score ($r2 = 0.40$ $p = 0.08$) in SLE patients.
Conclusions: Active SLE is associated with evidence of increased endothelial damage and endothelial dysfunction that improved with suppression of inflammation. Better control of active inflammatory disease may contribute to improved cardiovascular risk in SLE patients.

P074

Discoid Lupus Onset and Decrease Risk of Renal Disease in Patients with Systemic Lupus Erythematosus: Data from a Large Latin American Cohort

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Introduction: It has been reported that between 15 and 30% of patients with SLE have discoid lesions, and between 10 and 30% of patients with discoid lupus erythematosus (DLE) will develop SLE, with early progression in 70% of them. Clinical observation and data from small selected series suggest that when patients with DLE progress to SLE, they rarely have renal involvement. However, no studies have been conducted in longitudinal cohorts with large number of high-risk individuals. Using data from a large Latin-American multi-ethnic cohort, we examined whether DLE as a disease onset manifestation (DLE-onset) is a protective factor for lupus nephritis (LN) in patients who develop SLE.

Methods: The GLADEL's (Grupo Latino Americano De Estudio de Lupus) longitudinal inception cohort comprises SLE patients with a recent diagnosis (less than 2 years) from 34 centers in nine Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Perú and Venezuela). Board certified rheumatologists collect data on disease onset manifestations as well as clinical features that occur at or after the diagnosis of SLE. DLE-onset was defined as the presence of DLE before a diagnosis of SLE was established. LN was defined by: (1)ACR criterion (persistent proteinuria or the presence of cellular casts); or (2)renal biopsy demonstrating World Health Organization (WHO), class II–V histopathology; or (3)serum creatinine >2.0mg/dl. Multivariate logistic regression analysis was conducted to determine the odds ratio (OR) and 95% confidence intervals (95% CI) of LN in patients with DLE-onset, while controlling for the effect of sociodemographic factors.

Results: Out of 1480 GLADEL patients, 144 (9.7%) had DLE-onset and 773 (52.2%) developed LN at or after the diagnosis of SLE. Table 1 depicts the features of these patients as a function of LN, whereas Table 2 shows the multivariate logistic regression model for DLE-onset and sociodemographic factors associated with LN.

Conclusion: Our data from the largest Latin-American cohort of SLE patients supports previous clinical observations of the protective role of discoid lupus on the occurrence of LN. The risk of LN among SLE patients who had DLE-onset was 52% lower than among those without DLE-onset. The protection conferred by DLE was independent of other known risk factors, such as younger age, male gender, mestizo ethnicity and public medical coverage. Further studies are warranted to determine the potential pathways implicated in this association.

Table 1. Socio-demographic characteristics in SLE patients* as a function of LN

Features	*LN Yes (n= 773)*	*LN No (n= 707)*	*p-value*
Age at diagnosis, years (mean + SD)	27.9+11.7	31.3+12.7	<0.0001^
Gender			
Male	94 (62.7)	56 (37.3)	0.0070^^
Female	651 (48.9)	679 (51.1)	
Ethnic group			
Caucasian	283 (46.7)	323 (53.3)	
Mestizo	370 (57.4)	275 (42.6)	0.0010^^
African-Latin American	92 (49.5)	92 (50.5)	
Residence			
Urban	683 (51.2)	651 (48.8)	0.0080
Rural	85 (63.4)	49 (36.6)	
Socioeconomic Status			
Upper/upper-middle	54 (35.5)	98 (64.5)	
Middle	210 (49.2)	217 (50.8)	<0.0001^
Lower-middle/lower	509 (56.5)	392 (43.5)	
Education, years			
0-7	262 (55.9)	207 (44.1)	
8-12	352 (53.0)	312 (47.0)	0.015^^
>12	159 (45.8)	188 (54.2)	
Medical insurance			
Public	667 (56.2)	519 (43.8)	<0.0001^
Private	97 (34.8)	182 (65.2)	

*Except where indicated otherwise, values are the number (%) of patients; ^ t-test; ^^ Pearson Chi2

Table 2. Protective effect of DLE at onset on LN, while controlling by sociodemographic factors

Predictor factors	*OR*	*95% CI*	*p-value*
DLE at onset	0.48	0.33-0.70	<0.0001
Age at diagnosis, years	0.98	0.97-0.99	<0.0001
Gender (male)	1.58	1.10-2.26	0.0130
Ethnic group			
Caucasian		Reference group	
Mestizo		1.20-1.91	<0.0001
African-Latin American		0.75-1.49	0.7700
Medical Insurance (Public)		1.10-2.26	<0.0001

P075

Supervised physical exercise improves endothelial function but not the numbers of endothelial progenitor cells in patients with systemic lupus erythematosus.

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Background: disturbances in endothelial function (EF) are implicated in cardiovascular disease in systemic lupus erythematosus (SLE) and EF also depends on endothelial progenitor cells (EPCs) that enhance angiogenesis, promote vascular repair and have potential as a marker of cardiovascular disease. SLE patients have endothelial dysfunction

and fewer EPCs. The **objectives** of this study are to evaluate the effect of supervised physical exercise on EF, number of EPCs and on endothelium derived growth factor (VEGF) levels in SLE patients.
Patients and Methods: it is a prospective, non-randomized study, in which women with SLE (18 to 45 years old) with availability to perform the proposed physical exercise program were allocated in exercise group (EG) and those who were not available were allocated in the control group (CG). Intervention consisted of walking at speed of the ventilatory threshold-1 heart rate obtained from cardiopulmonary exercise test and monitored by frequency meter for one hour, three times a week, for 16 weeks. At baseline (T0) and after 16 weeks (T16), patients were assessed for endothelial function by brachial artery ultrasonography and flow-mediated dilation (FMD), EPCs were assessed by flow cytometry (CD34 FITC, CD133 PE and KDR APC) and VEGF by ELISA. Parametric and non-parametric tests were applied according the normality distribution of the variables. $P < 0.05$ was considered significant.
Results: Eighteen patients were allocated in EG and 20 in CG. The two groups were homogeneous and comparable regarding demographic and clinical variables. The mean age was 33.2±7.8 years and the mean disease duration was 94.2±80.5 months. After 16 weeks, there was an increase in FMD in EG (6.3±6.7% vs 14.1±9.1%, p=0.006), with no change in nitroglycerin-induced dilation (20.9±6.1% vs 24.3±7.9%, p=0.147). In the CG we observed no change in FMD (8.4±8.2% vs 9.4%±5.7%, p=0.598) neither in the nitroglycerin-induced dilation (26.7±7.1% vs 26.1±7.0%, p=0.985). Concerning the number of EPCs, fifteen patients in each group were evaluated and, at baseline and after 16 weeks, no difference was found in the two groups: EG [median 0.0078% (0 to 0.1230%) vs. 0.0037% (0 to 0.0300%); p=0.112], CG [0.0044% (0 to 0.2470%) vs. 0.0039% (0 to 0.0500%), p=0.394]. There was no difference at baseline and after 16 weeks in VEGF levels in EG (381.0±269.2pg/ml vs 320.3±236.8pg/ml, p=0.102) neither in the CG (393.4±213.2pg/ml vs 361.7±188.0pg/ml, p=0.619).
Conclusion: this is the first study demonstrating that physical exercise improves endothelial function which can be a useful strategy to prevent cardiovascular disease morbidity and mortality in SLE patients. This improvement seems not related to an increase in EPCs number or in VEGF levels.

P076

Premenopausal Systemic Lupus Erythematosus Women: High Incidence of One-year Bone Loss

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Introduction: Systemic Lupus Erythematosus (SLE) is associated with high risk of low bone mass and fractures. Data on prospective longitudinal bone loss is scarce in this disease and the only available report evaluating solely pre-menopausal women has not taken into account the least significant change of the method which may hamper the interpretation of the finding. The aim of this study was, therefore, to determine prospectively the one year incidence of bone loss and fractures in premenopausal lupus patients and the possible relevance of disease related factors and bone markers [RANKL and osteoprotegerin (OPG)].
Methods: Sixty four premenopausal SLE patients were enrolled. Exclusion criteria were renal impairment and ever use of bone active drugs. Clinical, laboratorial and densitometric evaluations were performed at baseline and after one year. Bone mass was assessed by dual-energy x-ray absorptiometry (DXA) at lumbar spine (LS), femur (F) and whole body (WB). Bone loss or gain were defined as measured bone mass change above the least significant change (LSC) in each site (LS: 3.3%, total F: 3.9%, WB: 3.0%). Vertebral fracture assessment by DXA was analyzed by Genant method. RANKL and OPG serum levels were determined by ELISA.
Results: Patients had mean age of 30.9±6.9y, disease duration of 5.2±3.8y. At baseline, low bone mass for chronological age (Z-score≤-2) was found in 25% and grade 1 vertebral fractures in 20% of patients. After one year, 40.6% of patients had bone mass loss and 20.3% had gain. Higher maximum GC daily dose was observed in patients with bone loss at LS (29±20vs. 7±10mg, p=0.008), total F (39±18vs. 8±10mg, p=0.024) and WB (35±18vs. 10±11mg, p=0.027) compared to patients with gain. Patients with LS bone loss also had higher one-year cumulative (5.1±3.4vs. 0.9±1.6g, p=0.003) and mean (12±8vs. 2±4mg, p=0.003) GC dose compared to patients with gain. At baseline OPG and RANKL levels were alike in patients with and without bone loss ($p > 0.05$). The one-year evaluation revealed lower OPG levels in patients with bone loss in LS (4.73±1.6vs. 6.48±2.24pmol/l, p=0.04) and WB (4.1±0.6vs. 6.23±0.95pmol/l, p=0.01) compared to patients with gain. RANKL levels were higher in patients with WB bone loss (0.42±0.32vs. 0.05±0.1pmol/l, p=0.046) compared to patients with gain. In logistic analysis, patients with bone loss in LS and WB had higher maximum GC daily dose ($p < 0.05$), but not lower OPG or higher RANKL levels compared to patients with gain. One patient had a new grade 1 fracture. No difference was observed concerning SLEDAI or SLICC.
Conclusion: This study provides clear evidence of high frequency one-year bone loss affecting trabecular and cortical bone in premenopausal lupus women associated with high GC daily dose. OPG and RANKL levels do not seem to have a predictive value but rather reflect the overall bone loss.

P077

High-Density lipoprotein subclasses and its associations with Disease Activity and Coronary-Artery Calcification in patients with Systemic Lupus Erythematosus (SLE).

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Introduction: Changes in conventional lipid profile partially explain the presence of coronary heart disease (CHD) in SLE patients. We examined whether measurement of high-density lipoprotein (HDL) particle subclasses provides additional information relative to factors associated with coronary-artery calcifications in an inception prospective cohort for the study of atherosclerosis.
Methods: Whole cohort was composed by 139 patients (93% females) with SLE of recent-onset at enrollment, w/o preexisting coronary heart disease. At enrollment, a standardized medical evaluation was done assessing lupus characteristics, medications, cardiovascular risk-factors, and laboratory tests (lipid profile, homocystein, hsCRP, autoantibodies). Patients were seen every 3-6 months, and assessed for disease activity and medications. Every year, information was updated and a blood sample drawn. At 5.5+2.9 years of follow-up, all the 139 patients were screened for coronary-artery calcifications using a 64-slice Multidetector Computed Tomography.

For this study, a nested analysis of lipids was conducted among all lupus patients with calcifications and a random sample without calcifications (ratio 1:4), matched for age, sex and disease duration. Measurements were done in samples drawn at enrollment, mid follow-up, and at screening: total cholesterol, cHDL, cLDL, triglycerides, Lp(a) lipoprotein, and Apo B; HDL size distribution and plasma concentrations were determined by lipid and protein content using an enzymatic cholesterol staining method in a polyacrylamide gradient gel

electrophoresis. Also, fasting levels of homocystein, and hsCRP were determined at enrollment and at screening.
Results: Coronary-artery calcifications were detected in 10 patients (7.2% of cohort), 40 matched SLE patients w/o calcification were randomly selected as controls. In comparison to patients w/o calcifications, patients with calcifications had higher baseline homocysteine, LDL cholesterol, Apo-B and Lp(a) levels. There were not differences at screening. Disease activity along the course of lupus was higher, median (range) (SLEDAI-2K Adjusted mean, 7.2 (1.6-10.8) vs 4.4 (0.6-10.9), P=0.05). Cumulative doses of prednisone and cyclophosphamide were higher ($P < 0.05$), but use of antimalarials lower (20% vs 70%, P=0.004). There were not differences in the use of aspirin, statins and fibrates. Longitudinal analyses of HDL subclasses showed an increase concentration of smaller size HDL subclass (HDL3c), 26.6% vs 30.4%, 33.9% vs 27.4% and 37.9% vs 27.7% when measured at enrollment, mid follow-up and at screening in patient with coronary-artery calcification vs patients w/o calcifications, ($P < 0.05$).
Conclusions: In this exploratory study, disease activity and an longitudinal increasing of small size HDL subclasses concentration were associated with coronary-artery calcifications in patients with SLE. Further studies are needed to confirm the clinical relevance to measure HDL subclasses in these patients.

P078

Comparing the Physicians Diagnosis and the SLICC Criteria for the Classification of SLE Patients Using Data from a Multiethnic Latin American Cohort

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Background/Purpose: The Systemic Lupus International Collaborating Clinics (SLICC) group classification criteria an instrument designed to improve the classification/diagnosis of SLE patients. The aim of our study was to determine whether these criteria might have helped physicians to perform an earlier diagnosis in a well-characterized SLE cohort.
Methods: SLE patients with a recent diagnosis (less than 2 years) from 34 centers in nine Latin American countries have been recruited into a longitudinal inception cohort. Board certified rheumatologists collected data on disease onset manifestations as well as clinical features that occurred at or after the physician-diagnosis of SLE. Fulfillment of 4 American College of Rheumatology (ACR) 1982 SLE criteria at the time of diagnosis was not mandatory, although 95.6% of the entire cohort fulfilled 4 or more criteria's during the course of the disease. Some SLICC criteria could not be applied (toxic epidermal necrolysis and some chronic forms of cutaneous lupus). To perform this study we used the physician's diagnosis date and we compared it with the one derived from the fulfillment of the SLICC criteria in order to study if these criteria were met before, at the same time or after physician's clinical diagnosis.
Results: Of the 1422 patients that comprise this cohort the 733 (49.5%) could be classified at the same time than the physician with the SLICC criteria; 432 could be classified earlier (29.2%) and 257 (17.4%) later compared to the physician's diagnosis; 58 patients were excluded because of missing dates for some of the SLICC criteria. Of the patients diagnosed before using the SLICC criteria, the majority did so because of the combination of acute cutaneous lupus, oral ulcers, arthritis, renal involvement, hemolytic anemia, leukopenia, ANA, anti Sm and low complement. Table 1 show the distribution of the physician diagnosis and SLICC criteria among all 3 groups.
Conclusion: Compared to experienced clinicians, the SLICC criteria allowed the classification of patients earlier in the course of their disease; this has implications for the conduct of longitudinal observational studies and clinical trials.

Table. SLICC criteria as a function of fulfillment of physician and SLICC criteria for diagnosis of SLE

SLICC criteria	*Group I SLICC criteria met later (%) N=257*	*Group II SLICC criteria met earlier (%) N=432*	*Group III SLICC criteria met at the same time (%) N=733*	*p-value*
Clinical criteria				
Acute cutaneous lupus	19.8	50.9	29.3	0.005
Chronic cutaneous lupus	21.7	50.5	27.8	NS
Oral ulcers	21.3	49.5	29.2	0.019
Nonscarring alopecia	17.2	51.7	31.1	NS
Artritis	18.7	50.2	31.1	0.067
Serositis	20.0	51.4	28.6	NS
Renal involvement	20.6	51.7	27.8	0.011
Neurologic involvement	18.9	46.7	34.4	NS
Hemolytic anemia	13.8	60.2	26.0	0.040
Leukopenia	19.4	51.5	29.1	0.044
Thrombocytopenia	19.7	48.3	32.0	NS
Immunologic criteria				
ANA	16.9	52.4	30.7	0.015
Anti-dsDNA	18.7	52.5	28.7	NS
Anti-Sm	15.5	55.6	28.9	0.0001
Antiphospholipid antibody	19.8	48.6	31.7	NS
Low complement	19.8	51.9	28.5	0.038
Direct Coombs' test	18.1	55.7	26.2	NS

P079

RNA-sequencing does not identify stimulation of inflammation or autoimmunity after Herpes Zoster vaccination in systemic lupus erythematosus (SLE) patients

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Background: SLE patients have increased risk of Herpes Zoster (HZ). A live-attenuated vaccine is available for healthy persons, but its safety in immunocompromised individuals is unknown. Two areas of possible concern regard the development of HZ-like lesions at the injection site, and increased disease activity following immune stimulation from an immunogenic vaccine. We sought to evaluate gene expression profiles between SLE patients and matched healthy controls to identify any potential increase in disease activity or immune system activation.

Methods: We performed a pilot open-label of HZ vaccine in 10 SLE patients with low disease activity and 10 healthy, matched (age, race, sex) controls. Peripheral blood was obtained at baseline, than at weeks 2, 6, and 10 following vaccination. Safety outcomes included vaccine-induced HZ or flare of underlying SLE following vaccination. Whole-blood RNA was collected in Tempus tubes to study early changes in immune related pathways at baseline and 2 weeks post-vaccination in a subset of 5 SLE patients and control pairs. RNA was extracted, globin transcripts was depleted, and sequence libraries were prepared using the NuGEN Encore complete kit. RNA-sequencing was done using an Illumina HiSeq 2000 with the resulting FASTQ files aligned to the human genome using STAR. DEseq was used to determine differential expression of RNA transcripts. Comparisons were made between the baseline and 2-week expression levels of the SLE cases (and healthy controls). The SLE cases expression levels were also compared to the healthy controls at both baseline and 2-weeks post-vaccination visits.
Results: No subjects developed vaccine-induced HZ during the 12 weeks of the study. SLE patients had quiescent disease at baseline, and no clinical flares were noted. RNA-seq expression showed no difference between baseline and the 2-week post-vaccination blood draws in either the SLE cases or the healthy controls. When comparing the baseline samples of the SLE cases to the healthy controls, we identified 158 differentially expressed genes including several that are known to be interferon-inducible (ADAR, AGRN, MX2, IL1RN, TDRD7, NM1, CEACAM1, and SERPING1 among others with $p < 4x10E-3$). These genes mapped to pathways involved in immune response (p=5.2x10E-7), innate immune response (p=4.6x10E-6), inflammatory response (3.34x10E-5), and cell adhesion (3.66x10E-5) among others. However, the post-vaccination comparison between SLE cases and healthy controls yielded no statistically significant differentially expressed genes.
Conclusions: HZ vaccine did not lead to clinical flares, nor increase in systemic inflammation or autoimmunity following vaccination in SLE patients with quiescent disease. At baseline, pathways identified as differentially expressed were consistent with other expression studies of SLE. Interestingly, the loss of the differential expression differences at 2 weeks post-vaccination indicates that the controls have responded to the vaccine and become indistinguishable from the SLE cases. Future studies in larger samples sizes are needed to confirm these results.

P080

The Number of Flares SLE Patients Experience Impacts on Damage Accrual: Data from a Multiethnic Latin American Cohort

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Background: The possible impact of the number of flares patients experience on damage accrual in Systemic Lupus Erythematosus (SLE) has not been previously examined.
Purpose: To determine if the number of flares a patient experiences is associated with damage accrual in SLE patients, independently of other known risk factors.
Methods: SLE patients from 34 centers in nine countries in Latin America with a recent diagnosis (≤2 years, ACR criteria fulfillment was not required) and with at least 3 evaluations were included in these analyses. Disease activity was ascertained using the SLEDAI. Flare was defined as an increase of at least 4 points in the SLEDAI between two study visits. Disease damage was ascertained using the SLICC/ACR damage index (SDI). The association between the number of flares and the SDI was evaluated using a lineal regression model adjusting for gender, age at diagnosis, years of education, socioeconomic level, disease duration, baseline SDI, baseline SLEDAI, adjusted mean SLEDAI, and the use of corticosteroids, immunosuppressors, and antimalarials. Statistical analyses were performed using the SPSS v. 16.0
Results: Nine hundred and one patients were included in this study; they had an average age at diagnosis of 28.9 (SD: 12.0) years; 809 (90.8%) were females and their mean follow-up was 5.1 (SD: 1.9) years. The baseline SDI was 0.9 (SD: 1.2), the baseline SLEDAI was 12.5 (SD: 7.8), the adjusted mean SLEDAI was 5.4 (SD: 4.8). The average SDI increase was 0.9 (SD: 1.3); 414 (45.9%) patients increased at least one point in the SDI; the average number of flares was 0.9 (SD: 1.0), and 500 (55.5%) patients presented at least one flare. The number of flares was associated with damage accrual (SDI) in the univariate analysis (β: 0.33 (95% CI: 0.35-0.52), $p < 0.001$); this association remained significant in the adjusted model (β: 0.20 (95% CI: 0.18-0.36); $p < 0.001$).
Conclusion: The number of flares a patient experiences increased the risk of damage accrual in SLE patients, independently of demographic characteristics, treatment, baseline damage and baseline and average disease activity. Prevention of flares, and not only controlling disease activity, should be part of our goals in the treatment of SLE patients.

P081

Lupus disease activity severely impairs pandemic influenza A/H1N1 vaccine immune response in patients without therapy

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The aim of this study was to determine the influence of disease activity without the effect of drugs in pandemic 2009 influenza A (H1N1) vaccine immune response in untreated systemic lupus erythematosus (SLE).
Methods: SLE patients without therapy [n=75] and healthy controls [n=170] were vaccinated with a single dose of a nonadjuvanted A/California/7/2009/H1N1 vaccine. Clinical and laboratorial data, including disease activity scores (SLEDAI), were monitored prevaccination and 21 days postvaccination. Anti-H1N1 titres, percentages of seroprotection (SP), and seroconversion (SC) were evaluated.
Results: After immunisation, untreated patients with SLEDAI=0 [n=22] had comparable SP (86.4%; 95%CI 72.0-100.7; p=1.0) and SC (86.4%; 95%CI 72.0-100.7; p=0.57) to controls whereas untreated patients with any level of disease activity (SLEDAI > 0) [n=53] had lower SP (69.8%; 95%CI 57.4-84.4 vs. 84.1%; 95%CI 78.6-89.6; p=0.028) and SC rates (66.0%; 95%CI 53.2-78.7 vs. 80.0%; 95%CI 74.0-86.0; p=0.041) compared to controls. Reinforcing this finding, a

significant lower SP (37.5%; 95%CI 13.8-61.2 vs. 79.6%; 95%CI 69.3-89.9; p=0.008) and SC rates (37.5%; 95%CI 13.8-61.2 vs. 77.9%; 95%CI 67.3-88.5; p=0.016) were observed in untreated SLE patients with SLEDAI > 6 [n=16] compared with those with SLEDAI < 6 [n=59], in spite of a similar mean lymphocyte count (1,260 ± 625 vs. 1,480 ± 840/mm3; p=0.33). Untreated SLE patients with low lymphocytes (< 1,000/mm3) [n=21] had similar SP (61.9%; 95%CI 41.1-82.4 vs. 72.2%; 95%CI 60.2-84.1; p=0.41) and SC rates (57.1%; 95%CI 35.9-78.3 vs. 72.2%; 95%CI 60.2-84.1; p=0.27) compared to untreated SLE patients with levels within normal range (> 1,000/mm3) [n=54]. SLE patients with anti-dsDNA+ [n=42] had lower postvaccine SP (59.5%; 95% CI 44.6 to 74.3 vs. 81.8%; 95% CI 68.6 to 94.9; p=0.046) and SC rates (57.1%; 95% CI 42.1 to 72.1 vs. 81.8%; 95% CI 68.6 to 94.9; p=0.027) compared to SLE patients without this antibody (anti-dsDNA-) [n=33].

Conclusion: This study provides clear evidence that SLE disease activity severely impairs pandemic influenza H1N1 vaccine immune response independent of lymphocyte counts or drugs.

P082

Major bleeding complications following percutaneous renal biopsy in lupus nephritis patients with antiphospholipid antibodies.

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Background: Renal biopsy remains the gold standard investigation for both diagnostic and prognostic purposes in the management of lupus nephritis. It is not however without potentially significant complications. In this study we determined the rate of significant bleeding post renal biopsy and identified risk factors associated with haemorrhagic complications in lupus nephritis patients.

Methods: Clinical data was retrospectively reviewed following 215 renal biopsies performed in 199 lupus nephritis patients over a 12 year period (1999-2012). Patients were categorised into 3 groups: a diagnosis of SLE alone (n=80), SLE with coexisting Antiphospholipid Syndrome (SLE/APS) (n=48) and a diagnosis of SLE with either positive anticardiolipin antibodies and/or lupus anticoagulant without clinical antiphospholipid manifestations (SLE/APL) (n=87).

Major complications were defined as those who required post procedural intervention such as blood transfusion, surgical revision of hematoma, embolization, sepsis, nephrectomy or death. Minor complications included subcapsular hematomas, perinephric hematomas regardless of size or hematuria requiring close observation only.

Results: An overall bleeding rate of 14.8% was observed. 8.8% experienced minor bleeding and 6% developed major haemorrhagic complications. The rate of major bleeding was significantly higher in SLE/APS (11%) and SLE/APL (8%) than SLE alone (1%). Lupus anticoagulant, older age at time of biopsy (> 40 years) and elevated serum creatinine (> 400 umol/L) were independent risk factors for increased risk of bleeding (p=0.03, p=0.04 and p=0.03 respectively).

20% and 25% of patients in our study were taking warfarin or aspirin respectively, neither of which were associated with an increased risk of bleeding. Coagulation parameters including prothrombin time (PT) and activated partial thromboplastin time (APTT) did not differ significantly between bleeding and non-bleeding groups.

Renal thrombotic microangiopathy (TMA) was significantly more common in SLE/APS and SLE/APL than in SLE (p=0.008 and p=0.009 respectively). TMA and severe arterial fibrous intimal hyperplasia on renal biopsy were significantly more common in those who developed severe bleeding which may reflect an underlying vasculopathy predisposing to haemorrhagic complications.

Conclusions: The role of renal biopsy remains pivotal in the management of lupus nephritis. Based on the findings of this study, patients with SLE/APS, SLE/APL and TMA are at increased risk of bleeding post biopsy. Antiphospholipid antibodies should be checked in all SLE patients prior to renal biopsy to stratify their risk of developing post procedure bleeding complications. In this subset of at risk patients additional caution needs to be exercised pre and post biopsy. Similar precautions should be taken in those lupus nephritis patients with elevated serum creatinine, thrombocytopenia and those aged over 40 years of age.

P083

White matter lesions are predominantly demyelinating in systemic lupus erythematosus. An support vector machines classification of texture parameters

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Background: Texture analysis (TA) is a branch of image processing which seeks to reduce image information by extracting texture descriptors from the image. White matter hyperintensities (WMH) are frequently observed in systemic lupus erythematosus (SLE), however the etiology is still unknown. Ischemic and demyelination have been proposed as possible etiologies. Support vector machines (SVM) are a group of supervised learning methods that can be applied to classification or regression.

Objectives: To develop a classifier based on neural network to identify the etiology of WMH in SLE.

Methods: TA was applied to axial T2-weighted magnetic resonance images (MRI) of 30 SLE, 30 MS, and 30 stroke patients and 30 normal age and sex-matched controls. The TA approach used was based on the Gray Level Co-occurrence Matrices (GLCM).The WMH were manually segmented for each subject, classified in periventricular and subcortical WMH and 256 texture parameters were computed for each lesion. A SVM classifier was developed based on texture features of normal white matter and WMH in MS and stroke patients. The classifier was then used to classify WMHin SLE patients. Nature of the classified WMH, demographic, clinical and laboratory features were included in a regression model to determine which variables could support the possible nature of WMH in clinical practice.

Results: We achieve an accuracy rate of 0.93 to classify normal white matter and WMH in MS and stroke patients using SVM technique. Of the 37 periventricular WMH, 29 (78%) were classified as demyelination, 4 (11%) as ischemic and 4 (11%) as normal white matter. Of 53 subcortical lesions, 26 (72%) were classified as demyelination, 6 (11%) as ischemic and 9 (17%) as normal white matter. Age (odds ratio [OR] 1.7, 95% confidence interval ([95% CI] 1.58-6.72), hypertension (OR=2.6; 95%CI 1.9-5.3) and positive antiphospholipid antibodies (aPL) (OR=1.9; 95%CI 1.2-7.3) were variables associated with stroke, whereas shorter disease duration (OR=3.1; 95%CI 2.2-7.5) and new onset of neurologic symptoms (OR=1.8; 95%CI 1.2-3.5) were associated with demyelination.

Conclusions: Although 75% of WMH were classified as demyelinating in nature, we identified approximately 25% of ischemic WMH or normal white matter in SLE. SVM of TA is a useful method to help to determine etiology of WMH in SLE. Age, hypertension and aPL were variables associated with ischemic; shorter disease duration and new onset neurologic symptoms were associated with demyelinating lesions in this cohort.

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P084

Speed processing tasks and thalamic volumes in systemic lupus erythematosus

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Objectives: To evaluate the relationship between thalamic volumes and speed processing tasks in systemic lupus erythematosus (SLE).
Methods: We screened consecutive female SLE patients followed in a longitudinal cohort followed at the McGill Lupus Clinic. We excluded patients with any clinical factors associated with cerebral atrophy or vasculopathy, renal insufficiency (creatinine >200mmol/dl on 1 occasion), transient ischemic attack or stroke, scleroderma features, diabetes, drug abuse, or malignancy] or not educated primarily in English or French. Healthy age-matched women were selected as controls. Speed information processing was assessed with the stroop, trail making, finger tapping, and digital symbol tests and raw data and z-scores were used for analysis. Magnetic resonance imaging (MRI) was performed on a Siemens 3 Tessla scanner and volumetric T1 1mm thick slices were used for automatic segmentation of the thalamus. Atrophy of the thalamus was defined as a volume smaller than 2 SD of the control mean. The thalamic volumes and cognitive testing were compared between groups using the t-test. The pearson correlation was used to determine the correlation between individual cognitive tests and thalamic volumes.
Results: One hundred and twenty seven patients <50 years were screened, 52 fulfilled the inclusion criteria, and data are currently available on 27 (mean age 34.08, SD 8.85). Ten controls (mean age 33, SD 8.3) participated. We observed significantly smaller right (mean volume 6413.48mm3; SD 664.78) and left (mean volume 6380.85mm3; SD 680.99) thalamic volumes in SLE patients when compared to controls [mean right volume 7006.82; SD 523.00 (mean difference -593.33; 95% CI -118.85, -1067.83) and mean left volume 7019.42; SD 495.37 (mean difference -638.56; 95%CI -158.76, -1118.37)]. Bilateral thalamic atrophy was identified in 6 patients and unilateral left in 2 patients. Speed information processing was similar between groups, except for finger tapping, in which SLE patients had significantly poorer results (mean difference -38.02; 95%CI -32.45; -43.56). Right thalamic volumes correlated directly with the stroop test (pearson correlation (PR) 0.55; p 0.0001), trail making test (PR 0.487; p 0.02), digital symbol test (PR 0.35; p 0.044), and finger tapping test (PR 0.44; p 0.006). Left thalamic volumes correlated directly with the stroop test (PR 0.56; p 0.001), trail making test (PR 0.55; p 0.005), and finger tapping test (PR 0.460; p 0.04).
Conclusions: We observed significantly smaller thalamic volumes in SLE patients when compared to healthy age and sex matched controls; speed information processing was similar with the exception of finger tapping which was poorer in SLE patients. Performance of speed processing tasks correlated directly with thalamic volumes, even in patients without atrophy. Correlation between structural volumes and specific cognitive testing can help identify underlying structural central nervous system pathology and explain cognitive impairment in visually normal appearing MRIs.
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P085

Current Clinical Practices in SLE: Challenges and Opportunities to Improve Care

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Introduction: Systemic lupus erythematosus (SLE) is associated with significant morbidity and mortality. Although earlier diagnosis and appropriate treatment improves survival rates of patients with SLE, the assessment and management is challenging for most physicians due to its relapsing and remitting course and impact on several organ systems. This study's objective was to assess current clinical practices of rheumatologists, nephrologists, and primary care physicians (PCPs) compared to evidence-based recommendations in the SLE care to identify knowledge, competency, and practice gaps and barriers to improving patient care.
Material and Methods: A clinical practice assessment survey consisting of a series of case vignettes with 21 survey items launched on May 31, 2012. Participant responses were collected through October 31, 2012. The design, previously validated as a method to measure performance, included knowledge- and case -based, multiple-choice questions made available online via www.medscape.org to healthcare providers without monetary compensation or charge. Confidentiality was maintained and responses were de-identified and aggregated prior to analyses. The case vignettes and questions were based on current evidence-based recommendations for the assessment and management of patients with SLE.
Results: In total, 3215 physicians responded to the survey, including 681 rheumatologists, 384 nephrologists, and 1598 PCPs. When presented with a patient case scenario with sufficient data for making a diagnosis of SLE, many rheumatologists (26.5%), nephrologists (49.7%), and PCPs (55.6%) could not make the diagnosis. Considerable variation in SLE treatment selection was reported: only 44% of rheumatologists selected the correct initial therapy with high-dose nonsteroidal antiinflammatory drugs and about a third chose azathioprine. Nephrologists were equally divided between mycophenolate mofetil and cyclophosphamide (approx. 30% each) as their top choice. In another patient case with a 15-year history of SLE who was stable for the past 2 years and had stopped all her medications but presented with fatigue and rash, a large percentage of physicians recommended monitoring without any medication (51.1% of rheumatologists, 45.7% of nephrologists, and 55.3% of PCPs).Only about one-third of these physicians chose the appropriate step of short-course low-dose prednisone. Additionally, significant gaps were identified with respect to knowledge of mechanisms of action of available and emerging therapies, knowledge of clinical trial data on the efficacy and safety, and competence in evaluating and appropriately treating cardiovascular comorbidities in SLE. The greatest clinical challenges with respect to the management of patients with SLE reported by participants were "deciding which medication is best for a given patient" (45% - 65%) and "evaluating disease activity" (18% - 27%).
Conclusions: With the goal of improving physician practices and patient care, this assessment of healthcare providers' clinical practices identified knowledge and competency gaps among rheumatologists, nephrologists, and PCPs in several key areas in the assessment and treatment of patients with SLE. Further assessment of physicians after participating in educational interventions is planned to demonstrate improvement in clinical practice.

P086

Atherosclerotic Vascular Events in a Multinational Inception Cohort of Systemic Lupus Erythematosus: Incidence Over a Ten Year Period

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Background/Purpose: A large multicentre multinational inception cohort was established to study risk factors for atherosclerosis (AS)

in SLE. The purpose of this study was to determine the incidence of vascular events during a 10 year follow-up and their attribution to AS.
Methods: An inception cohort of SLE patients from 31 centres from 12 countries has been assembled according to a standardized protocol between 2000 and 2012 to study risk factors for atherosclerosis. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Vascular events (VE) are described and attributed to SLE and AS on a specialized form. Events recorded include myocardial infarction (MI), angina, congestive heart failure (CHF), intermittent claudication (PVD), stroke, transient ischemic attack (TIA). Diagnosis of an event was confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to AS was made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. The incidence of VE was calculated over the 10 years for all VE occurring after diagnosis, and then for atherosclerotic VE (AVE). Kaplan-Meier curves were used to estimate the cumulative incidence rates since SLE diagnosis
Results: Since 2000 1844 patients have been entered into the cohort (88.9%F, age at SLE 34.7y). Caucasian 49.2%, Black 16.5%, Asian 14.9%, Hispanic 15.3%, other 4.1%. Thus far there have been 157 VE in 115 patients after the diagnosis of SLE. These include: MI (14), angina (26), CHF (36), PVD (11), TIA (27), stroke (38), pacemaker insertion (5). 64 of the events were attributed to active lupus and 44 to other causes or missing. 49 events in 37 patients were attributed to AS including: MI (8), angina (19), CHF (6), PVD (6), TIA (5), pacemaker (3), stroke (2).

Table 1. Spearman Correlation Coefficients (p value) between Accelerometer-based Measures and Selected Covariates (n = 92)

	Accelerometer counts	*Accelerometer non-sedentary min*	*Accelerometer light min*	*Accelerometer MVPA min*	*Accelerometer MVPA min in Bouts*
FSS	-0.24 (0.02)	-0.17 (0.10)	-0.10 (0.36)	-0.28 (0.007)	-0.33 (0.002)
PROMIS-Fatigue	-0.17 (0.11)	-0.17 (0.10)	-0.13 (0.23)	-0.21 (0.04)	-0.25 (0.02)
PROMIS-Anxiety	-0.06 (0.55)	0.0002(>0.99)	0.05 (0.62)	-0.04 (0.70)	-0.06 (0.58)
PROMIS-Pain	-0.40 (<0.0001)	-0.27 (0.01)	-0.18 (0.08)	-0.43 (<0.0001)	-0.38 (0.0002)
PROMIS-Depression	-0.15 (0.15)	-0.09 (0.37)	-0.06 (0.60)	-0.18 (0.09)	-0.19 (0.07)
PROMIS-Sleep disturbance	-0.10 (0.34)	-0.13 (0.22)	-0.12 (0.26)	-0.15 (0.15)	-0.17 (0.11)
PROMIS-Sleep impairment	-0.08 (0.47)	-0.12 (0.25)	-0.12 (0.25)	-0.06 (0.58)	-0.10 (0.36)

Conclusion: Over the follow-up of an inception cohort with SLE there were 157 vascular events of which 49 were attributable to AS. The incidence of AVE increased by 0.5% per year reaching a total of 4.4% at 10 years.

P087

Headache as manifestation of central nervous system involvement in systemic lupus erythematosus

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Background: A vast range of neuropsychiatric (NP) manifestations have been described in patients with systemic lupus erythematous (SLE). Headache have a high prevalence in the general population, and thus the attribution is exceedingly difficult to establish, leading to doubts as to whether it is a true manifestation of central nervous system (CNS) involvement in SLE.
Aim: Evaluate whether there is a characteristic inflammatory profile in cerebrospinal fluid (CSF) of patients with headache as CNS manifestation of SLE.
Methods: We conducted a post-hoc analysis focusing on headache from data published previously. Seven patients with headache and 27 patients with other NP manifestations attributed to SLE by a multidisciplinary group, according to the ACR nomenclature and case definitions for neuropsychiatric lupus syndromes. Manifestations were attributed to SLE based on the absence of exclusion factors for the attribution of the NP manifestations. The patients had been hospitalized because of NP manifestations and were evaluated at hospitalization and 6 months later; a CSF sample was obtained at each evaluation. As controls, CSF from 16 SLE patients with no history of NP manifestations (non-NPSLE), and 25 patients with nonautoimmune diseases (non-AI) were also studied. Soluble molecules, including cytokines IL-2, IL-4, IL-6, IL-10, TNF-α and IFN-γ and chemokines MCP-1, RANTES, IL-8, MIG, and IP-10 were measured with the use of cytometric bead array kits. IFN-α was measured using luminometry. All patients signed the informed consent.
Results: CSF levels of the following molecules were increased in headache patients as compared with non-NPSLE and non-AI control patients, respectively [median (IQR)]: IL-6 [208.5 (5.7–358.5) vs. 3 (1.32–5.75) vs. 3 (2.1–3.9)], IL-8 [406.6 (32.2–874.2) vs. 30 (21.4–48.5) vs. 19.7 (13.6–24.9)], IP-10 [4673 (853.5 – 5636.7) vs. 329.7 (190.1 – 583.6) vs. 133.6 (84.2 – 164.5)], RANTES [7.5 (3.2–18.8) vs. 2.5 (2–3.4) vs. 2.2 (1.9–4.1)] and MIG [944.7 (1.9–4.1) vs. 11.4 (1.9–4.1) vs. 3.5 (2–6.4)]; $p < 0.05$ for all comparisons. Low or undetectable levels of IL-2, IL-4, IL-10, TNF-α, and IFN-γ were found in all groups. When the headache patients where compared with the NPSLE group, only IFN-α (higher in NPSLE) and MIG (higher in headache) were significantly different ($p < 0.05$). Six months later and in the absence of NP manifestations, all elevated molecule levels in the headache group had considerably decreased.
Conclusion: Our findings support the tenet that there is a group of SLE patients with headache which has an inflammatory profile in the CSF characterized by IL-6 and chemokines, and for whom headache is quite probably a manifestation of disease activity at the CNS level.

P088

Membranous Lupus Nephritis: Do Co-Existing Proliferative Lesions Affect Outcomes

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Background/Purpose: Lupus nephritis (LN) affects up to 60% of SLE patients and is worse in minority communities. Traditionally membranous LN confers a better prognosis than proliferative, but a significant number of patients do develop renal failure. Moreover, mixed

membranous and proliferative histology is not uncommon. To determine if co-existing proliferative lesions worsen the prognosis of membranous disease, we studied SLE patients who underwent renal biopsy at a large tertiary center.

Methods: We analyzed all biopsies with classes: III±V, IV±V and V from January 1997-December 2011, and confirmed that all patients met ≥4/11 ACR SLE criteria. We collected baseline demographic and laboratory information at the time of biopsy as well as medications given. Our composite endpoint was the development of end stage renal disease (ESRD) requiring dialysis and/or death.

Results: Of the 202 patients included, 81.3% were female and the median age was 30.5y. The predominant race was black (54.5%), followed by Hispanic (37.1%) and 8.4% were another race/ethnicity. There was no significant difference between the groups in age, gender or disease duration.

123 patients had proliferative LN (Class III or IV, P), 55 had membranous LN (Class V, M), and 24 had mixed disease (P+M). Black patients were more likely to have class V (p=0.02). Creatinine was higher in P ($p < 0.01$) but there was no difference between M or P+M (p=0.12). There was no difference in median protein to creatinine ratios, serum albumin, and BP between groups.

62/202 (31%) patients reached the composite end point: 41.5% P, 14.6% M, and 12.5% P+M ($p < 0.01$). Survival was significantly worse for P compared to M ($p < 0.01$) and P+M (p=0.05), but no difference was seen between M and P+M (p=0.74). As previously reported, on univariate analyses, urine protein to creatinine ratio ($p < 0.01$), creatinine ($p < 0.01$), systolic BP (p=0.02), and age (p=0.05) were associated with the end point. There was no association with cyclophosphamide (p=0.07) or mycophenolate induction (p=0.2), ACEI/ARB use (p=0.85), or treatment with anti-malarials (p=0.2). In multivariate models, M as compared to P had improved survival (HR=0.31, p=0.02) but there was no longer a significant difference between P and P+M (p=0.18) As in the univariate analysis, age (p=0.03), protein to creatinine ratio (p=0.03), and creatinine at biopsy ($p < 0.01$) were all associated with a decreased risk of survival.

Conclusion: At first glance membranous with or without proliferative lesions on histology have a similar prognosis. However, in multivariate models the difference between proliferative and mixed disease was no longer seen when adjusted for age, protein to creatinine ratio and creatinine at biopsy. Therefore proliferative lesions alone on biopsy do not confer a worse prognosis for membranous disease rather it is likely disease severity itself that drives prognosis.

P089

What is the Optimal Screening Test to Detect Latent Tuberculosis Infection in High Risk Patients with Systemic Lupus Erythematosus? Findings from a U.S., Inner City, High-risk, SLE Cohort

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Background: Screening for latent tuberculosis infection (LTBI) with the tuberculin skin test (TST) has low sensitivity when used in SLE, leading to increased false negative results. Interferon-γ release assays (IGRAs) have become available for LTBI detection, albeit their applicability in SLE patients has not been thoroughly examined. The aim of our study is to compare the IGRA QuantiFERON-TB Gold (QFT-G) test with TST for the detection of LTBI in our SLE cohort.

Methods: A retrospective study of patients with SLE was conducted in a teaching hospital rheumatology clinic, serving a large inner city population. 150 SLE patients, fulfilling the 2012 SLICC SLE diagnostic criteria, were identified. LTBI screening was performed using TST (positive if > / 5mm), QFT-G, or both tests. Only positive or negative QFT-G results were used. Patients were diagnosed with LTBI if TST and/or QFT-G were positive and were treated with 9 months of Isoniazid/B6, after active pulmonary tuberculosis (TB) was ruled out by chest radiography. Findings from a previously presented study in RA with similar methodology were used for comparison.

Results: Of the 150 SLE patients studied, 60 (40%) had documented LTBI screening. 37 (24.7%) were screened with TST and 23 (15.3%) with QFT-G, of which 13 (8.6%) had both tests. Out of the 37 screened with TST, 6 (16%) were positive, while of the 23 patients screened with QFT-G, 7 (30.4%) had positive and 13 (56.4%) negative results. When comparing patients who had both tests done, 1/13 tested positive and 9/13 tested negative for both tests. In the study done for RA patients, 137 patients were studied, of which 50 (38%) were diagnosed with LTBI with either a positive TST 42 (32%) and/or QFT-G 23 (17%). 15 (11%) were positive and 83 (62%) were negative for both tests. The agreement between TST and QFT-G was 76.92% with a kappa value of 0.264 (CI-95% -0.350-0.878) versus kappa 0.306 (CI-95% 0.136-0.477) in the RA study. 2.6% of the SLE patients were diagnosed with LTBI in comparison to 38% in RA.

SLE Study			
Screening	*TST Positive*	*TST Negative*	*Total*
Quantiferon G Positive	1 (7.7%)	2 (15.4%)	3 (23.1%)
Quantiferon G Negative	1 (7.7%)	9 (69.2%)	10 (76.9%)
Total	2 (15.4%)	11 (84.6%)	13
RA Study			
Quantiferon G Positive	15 (11%)	8 (6%)	23 (17%)
Quantiferon G Negative	27 (21%)	83 (62%)	110 (83%)
Total	42 (32%)	91 (68%)	133

Conclusion: In the absence of a gold standard LTBI screening test, new screening strategies are needed in SLE, as in RA, where the underlying immune dysregulation and concurrent medications may influence the sensitivity of screening tests. Although the prevalence of LTBI in SLE may be lower than in RA, the need may become more pressing with several potent biologic agents being developed for the treatment for SLE. Combining TST and IGRAs may be a safe, comprehensive approach for LTBI detection.

*equal contribution

P090

Pulmonary Hypertension in Systemic Lupus Erythematosus of Latin American Prospective Inception Cohort (GLADEL)

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Introduction: Pulmonary hypertension (PH) is a serious complication of systemic lupus erythematosus (SLE). The frequency of occurrence is highly variable, from 0.5 to 16% due to the different criteria used for diagnosis, the definition and the group of patients studied. PH associated with SLE has a high mortality, which is independent of the degree of lupus activity and higher than the idiopathic type.

Objectives: Establish the prevalence of PH in patient with SLE. Analyze the socioeconomic-demographic, clinical and serological features, and mortality in patients with SLE and PH.
Material and methods: Was included 1480 patients with a recent SLE diagnosis (≤2 years) and were followed for 4.5 years, from 34 centers of 9 Latin-American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela). We compared the socioeconomic-demographic, clinical and serological variables among patients with/without PH. The statistical analysis included chi-square test for categorical variables and t test or Mann Witney test for continuous variables. Results with $p < 0.1$ were included for multivariate logistic regression analysis and significant $p \leq 0.05$. Kaplan Meier survival curve was examined.
Results: Thirty-two patients had PH, representing 2.2% of the total (32/1480) and 6.5% of patients with pleuropulmonary manifestations (32/486), 27 (84.4%) were female with a mean age (SD) at SLE onset of 27.5 (12.3) years. Eight (25%) patients had PH before the diagnosis of SLE. Table 1 shows socioeconomic-demographic, clinical and serological feature the patients with /without PH. In multivariate analysis the presence of PH was associated with Ischemic Heart compromise ($p < 0.01$. OR: 4.9; 95%CI: 1.8-13.1). During the follow-up period 8 (25%) patients died with PH vs. 82 (5.6%) patients without PH ($p < 0.01$. RR: 5.6; 95%CI: 2.4-12.9).

Table 1. Socioeconomic-Demographic, Clinical and Serological Feature Patient with Systemic Lupus Erythematosus According to whether they have or not Pulmonary Hypertension. Univariate Analysis

	With PH (n 32)	*Without (n 1448)*	*p*
Female n (%)	27 (84.8)	1303 (90)	0.3
Age of SLE onset m (SD)	27.5 (12.3)	28 (12)	0.7
Ethnicity White n (%)	14 (43.8)	592 (40.9)	0.7
Ethnicity White/Indian n (%)	15 (46.9)	630 (43.5)	0.7
Ethnicity African/Latin/American n (%)	2 (6.3)	184 (12.7)	0.7
Ethnicity Others n (%)	1 (3.1)	42 (2.9)	0.7
SES hih/medium hig n (%)	4 (12.5)	148 (10.2)	0.8
SES medium n (%)	10 (31.3)	417 (28.8)	0.8
SES medium low/Low n (%)	18 (56.3)	883 (61)	0.8
Systemic Manifestations n (%)	30 (93.8)	1187 (82)	0.1
Musculoskeletal Manifestations n (%)	27 (84.4)	1348 (93.1)	0.07
Ocular Manifestations n (%)	6 (100)	253 (17.5)	0.8
Cutaneus Manifestations n (%)	30 (93.8)	1357 (93.7)	1
Heart Compromise n (%)	**32 (100)**	**290 (20)**	**< 0.001**
Ischemic Heart n (%)	**9 (28.1)**	**81 (5.6)**	**< 0.001**
Renal Compromise n (%)	24 (75)	852 (58.8)	0.06
Neurologic Manifestations n (%)	**17 (53.1)**	**508 (35.1)**	**0.03**
Hematologic Manifestations n (%)	26 (81.3)	1142 (78.9)	0.9
ANA positive n (%)	31 (96.9)	1362 (94.1)	1
Anti DNA positive n (%)	22 (68.8)	869 (60)	0.3
Anti RNP positive n (%)	**12 (37.5)**	**310 (21.4)**	**0.02**
Anti Sm positive n (%)	9 (28.1)	341 (23.5)	0.6
Anti Ro positive n (%)	8 (25)	335 (23.1)	0.8
Anti La positive n (%)	6 (18.8)	185 (12.8)	0.2
Lupus Anticuagulant positive n (%)	3 (9.4)	92 (6.4)	0.4
Anti cardiolipin IgG n (%)	10 (31.3)	353 (24.4)	0.3
Anti cardiolipin IgM n (%)	7 (21.9)	247 (17.1)	0.4
Anti BG1 positive n (%)	2 (6.3)	35 (2.4)	0.1
Hypocomplementemia n (%)	21 (65.6)	835 (57.7)	0.3
Antiphospholipid syndrome n (%)	3 (9.4)	58 (4)	0.1
SLICC excluiding respiratory M(min-max)	**2 (0-8)**	**1 (0-9)**	**0.002**
SLEDAI average M (min-max)	6.5 (0-38)	3.5 (0-51)	0.07

SLICC: Systemic Lupus International Collaborating Clinics SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

Conclusions: The prevalence of PH in this cohort of patients with SLE is 2.2%. The presence of PH is associated with the presence of cardiac and neurological manifestations, positive RNP and higher SLICC. The PH is independently associated with ischemic heart compromise. The presence of PH increases the risk of death 5.6 times.

P091

Diagnostic value of the new classification criteria for Systemic Lupus Erythematosus (SLE) developed by The Systemic Lupus International Collaborating Clinics (SLICC) group in an Argentinian Cohort of patients with SLE.

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Background: The SLICC group revised the ACR SLE classification criteria and validated new criteria in order to improve clinical relevance and incorporate new knowledge of SLE inmunology. The new SLICC classification criteria performed well on a large set of patient scenarios rated by experts. They require four criteria with at least one clinical criterion and one immunologic criterion to be present to fulfill SLE classification criteria. Objective was to determine the diagnostic value of SLICC criteria in a cohort of patients with SLE in Argentina.
Material and methods: One hundred and ninety two consecutive patients ≥ 16 years old, diagnosed with SLE according to expert opinion were included and 100 controls. Controls were patients with rheumatic diseases other than SLE: rheumatoid arthritis, myositis, chronic cutaneous lupus, undifferentiated connective tissue disease, vasculitis, Bechet's syndrome, polychondritis, sarcoidosis, primary antiphospholipid antibody syndrome, undifferentiated arthritis, scleroderma, fibromyalgia, Sjögren syndrome and gout. Data analysis: Each patient was evaluated for SLICC criteria and ACR SLE criteria. Sensitivity (S), specificity (Sp), predictive values (PV) and likelihood ratio (IP) were calculated. Kappa coefficient was used to determinate concordance between the diagnosis and classification criteria.
Results: SLE group: 89% women; average age: 38 years old (DE13) (range: 16-84); ethnicity: 43% White, 41% Mestizo, 13% Amerindian and 0.5% Afro-Latino; 65% of patients had between 7 and 13 years of formal education. Age at diagnosis: 29 years old (DE12) (range: 5-63), 18 patients with juvenile-onset SLE (< 16 years) and 11 patients with late-onset SLE (> 50 years). Median time since onset of SLE: 80 (IQR 30-160) months.

	Sensitivity %	*Specificity %*	*mis-classified cases*	*Positive PV*	*Negative PV*	*LR+*	*Kappa*
1997 ACR Criteria	97	90	14	95	95	9.7	0.88
SLICC criteria	100	86	14	93	100	7.1	0.89

Conclusion: In this study the SLICC classification criteria perform better than the revised ACR criteria in terms of sensitivity but not specificity. They include new clinical concepts and methodological advances in SLE.

P092

Comparison of the ACR and the SLICC Criteria for the Classification of SLE Patients Using Data from a Multiethnic Latin American Cohort

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Background/Purpose: In 2012 a new set of criteria for SLE were proposed by SLICC group in order to increase the accuracy of SLE diagnosis. The present study aims to compare these criteria with the 1982 ACR criteria in well-characterized SLE cohort.

Methods: We examined patients from a longitudinal inception cohort, which comprises SLE patients with a recent diagnosis (less than 2 years) from 34 centers in nine Latin American countries. Board certified rheumatologists collected data on disease onset manifestations as well as clinical features that occurred at or after the physician's diagnosis of SLE. Fulfillment of 4 ACR 1982 SLE criteria at the time of physician's diagnosis was not mandatory, although 95.6% of the entire cohort fulfilled 4 or more criteria during the course of the disease. To perform this study we used the date at which the ACR and SLICC criteria were first met. Some SLICC criteria could not be applied (toxic epidermal necrolysis and some chronic forms of cutaneous lupus). We compared groups of patients based on whether the SLICC criteria were met before, at the same time or after the ACR criteria were met.

Results: Of the 1397 patients that comprise this cohort 855 (57.8%) were classified at the same time using either criteria set, 248 earlier with the SLICC criteria (16.8%) and 294 (19.9%) later; 83 patients (5.6%) from this cohort could not be included because of missing dates for either the ACR or the SLICC criteria. Sixty six of the 248 earlier patients (26.6%) met the SLICC rule of lupus nephritis (LN) plus 1 immunologic criterion. Tables 1 and 2 show the distribution of the ACR and SLICC criteria among all 3 groups; only those criteria, which differ between the 2 sets, are shown in Table 2.

Conclusion: Although about a fifth of the SLE patients could have been classified earlier with the SLICC than with the ACR criteria, about the same proportion could have ended classified later. No particular feature emerged as indicative of an earlier SLE classification but some of the earlier patients met the Renal criterion. Given the importance of classification criteria for the identification of SLE patients for the conduct of longitudinal observation studies and clinical trials and based on the data presented, it is likely that both sets of criteria will be used in the near future for such a purpose.

Table 1. Patients who met ACR criteria

SLICC criteria	*Group I SLICC criteria met later (%) N=294*	*Group II SLICC met at the same time (%) N=855*	*Group III SLICC criteria met earlier (%) N=248*	*p-value*
Clinical criteria				
Acute cutaneous lupus	24.1	61.1	14.8	<0.0001
Chronic cutaneous lupus	33.3	56.6	10.1	<0.0001

(continued)

Table 2. SLICC criteria in SLE patients

ACR Criteria	*Group I SLICC criteria meet later (%) N=294*	*Group II SLICC criteria meet at the same time (%) N=855*	*Group III SLICC criteria meet earlier (%) N=248*	*p-value*
Malar rash	30.7	60.3	9.0	<0.0001
Discoid lupus	40.3	49.6	5.6	<0.0001
Photosensitivity	27.7	62.3	10.0	<0.0001
Oral ulcers	36.6	53.4	10.0	<0.0001
Arthritis/arthralgias	23.6	61.1	15.3	<0.0001
Pleuritis	25.4	62.8	11.8	0.0190
Pericarditis	26.1	58.0	15.9	NS
Proteinuria/cylindruria	23.6	64.2	12.2	0.0010
Psychosis/seizures	25.3	58.5	16.2	NS
Hematological disorder	22.7	63.6	13.7	<0.0001
Immunologic criteria	16.5	66.9	16.6	<0.0001
ANA	13.7	66.5	19.8	<0.0001

P093

Infections in a Latin-American Lupus Cohort.

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Introduction: Infection is a major source of morbidity and mortality in patients with systemic lupus erythematosus (SLE). The objective of this study was to evaluate the factors associated with the occurrence of infections in an inception cohort of SLE patients from Latin America.
Patients and methods: SLE patients (< 2 years from diagnosis) from 34 centers in 9 Latin American countries, constitute this cohort. We examined the socio-demographic characteristics, clinical manifestations and treatments until the time of diagnosis, as well as the site of infection and associated mortality.The definition of infection was clinical and was left to the discretion of the investigators at each center.

The incidence of infections (overall and by subgroup defined by socio-demographic and clinical characteristics) was summarized as rates per 100 patient-years of follow-up (%/yr). Cox regression models were used to derive hazard ratios comparing the risk of infection by subgroup.
Results: Among the 1480 patients (1330 women) enrolled in this cohort, with a median follow-up time of 56 months (quartiles: 54-59 months), 547 infections were detected (37% - 11.54 rate of 100 pts/yr). Table 1 depicts the features of these patients as a function of infections.

The most common sites of infection were: skin/mucosal 16%, urinary tract 13.6% (lower 6.3%, upper 3.0%), respiratory track 11.4% (lower 5.3%), gastrointestinal: 4.3%, obstetric-gynecological: 3.8%; bloodstream: 2.4%, musculoskeletal: 2.1%, CNS: 1.4%, ocular: 0.5% and cardiovascular: 0.2%. The probability of an infection after diagnosis, were within: first year: 17.4%, second year: 26.6%, third year: 32.8% and within five years: 41.6%. A total of 57/547 infected patients died (10.4%) versus 32/933 patients without infections (p=0.0023).
Conclusions: in our cohort, infections were significantly associated with ethnic groups (Mestizo/Others), lower educational level, complete medical insurance, neurologic involvement, leukopenia, SLICC/ACR ≥1, higher doses of corticosteroids and the use of immunosuppressive agents. The use of antimalarials was not protective. The possibility of an infection increases within the first 2 years after diagnosis. The most frequently affected sites were skin/mucosal, urinary and respiratory tracts. Infections were significantly associated with mortality.

Table 1. Characteristics of SLE Patients as a Function of Infection.

Features	*HR*	*95% CI*	*p-value*
Age at diagnosis, ≥40 years	0.99	0.79–1.22	0.8694
Male	0.94	0.71–1.25	0.6756
Ethnic group			
Caucasian (reference group)	-	-	-
Mestizo	1.20	0.99–1.44	
African-Latin American	0.96	0.71–1.28	0.0034
Others	2.07	1.34–3.22	
Educational level			
0-7 years (reference group)	-	-	-
8-12 years	0.87	0.72–1.05	0.0420
> 12 years	0.74	0.59–0.94	
Medical insurance			
Partial (reference group)	-	-	-
Complete	1.22	1.02–1.46	0.0261
Socioeconomic status			
High (reference group)	-	-	-
Middle	1.17	0.84–1.63	0.0759
Low	1.36	0.99–1.84	
Clinical/Laboratory			
Neurologic involvement	1.32	1.05–1.66	0.0188
Leukopenia	1.36	1.15–1.62	0.0003
SLEDAI > 6, at diagnosis	1.19	0.95–1.50	0.1337
SLICC/ACR ≥1, at diagnosis	1.82	1.53–2.16	< 0.0001
Treatments			
Glucocorticoid, oral			
Low (≤20mg)	1.43	0.77–2.65	
Medium (> 20 – < 60 mg)	2.96	1.65–5.29	< 0.0001
High (≥60mg)	3.99	2.24–7.12	
Glucocorticoid, pulse	2.27	1.92–2.69	< 0.0001
Immunosuppressive (all)	2.11	1.76–2.52	< 0.0001
Cyclophosphamide, pulse	2.09	1.77–2.47	< 0.0001
Antimalarials	1.06	0.84–1.35	0.6314

References

1 HR: hazard ratio; CI: confidential interval, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborating Clinics /American College of Rheumatology Damage Index.

P094

Lupus Nephritis: description of a cohort of Hispanic patients and detection of remission predictors at 12 months.

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Background: Lupus Nephritis (LN) affects 50% of Hispanic patients with Systemic Lupus Erythematosus (SLE); patients who do not meet remission criteria are at higher risk of developing chronic renal failure. Baseline Activity Index (AI), Chronicity Index (IC), creatinine level, and proteinuria have been associated with failure in achieving remission in proliferative LN (PLN).

The purpose of this study was to observe the remittance rate of a cohort of patients with LN followed in two university hospitals, and to identify unsuccessful remission inducing predictors at 12 months in PLN subjects.
Material and Methods: A nested case-control study was conducted that included all consecutive patients with SLE according to 1997 ACR criteria with NL classified by ISN/RPS.
Results: We enrolled 149 patients, 84% female and 16% male. The mean age at diagnosis of SLE was 24.7 years (16-31): 21 years (16-

29) for women, and 27 years (17.5 - 39.7) for men; the mean time between diagnosis of SLE and LN was two months (0 - 35.25).

83.87% of patients had PLN (III: 13.42%, IV: 63.75%, V/III: 3.35%, V/IV: 3.35%); 10.73% had membranous pure NL, and 5.36% had mesangial NL.

The PLN Subgroup presented early in the evolution of SLE (49% during the first month, 19% between months: 1 and 12; 18% between months: 12 and 60; 9% between months: 60 and 120; and 5% after 120 months). Mean AI was 6.18 ± 4.55, mean CI was 1 (0-3), mean 24-hour proteinuria was 2000 mg (667-4770) and mean creatinine was 0.9 mg% (0.7 – 1.3)

Table 1. Response to remission induction 125 patients with PLN

	Total population (n=125)		*Induction with Cyclo-phosphamide (74.1%)*		*Induction with Mycophenolate (25.9%)*	
Remission	6 Month	12 Month	6 Month	12 Month	6 Month	12 Month
Partial	19.2%	20.32%	19.76%	18.6%	26.7%	32.14%
Complete	29.6%	39.02%	27.9%	37.2%	23.3%	32.14%
No	51.2%	40.6%	52.32%	44.2%	50%	35.7%

In bivariate analysis, baseline predictors of failure to obtain complete or partial remission at 12 months were: creatinine ($p = 0.000$), proteinuria ($p = 0.002$) and CI ($p = 0.024$). Conforming to multivariate analysis, elevated baseline creatinine level (OR 3.7, 95% CI 1.58 – 8.63, p= 0.002), 24-hour proteinuria over 1500 mg (OR 3.58, 95% CI 1.27 – 10.07, p= 0.016), and nephrotic syndrome (OR 4.44, 95%IC 1.49 - 13.2, p=0.007) were independent predictors of unsuccessful attempt in acquiring remittance.

Conclusions: 40.66% of PLN patients didńt obtain remission at 12 months. Baseline elevated creatinine, 24-hour proteinuria and nephrotic syndrome were predictors failure in completing remission. Partial or complete remision was achieved in 64.3% and 47.5% of patient treated with Mycophenolate and Cyclophosphamide repectly

P095

Bone Mineral Density and Bone Microarchitecture Changes in Systemic Lupus Erythematosus on Long-term Glucocorticoid: A Prospective Study

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Background and Objective: Prevalence of osteoporosis and fracture is high in systemic lupus erythematosus (SLE) patients on long-term glucocorticoid (GC). Disparity between decrease in areal bone mineral density (aBMD) by dual-energy x-ray absorptiometry (DXA) and increase in fracture rate was noted in SLE patients and GC users, indicating bone quality alters in SLE with GC therapy was beyond that captured by aBMD. With the advent of the novel non-invasive three dimensional imaging techniques, in particular, high-resolution peripheral quantitative computed tomography (HR-pQCT) can help detect alterations of volumetric BMD (vBMD) and bone microarchitecture in vivo enabling a better understanding of GC induced bone loss than traditional methods such as radiography or DXA. The objective of this study is to evaluate the changes of vBMD and bone microarchitecture by HR-pQCT over time in SLE patients on long-term GC.

Methods: We performed a 1 year prospective controlled study in female SLE patients on long-term GC and controls. Changes were evaluated by HR-pQCT in bone geometry, vBMD and bone microarchitecture at distal radius and by DXA in aBMD at femoral neck (FN), total hip (TH), lumbar spine (LS) and distal radius.

Results: A total of 180 SLE patients and 180 age- and sex-matched healthy controls were recruited at baseline, while 165 patients (92%) and 164 controls (91%) finished the follow-up of 12±0.6 months. The two groups were comparable with respect to age (43 years) and height at baseline. Significantly lower weight and high prevalence of postmenopausal were in patients than controls. All patients were currently on at least 5 mg/d prednisolone at study entry, with median cumulative dose of 19 g for a mean duration of 10 years. During the follow-up, aBMD at four measured sites reduced in patients and controls, but none of the reductions reached significant level. Trabecular and cortical area, cortical perimeter and thickness decreased in patients ($p < 0.05$) while no significant change in controls. Trabecular vBMD and meta-trabecular vBMD increased in patients but decreased in controls ($p < 0.05$). Trabecular microarchitecture was improved in patients through significantly increased trabecular volume fraction (BV/TV) but was deteriorated in controls through reduced BV/TV and increased trabecular spacing ($p < 0.05$). Correlation analyses between baseline characteristics and changes in bone quality as assessed by HR-pQCT showed serum levels of dickkopt-1 were negatively associated with percentage change in cortical thickness ($r=-0.15$, $p < 0.05$) and negative associations were found between serum levels of alkaline phosphatase and cortical and trabecular bone area, vBMD, cortical thickness and trabecular BV/TV ($r:-0.15\sim -0.31$, $p < 0.01$).

Conclusion: This study showed that SLE female patients on long-term GC had deteriorated cortical bone geometry and structure but increased trabecular vBMD through cortical bone trabeculization leading to overestimation of trabecular density, reserving or attenuating age-related changes observed in controls. Suppression of bone formation activity is a potential and critical mechanism for bone loss in SLE patients on long-term GC.

P096

Systemic Lupus Erythematosus and Cancer? - A Meta analysis

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Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, the prognosis of which has improved during the last decades. Life expectancy is, however, still shortened compared with the general population, mainly due to organ damage, infections, and an increased cardiovascular morbidity. Whether cancer also contributes to this increased mortality is not clear. Studies done in patients with SLE to assess the risk of cancers have yielded mixed results. Therefore, this meta-analysis was performed to investigate the link between SLE and incidence of cancers.

Methods: A systemic review of literature was done according to preset inclusion and exclusion criteria. Both prospective and retrospective studies were included. Two investigators independently abstracted data from eligible studies. End points extracted included standardized incidence ratios (SIR) of all cancers and specific cancers in patients with and without SLE. Standardized incidence ratios (SIR) across all the studies and the 95% confidence intervals (CI) were determined. A two-sided alpha error < 0.05 was considered statistically significant. Publication bias was assessed by visual examination of funnel plots.

Results: A total of 52,140 patients from 14 studies were analyzed using the Mantel-Haenszel random effect model to extract incidence of cancers in SLE. Compared to patients without SLE, those with SLE were found to be at significantly higher risk of all cancers [SIR: 1.25 (95 %

CI -1.156 to 1.351), p=0.000]. Analysis done for specific cancers revealed significantly higher risk of hematological malignancies [SIR: 2.631 (95% CI 2.209 to 3.134), p=0.000], and lung cancers [SIR: 1.633(95% CI – 1.466 to 1.820), p= 0.000] in patients with SLE. However, there was no increased risk of skin cancers in patients with SLE [SIR: 0.997 (95% CI 0.57 – 1.743), p=0.99].
Conclusion: This meta-analysis indicates that SLE conferred an increased risk for all cancers, hematological malignancies and lung cancers but not for skin cancers. As a result of increased life expectancy of lupus patients, chronic organ damage and late complications like malignancies have become major determinants of morbidity and mortality. Physicians should be more cognizant of the increased risk of cancers in SLE patients and further studies are needed to assess the need for new screening methods or more frequent screening intervals.

P097

Clinical significance of Hemolytic Anemia in a cohort of 1000 Brazilian patients with systemic lupus erythematosus
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Background: Systemic lupus can affect multiple organs and it is associated with significant morbidity and mortality. Hematological manifestations in lupus are common and autoimmune hemolytic anemia (AHA) is a SLE classification criterion as well thrombocytopenia and leucopenia. It's usually related with the more severe cases of SLE.
Objective: To analyze the frequency of hemolytic anemia in a Brazilian cohort of 1000 patients with SLE and the clinic manifestations that might be related to hemolytic anemia as their clinic evolution.
Methods: We reviewed retrospectively all cases of AHA from our lupus cohort of 1000 cases followed up between 1974 and 2011. Clinical data used in this study were extracted from the medical records of Hospital das Clínicas of State University of Campinas, Brazil. Hemolytic anemia was defined according to the American College of Rheumatology criteria for the classification of SLE and was not considered when secondary to drugs. We classified AHA in 75 patients according to severity in mild to moderate (women's hemoglobin 7 g/dL - 11 g/dL and men's hemoglobin 7 g/dL – 13 g/dL) or severe ($\leq$ 7 g/dL); time of occurrence when at onset of SLE (first 6 months) or during the course of SLE (after 6 months) and frequency: a single episode or recurrent episodes. We compared patients with and without hemolytic anemia concerning to different clinical manifestations of the disease.
Results: Hemolytic anemia was present in 112 patients (11,2%) of all cases of SLE. The mean age of the patients was 27.13 years. There were 105 women and 7 men; 77 Caucasian and 35 non -Caucasian. Lupus patients with hemolytic anemia had more pleuritis ($1.01 < OR < 2,99$; P=0,029), nephritis ($1.09 < OR < 2,51$; P=0,012), leucopenia ($1.12 < OR < 2,85$;P=0,001) and thrombocytopenia ($2.10 < OR < 5.14$; P=0,00000001) and anti-DNA antibodies ($0,38 < OR < 0,89$; P=0,008). Patients with Hemolytic anemia died more than patients without this manifestation ($1,11 < OR < 3.38$; P=0,009). In 75 patients we observed AHA as a single episode in 64 (85%), recurrent episodes in 11 (15%) and at onset of SLE in 53 cases (71%) and in the evolution in 22 (29%). AHA was mild to moderate in 38,5% and severe in 61,5%.
Conclusion: Hemolytic anemia occurred in 11,2% of SLE, usually severe, at the onset of the disease and in a single episode. Pleuritis, nephritis, other cytopenias and Anti-DNA antibodies were strongly related to AHA. The higher death rate (18%) when compared to the patients without AHA (10.4%) was assigned to the multi systemic involvement, with high percentage of nephritis and other severe manifestations.

P098

High prevalence of a positive family history of Systemic Lupus Erythematosus in juvenile-onset versus adult-onset disease: a comparative study.
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Background: The pathogenesis of SLE is complex and poorly understood. A genetic contribution is evident from a monozygotic twin concordance rate of 30-40%. Juvenile-onset SLE is often severe at presentation compared to adult onset disease. We compared family history of SLE, immunology, severity of organ involvement and differences between medications used in both groups.
Methods: Clinical and demographic data was collected on 25 juvenile-onset SLE patients (jSLE) and compared with 65 matched patients with adult-onset disease. All patients met the American College of Rheumatology (ACR) classification criteria for SLE. Juvenile-onset was defined as those who were diagnosed with SLE before16 years of age. Data collected included ethnicity, family history of SLE/autoimmune disease, autoantibody profile, lupus-related disease manifestations and medications used.
Results: 36% of jSLE patients had a positive family history of SLE compared to 12% of adult-onset disease patients (p=0.011). Family history of other autoimmune conditions such as rheumatoid arthritis, hypothyroidism did not differ significantly between the two groups. In jSLE patients 21(84%) were female and 4 (16%) male. Mean age of disease onset was 13 years (range 10-16 years). 13 (52%) were Afro-Caribbean, 7(28%) Caucasian, 4 (16%) Asian and 1 (4%) was of mixed ethnic origin. In adult-onset disease, 60 (92%) were female and 5 (7%) male. Mean age of disease onset was 29 years (17-50 years). 29 (44%) were Afro-Caribbean, 13 (20%) Asian, 21(32%) Caucasian and 2 (3%) were of mixed ethnicity. 18(72%) patients of jSLE patients had lupus nephritis while 43(66.1%) patients of adult-onset SLE patients had lupus nephritis.
Conclusions: A family history of SLE was significantly more common in jSLE than in adult-onset patients. Frequencies of lupus nephritis and anti-dsDNA antibody positivity were higher in jSLE which may reflect a more severe clinical phenotype. The majority of jSLE patients were of African ancestry, who are known to have worse clinical outcomes. Medications and clinical interventions such as mycophenolate mofetil, cyclophosphamide, rituximab were more frequently used in jSLE patients, supporting the likelihood of more severe and difficult to manage disease in this subset of patients.

	Juvenile-onset SLE (n=25)	*Adult-onset SLE (n=65)*
ANA	92%	98%
Anti-dsDNA	72%	49%
Anti-Ro (SSA)	36%	36%
Anti-La (SSB)	13%	10%
Anti- Sm	31%	32%
Anti-RNP	40%	36%
Prednisolone	84%	81%
Hydroxychloroquine	72%	84%
Mycophenolate mofetil	68%	49%
Azathioprine	20%	29%
Cyclophosphamide	20%	15%
Rituximab	24%	10%
Plasmapheresis	8%	0
Intravenous immunoglobulin	4%	0

P099

Support vector machines classification of texture parameters of white matter lesions in childhood-onset systemic lupus erythematosus. possible mechanism to distinguish between demyelination and ischemia

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Background: Texture analysis (TA) is a branch of image processing which seeks to reduce image information by extracting texture descriptors from the image. White matter hyperintensities (WMH) are frequently observed in childhood-onset systemic lupus erythematosus (cSLE); however the etiology is still unknown. Ischemic and demyelination have been proposed as possible etiologies. Support vector machines (SVM) are a group of supervised learning methods that can be applied to classification or regression
Objectives: To determine etiology of WMH in cSLE patients using texture analysis of magnetic resonance (MR) parameters basedon neural network
Methods: TA was applied to axial FLAIR magnetic resonance images (MRI) in 43 patients with cSLE (mean age 17.25 years (SD ± 3.57), 30 patients with multiple sclerosis (MS), 30 patients with stroke and 30 normal age and sex-matched controls. The TA approach used was based on the Gray Level Co-occurrence Matrices (GLCM). The WMH were manually segmented for each subject, classified in periventricular, subcortical, deep white matter and cortical WMH and 256 texture parameters were computed for each lesion. A SVM classifier previously developed and validated (accuracy 93%) was used to classify WMH in patients with cSLE. Nature of the classified WMH, demographic, clinical and laboratory features were included in a regression model to determine which variables could support the possible nature of WMH in clinical practice
Results: In cSLE, of the 125 of periventricular lesions, 59% were classified as ischemic and 41% as demyelinating. Of the 738 subcortical lesions 63% were classified as ischemic and 37% as demyelinating. Of the 64 cortical lesions, 61% were classified as ischemic and 39% as demyelinating. Of the deep white matter WMH, 72% were classified as ischemic and 28% as demyelinating in nature. In controls all lesions were classified as ischemic. Positive antiphospholipid antibodies (aPL) (OR=3.2; 95%CI 1.2-7.3) and higher total corticosteroid dose (OR=2.1; 95%CI 1.2-3.7) were variables associated with stroke, whereas cutaneous vasculitis (OR=4.2; 95%CI 2.1-7.2), anti-SM antibodies (OR=2.9; 95%CI 1.3-8.7) and disease activity (OR=3.7; 95%CI 1.3-7.8) were associated with demyelination in all cerebral regions.
Conclusions: In cSLE, the majority of WMH were classified as ischemic in nature; however aproximately 30% of the lesions were demyelinating. Positive aPL and higher total corticosteroid dose were variables associated with stroke, whereas cutaneous vasculitis, anti-SM antibodies and disease activity were associated with demyelination in all cerebral regions.SVM of TA is a useful method to help to determine etiology of WMH in cSLE.
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P100

Measuring Partial and Complete Recovery in Active Organ Systems of Lupus Patients On Standard of Care Treatment

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Background: SLE Disease Activity Index 2000 (SLEDAI-2K) measures only complete recovery in active descriptors. SLEDAI-2K Responder Index-50 (S2K RI-50) is a novel index that measures partial, ≥50% improvement.
Purpose: To determine: 1) partial and complete recovery in active systems on standard of care treatment and 2) the benefit of measuring ≥50% improvement.
Methods: Consecutive patients seen between February 2009-May 2012 were analyzed. SLEDAI-2K has 9 systems. Patients were included if they had at least one active system. We excluded patients with CNS manifestations or with nephrotic range proteinuria from the analysis to reflect inclusion criteria of current lupus trials. Complete recovery in active systems was measured with SLEDAI-2K and partial recovery with S2K RI-50.
Results: 548 patients (90% F) with at least one active SLEDAI-2K system were analyzed. 63% were Caucasian, 16% Black, 10% Asian and 11% Others. Disease duration at study inclusion was 15.2 ± 11.0 years. Amongst the 8 systems studied at baseline, the most common were immunology, renal, mucocutaneous and musculoskeletal Table 1). For example, in 117 patients with mucocutaneous involvement, complete recovery by SLEDAI-2K was achieved by 68 patients at 6 months, by 95 patients at 12 months and 106 patients at 2 years. Partial and complete recovery by S2K RI-50 was identified in 83 patients at 6 months, 105 patients at 12 months and 113 patients at 2 years.

	Within 6 months	*Within 12 months*	*Within 24 months*
VASCULITIS (n=9)			
Complete Recovery	7	8	8
Partial Recovery	1	1	1
Partial or Complete	8	9	9
MUSCULOSKELETAL (n=10) (arthritis or myositis)			
Complete Recovery	62	75	82
Partial Recovery	6	3	4
Partial or Complete	68	78	86
SEROSAL (n=10) (pleurisy and/or pericarditis)			
Complete Recovery	5	6	7
Partial Recovery	2	2	1
Partial or Complete	7	8	8
MUCOCUTANEOUS (n=117) (rash, alopecia and/or musosal ulcer)			
Complete Recovery	68	95	106
Partial Recovery	15	10	7
Partial or Complete	83	105	113
IMMUNOLOGY (n=373) (low complement and/or high anti-DNA)			
Complete Recovery	88	121	158
Partial Recovery	75	101	120
Partial or Complete	163	222	278
HEMATOLOGY (n=72) (thrombocytopenia and/or leucopenia)			
Complete Recovery	46	53	58
Partial Recovery	5	6	5
Partial or Complete	51	59	63
CONSTITUTIONAL (Fever) (n=2)			
Complete Recovery	2	2	2
Partial Recovery	2	2	2
Partial or Complete	4	4	4
RENAL (n=205) (proteinuria, pyuria and/or casts)			
Compete Recovery	111	143	158
Partial Recovery	17	23	15
Partial or Complete	128	166	173

The total possible score for the mucocutaneous system (3 descriptors: rash, alopecia and mucosal ulcers) by SLEDAI-2K is 6. At baseline visit the mean total score for the mucocutaneous system was 2.56±1.01. At 6 months it decreased to 1.02±1.51, at 12 months to 0.47±1.07 and to 0.27±0.91 at 2 years by SLEDAI-2K. S2K RI-50 scores were 0.87±1.35 at 6 months, 0.40±0.95 at 12 months and 0.20±0.67 at 2 years. Change of scores over time for all 8 systems detected by SLEDAI-2K and S2K RI-50 is found in table 2.

	Onset	*6 months*	*12 months*	*24 months*
VASCULITIS	n = 9	n = 8	n = 9	n = 9
SLEDAI-2K	8.0	1.0 ± 2.8	0.89 ± 2.67	0.89 ± 2.67
S2K RI-50	8.0	0.5 ± 1.4	0.44 ± 1.33	0.44 ± 1.33
MUSCULOSKELETAL	n=90	n=84	n = 89	n = 90
SLEDAI-2K	4.04 ± 0.42	1.05 ± 1,77	0.67 ± 1.62	0.40 ± 1.35
S2K RI-50	4.04 ± 0.42	0.90 ± 1.60	0.65 ±1.59	0.33 ± 1.21
SEROSAL	n = 10	n = 9	n = 10	n = 10
SLEDAI-2K	2.20 ± 0.63	0.89 ± 1.05	0.80 ± 1.03	0.60 ± 0.97
S2K RI-50	2.20 ± 0.63	0.67 ± 0.87	0.60 ± 0.84	0.50 ± 0.85
MUCUCUTANEOUS	n = 117	n = 108	n = 116	n = 117
SLEDAI-2K	2.56 ± 1.01	1.02 ± 1.51	0.47 ± 1.07	0.27 ± 0.91
S2K RI-50	2.56 ± 1.01	0.87 ± 1.35	0.40 ± 0.95	0.20 ± 0.67
IMMUNOLOGY	n = 373	n = 338	n = 365	n = 373
SLEDAI-2K	2.64 ± 0.94	2.11 ± 1.51	1.88 ± 1.55	1.70 ± 1.64
S2K RI-50	2.64 ± 0.94	1.85 ± 1.40	1.64 ± 1.40	1.43 ±1.43
HEMATOLOGY	n = 72	n = 67	n = 71	n = 72
SLEDAI-2K	1.0 ± 0	0.33 ± 0.50	0.27 ± 0.48	0.21 ± 0.44
S2K RI-50	1.0 ± 0	0.29 ± 0.47	0.23 ± 0.44	0.17 ± 0.40
CONSTITUTIONAL	n = 2	n = 2	n = 2	n = 2
SLEDAI-2K	1.0	0	0	0
S2K RI-50	1.0	0	0	0
RENAL	n = 205	n = 188	n = 200	n = 205
SLEDAI-2K	5.21 ± 2.85	2.43 ± 3.52	1.76 ± 3.32	1.44 ± 3.13
S2K RI-50	5.21 ± 2.85	2.23 ± 3.26	1.59 ± 3.14	1.34 ± 2.98

Conclusion: With standard of care therapy, patients improve progressively over a 2 year period. The use of S2K RI-50 allows the capture of an additional number of patients with ≥50% improvement in active systems not discerned by SLEDAI-2K. This will allow for an earlier signal of efficacy with new agents in therapeutic trials.

P101

Headache in Systemic Lupus Erythematosus (SLE): results from a prospective, international, inception cohort study

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Introduction: We examined headache frequency and characteristics, association with global disease activity and impact on health related quality of life in a large, prospective, inception cohort of SLE patients.
Patients and Methods: An international research network enrolled patients within 15 months of SLE diagnosis. Headache (5 types) and other neuropsychiatric (NP) events defined by ACR case definitions were documented annually for up to 10 years. Demographic and clinical variables, SLE global disease activity (SLEDAI-2K), SLICC/ACR damage index (SDI) and self-report mental (MCS) and physical (PCS) component summary scores of the SF-36 were recorded. Statistical analyses of time to first headache were based on Cox's proportional hazards model. SF-36 scores were examined by linear regression with generalized estimating equations to account for within patient correlation.
Results: Of the 1732 enrolled patients 89% were female with the following racial/ethnic distribution: Caucasian (48%), African (16%), Asian (16%), Hispanic (16%) and other (4%). At enrollment the mean (± SD) age was 34.6 ± 13.4 years, disease duration was 5.6 ± 4.8 months and followup was 3.8 ± 3.1 years. Mean SLEDAI-2K at enrollment was 4.0 ± 5.3 and SDI was 0.32 ± 0.78. Within the enrollment window (6 months pre-diagnosis up to the enrollment visit) the proportion of patients with headache was 17.8% subdivided into: migraine (55.2%), tension (35.1%), intractable non-specific (6.5%), cluster (2.4%) and intracranial hypertension (0.9%). The estimated proportion of patients ever reporting a headache increased to 57% after 10 years (Kaplan-Meier estimate) with similar subset distribution. Only 2% of patients in 0.6% of assessments had "lupus headache" in SLEDAI-2K scores. Headache was associated with other NP events as indicated by Hazard Ratio (HR) estimates (95% CI) for: aseptic meningitis 3.8 (1.2, 12.0), autonomic disorder 13.3 (3.3, 53.6), cerebrovascular disease 2.3 (1.5, 3.6), anxiety disorder 2.2 (1.5, 3.2) and mood disorder 2.1 (1.6, 2.7). The estimated risk for any 5 unit increase in SLEDAI-2K (excluding "lupus headache" variable). corresponded to an HR (CI) of 1.13 (1.03, 1.23). The mean (SD) SF-36 MCS scores were lower in patients with headache compared to patients without headache (mean ± SD: 42.5 ± 12.2 vs 47.8 ± 11.3; $p < 0.001$) as were PCS scores (38.0 ± 11.0 vs 42.6 ± 11.4; $p < 0.001$). Comparable results were found for migraine alone. All associations remained significant after adjustment for gender, race/ethnicity, geographic location and age at diagnosis.
Conclusions: Headaches, particularly migraine and tension types, occur frequently among SLE patients and are associated with other types of NP events. Although the majority of headaches are not attributable to active lupus, they are associated with higher global SLE disease activity and lower self-reported health-related quality of life.

P102

Prevalence of autoantibodies to P ribosomal proteins in pediatric-onset systemic lupus erythematosus compared with the adult-onset disease: a multicenter study

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Objective: To determine the prevalence and clinical correlation of anti-P ribosomal antibodies in pediatric-onset systemic lupus erythematosus (SLE) in comparison with the adult-onset SLE.
Patients and methods: One-hundred and twenty consecutive patients who meet the American College of Rheumatology revised criteria for SLE were prospectively included in the study. Patients who started their disease before the age of 16 were considered pediatric-onset SLE. Clinical manifestations were collected from the medical records. Serum samples for immunological measurement were centralized in CEMIC laboratory. Measurement of anti-P ribosomal antibodies was determined by enzyme-linked immunosorbent assay (ELISA). Anti-SSA/Ro, anti-SSB/La, anti-Sm and anti-nRNP were determined by double-diffusion method.
Results: Clinical and serological data of 30 patients with pediatric-onset SLE were compared with data of 90 patients with adult-onset SLE. Mean age at diagnosis was 12 ± 3.56 years for pediatrics and 30 ± 11.46 years for adult SLE patients. Mean age at sampling was 22.9 ± 8.4 years for pediatrics and 39.73 ± 12.37 years for adult patients. Anti-P ribosomal antibodies were found significantly more often in pediatric-onset SLE patients [26.7% vs. 6.5%; OR=5.21 (CI 95%: 1.6-16.5, p=0.003)], whereas anti-SSA/Ro antibodies were found more often in

adult-onset SLE patients [20.7% vs. 42.4%; OR=0.35 (CI95%: 0.13-0.96), p=0.01]. Among the clinical manifestations, malar rash [89.7% vs. 68.5%; OR=3.9 (CI95%: 1.11-14.25) p=0.01], photosensitivity [76.7% vs. 55.4%; OR=2.64 (CI 95%: 1.03-6.76), p=0.01], neurological signs/symptoms [30% vs. 12%; OR=3.15 (CI95%: 1.15-8.6), p=0.01], seizures [23% vs. 7.2%; OR=3.85 (CI95%: 1.12-13.22), p=0.02] and psychosis [24% vs. 7.3%; OR=4.0 (CI95%: 1.15-13.79), p=0.01] occurred significantly more often in pediatric-onset SLE patients. Anti-P ribosomal antibodies were associated only with alopecia in both groups of SLE patients [37.4%; OR=4.1 (CI95%: 1.2-14.23), p=0.009].
Conclusions: Anti-P ribosomal antibodies are more prevalent in pediatric-onset SLE than in adult-onset SLE patients, and are associated with alopecia. Patients with pediatric-onset SLE more often have malar rash, photosensitivity and some neurological manifestations (seizures and psychosis).

P103

Neuroimaging abnormalities in early Systemic Lupus Erythematosus

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Introduction: To assess the prevalence of brain abnormalities in a monocentric cohort of patients with early SLE onset with or without neuropsychiatric (NP) manifestations.
Methods: SLE patients, less than fifty years old, diagnosed according to the 1997 American College of Rheumatology criteria, who underwent SPECT (single-photon-emission computed tomography) and MRI (magnetic resonance imaging) examinations within 12 months from the disease onset were evaluated. Brain MRI results were examined considering absence or presence of focal T2-weighted hyperintense lesions and/or atrophy. SPECT findings were evaluated, considering areas of focal, multifocal or diffuse hypoperfusion of the radio-tracer. Neuroimaging evaluations were performed by two independent and experienced neuroradiologists accordingly to a previously established local protocol. To assess whether early neuroimaging alterations could have a predictive role for the occurrence of subsequent NP events, especially in patients without clinical NP involvement but abnormal neuroimaging findings at baseline, the occurrence of new NP events was evaluated along a median follow up period of 60 months.
Results: 74 out of 752 patients included in the database of our lupus unit met the inclusion criteria. Their mean age was 33.6 (14- 49 yrs), 93.1 % female. Of these, 41 patients had at least one NP event (55.4 %). MRI was performed in all 74 patients and SPECT in 62 patients, 31 NP-SLE and 31 SLE. As a whole, 53 patients showed abnormalities in at least MRI or SPECT (71.6%) while 15 patients (20.3%) had abnormalities in both techniques.

Among SLE patients, 18 had abnormalities in at least one of the two neuroimaging techniques (54.5%), 9 MRI (27.2%), 14 SPECT (42.4%). Among the NP-SLE patients, 85, 4% had abnormalities in at least one of the two neuroimaging techniques (35 patients): 23 MRI (56.1%) and 22 SPECT (53.7%). Only 19/62 (30.6 %) patients had normal SPECT and MRI, 45.1% of SLE (14 cases out of 31) and 16.1% of patients NP-SLE (5 cases out of 31) ($p = 0.02$).

The follow up evaluation of 31 SLE patients without history or current NP involvement at the time of the neuroimaging evaluation, stratified in those who had abnormal (18 patients) and those with normal imaging (13 patients) at baseline revealed that 8 out of 31 patients with SLE had at least one new NP event: 4 of them had abnormal neuroimaging and 4 had normal neuroimaging at baseline.
Conclusion: neuroimaging abnormalities are present in a high percentage of early SLE patients.

Although in this study the predictive value of baseline neuroimaging has not been demonstrated, due to the high probability of new NP events in the course of follow-up (25 %) a baseline neuroimaging evaluation in young patients with newly diagnosed SLE should be recommended to facilitate the correct interpretation when new NP events do occur and new neuroimaging pictures will be obtained. The predictive value of neuroimaging in early SLE need to be re-evaluated in larger prospective cohort of patents.

P104

Preliminary Consensus Definition of a Low Disease Activity State in Systemic Lupus Erythematosus

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Background: In systemic lupus erythematosus (SLE), disease activity leads to organ damage, morbidity and ultimately mortality. While the diversity of clinical features of active SLE makes quantification of disease activity problematic, a definition of a state of low disease activity might be used to define success in therapy and clinical trials, or guide prognosis. In contrast to the situation in rheumatoid arthritis, in SLE there is currently no accepted definition of a low disease activity state and thus no related outcome data. We therefore sought to define a 'lupus low disease activity state' (LLDAS).
Methods: We defined LLDAS conceptually as 'a state which, if sustained, is associated with a low likelihood of adverse outcome'. Items for potential inclusion in a definition of LLDAS were generated by a panel of experts from Hong Kong, China, Philippines, Thailand, Singapore, Indonesia and Australia. These items were scored on a 5-point scale and reduced using the Delphi method. In the first round of Delphi, six experts participated, and items with a mean score of 3 or greater were retained. Eleven experts then participated in a consensus meeting using the nominal group technique, in order to discuss the items retained, and in the second round of Delphi, in which items with a mean score of 4 or greater were retained.
Results: Fifty-six 'unique' items were initially generated. These fell into two domains: (i) descriptors of disease activity, and (ii) immunosuppressive medication use. Following two rounds of Delphi and the consensus meeting, unanimous agreement on the preliminary definition of LLDAS was reached. The final list of five items defining LLDAS comprised:

Conclusion: Using consensus methods, we have defined LLDAS. As Asia-Pacific ethnicity is associated with an increased prevalence of SLE, and of severe organ manifestations, this LLDAS definition will be validated in a large multicenter Asian-Pacific lupus cohort, using outcomes including organ damage and death. Once validated, LLDAS may serve alone, or in combination with other variables such as patient reported outcomes, as a treatment target in SLE.

We acknowledge the financial support of GlaxoSmithKline. SLEDAI-2K $\leq$4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anemia, fever) and no gastrointestinal activity;No new features of lupus disease activity compared to the previous assessment;SELENA-SLEDAI physician global assessment (PGA, scale 0-3) $\leq$1;Current prednisolone (or equivalent) dose $\leq$ 7.5 mg daily; andWell-tolerated standard maintenance doses of immunosuppressive drugs and approved biologic agents, excluding investigational drugs.

P105

Pauciimmune crescentic anca associated glomerulonephritis in patients with lupus nephritis

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Introduccion and Aims: Lupus Nephritis (LN) es characterized by a focal segmental or diffuse membranoproliferative pattern associated to sub endothelial deposits and in few cases accompanied with crescents. On the other hand, ANCA Associated Glomerulonephritis tipically is characterized by a necrotizing vasculitis lesion and extracapillary proliferation with crescents in mor than 50% of glomeruli; Immunofluorescence (IF) typically is Pauciimmune. The aim of this study is to determine the histological features of ANCA Associated Glomerulonephritis in patients with LN.
Methods: We reviewed 14 cases of patients with Systemic Lupus Erythematosus (SLE) and ANCA positive serology who presented nephritic syndrome and acute renal failure. SLE diagnosis was made with American College of Rheumatologist Criteria. Clinical and epidemiological data was reviwed, renal biopsies were studied with HE, PAS and Masson staining, and IF were performed. ANCA serology was performed by IF for Cytoplasmatic and Perinuclear pattern; and after confirmed by ELISA for MPO and PR3 enzyme reaction.
Results: Twelve of 14 patients were women. Mean age was 36.07 +/-9.9 y. All patients had at least 4 ACR Criteria for SLE. Eleven patients were positive for ANCA MPO (106 +/- 44 ug/ml) and 3 patients for PR3 ANCA (102 +/- 67 ug/ml). Anti DNA ds mean values 76 +/- 18 ug/ml and SLEDAI score was 15 +/- 8. The onset mean creatinine 6.1 +/- 1.3 mg/dl, BUN 127 +/- 41 mg/dl, hemoglobin 9.1 g/dl. hemolytic anemia was confirmed in 9 patients. C3 complement was lower in 6 cases; proteinuria 1.8 +/- 1.2 g/d. Hematuria was present in all cases, 12 patients started with dialysis at the onset of the disease and 3 patients showed lung hemorrhage.

Biopsies had 21 +/- 8 glomeruli and 23% had global sclerosis. Mild to moderate tubular atrophy in 8 cases and severe atrophy in only 2. Four cases of mild interstitial fibrosis and the rest of them interstitial mononuclear inflamation. 71.4% was classified as LN Class III and 28.6 class IV. Crescents were present in 57.1 +/- 16% and most of them were epithelial type. Necrotizin vasculitis was observed in 85.6 %, cariorrexis in 42.9% of biopsies. IF showed pauciimmunity in all cases: absence of deposits in 78.6 % and mild (+/4+) deposits of C3 in capillary loops in 21.4% of glomeruli.
Conclusions: The patients with diagnosis of SLE with renal involvement who developed rapidly progressive glomerulonephritis were characterized by a crescentic necrotizing glomerulonephritis without deposits at IF examination in contrast that would be expected in typically Proliferative Lupus Nephritis. LN III was more frecuent to be associated with this features, and this could be by a differente physiopathological pathway involved. We recommend that all patients with LN should be tested for ANCA serology by ELISA and IF and should be performed aswell to define pauciimmunity in renal biopsies to investigate clinical onset and renal prognosis of these cases.

P106

Spinal Cord Inflammation in Systemic Lupus Erythematosus

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Background: Spinal cord inflammation (SCI) occurs in 1-2% of patients with systemic lupus erythematosus (SLE). Like brain involvement in SLE, the pathogenesis may include antiphospholipid antibody (APA) related spinal artery thrombosis or immune-mediated inflammation, secondary to autoantibodies such as neuromyelitis optica (NMO). We hypothesized that the clinical evolution of SCI with hyperacute onset will lead to poorer functional outcome since it might be related to an ischemic event.
Methods: We performed an analysis of 93 patients with SCI. This included 12 patients with 24 episodes from our own institution and 81 patients with 87 episodes from a literature review from 1980 to 2012. We defined the onset as hyperacute if maximal severity of neurological deficit was reached within 12-24 hours and acute/subacute if there was a slower onset of progressive deficits increasing beyond 24 hours. We predefined outcome as good, fair or poor depending on functional status at 6 months after the acute event, with poor outcome as minimal neurological improvement, deterioration, or death. Cases from the literature were accepted for analysis only if there was a clear description of onset and outcome. Neurological severity and MRI results were recorded as were the types of treatment used and laboratory data, including the results of APA testing. Analysis was done by Chi square or Fisher's exact.
Results: In total, 111 episodes in 93 patients were analyzed. Eleven patients (10%) had multiple (29) episodes of SCI. The onset of SCI was hyperacute in 25 (22.5%) and acute/subacute in 86 (77.5%) episodes. Good outcome was noted in 73 (65.8%) episodes, fair in 13 (11.7%) and poor in 25 (22.5%). A higher percentage of episodes with hyperacute onset had a fair/poor outcome than those with acute/subacute onset (60.0% vs. 26.7%, p=0.002). Severe neurological deficits were noted in 16 (64.0%) of episodes with hyperacute onset and 37 (43.0%) with acute/subacute onset (p=0.065). Episodes with severe deficits had a good outcome in only 25 (47.2%) compared with those with moderate 35 (79.6%) and mild 13 (92.9%) deficits, (p=0.0003). APA, recorded in 61(55.0%) episodes, was positive in 24 (39.3%). There was marginal association of APA with hyperacute onset (59% vs. 32%, p=0.053). Improvement in MRI (48 episodes) was not associated with type of onset but was associated with good clinical outcome (p=0.014). Thoracic cord was affected in 79%, either isolated (32%) or multilevel. Immunosuppressive medications, in addition to corticosteroids, were used in 65 (59%) episodes but had no influence on outcome.
Conclusion: SCI with hyperacute onset was associated with severe neurological deficits and a fair/poor outcome, whereas acute/subacute onset was associated with moderate or mild deficits and a good outcome. This supports our hypothesis that the pathophysiology of SCI may be multifactorial. Therefore, treatment strategies await the results of prospective larger case cohort studies.

P107

The validation of a new simple disease activity tool in Systemic Lupus Erythematosus (SLE): the Lupus Activity Scoring Tool (LAST) as compared to the SLEDAI SELENA modification.

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Background: SLE is a chronic autoimmune disease with variable manifestations. New developments in the understanding and treatment of SLE mandated closer monitoring of the disease activity and its response to treatment. Current disease activity indices (e.g. SLEDAI SELENA, BILAG & SLAM) have their own limitations. We designed a new disease activity evaluation tool: the Lupus Activity Scoring Tool (LAST) that simplifies the approach to quantify SLE activity while maintaining high sensitivity. We have also developed an easy to use electronic application of this tool.

Objectives: Primary: To validate a SLE activity tool with it correlation to the SLEDAI SELENA modification. Secondary: To test the usability and the accuracy of electronic application of the same tool in clinical settings.
Methods: The new disease activity tracking and evaluating tool included patient global assessment of disease activity (PGA), physician global assessment of disease activity (PHGA), and a formula incorporating the current immunomodulating medication used as an indication of SLE activity. The LAST included C3, C4 and Anti-ds Anti-DNA titer abnormalities as an activity indicator. Patients were seen in a rheumatology clinic within the last 12 months and had the laboratory investigations done within 2 weeks of their visit. The SLEDAI was calculated for each visit. The patients met the SLE ACR 1997 criteria update. Five different systems (algorithms) of weighting the different variables of disease activity were calculated. Apple iPad and Windows web-based applications were developed for the LAST and a clinical only LAST (without incorporating serological values). Descriptive statistics and correlation bivariates (Pearson's & Spearman's) were conducted. Each algorithm result and the disease activity of patients with multiple assessments were compared to the SLEDAI_SELENA scores.
Results: 23 patients (91% females) with 43 assessments were included. Scores from 5 algorithms of the variables in addition to the SLEDAI_SELENA scores were obtained at each visit. The mean (SD) age was 47.97 (14.61) years and the mean (SD) of disease duration was 12.26 (6.47) years. The mean (SD) SLEDAI score was 6.30 (4.01). The mean (SD) LAST (with C3, C4 and Anti-ds DNA) score was 39.85 (18.67). The correlation between the two new activity indices was very high: 0.920 with $p < 0.001$. The SLEDAI scores were consistent with the LAST scores at the baseline and follow-up visits: SLEDAI scores 0-4 corresponded to the LAST scores of 0-30 while SLEDAI scores of 8 or higher corresponded to 50 and higher, respectively. The electronic applications of the LAST were easy to use and no errors were found with their results as compared to the manually obtained scores.
Conclusion: Lupus Activity Scoring Tool (LAST) is a new disease activity index correlated well with the SLEDAI_SELENA modification. The use of simple clinical variables as a measure of SLE activity seems to be valid. The development of easy to use electronic apps will make the use of these activity tracking tools easier to calculate and can be possibly utilized in non-specialist settings.

P108

Effect of disease activity patterns on damage accrual in systemic lupus erythematosus: a seven-year follow-up study.

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Aim: to evaluate damage accrual and predictors of damage in a cohort of patients affected with systemic lupus erythematosus (SLE).
Patients and methods: we used our Lupus Database which includes patients recruited between 1970 and 2012. Patients diagnosed with SLE before 2004 and regularly seen from 2004 to 2010 were considered. Clinical and laboratory parameters were recorded at each visit.

Damage accrual was defined using "Systemic Lupus International Collaborating Clinics (SLICC)/ACR" damage index. SLICC was evaluated in 2004 (T0) and in 2010 (T1).

Disease activity patterns during the follow-up were defined using SLEDAI-2K, excluding serology, as follows: serological active clinical quiescent disease (CQD): a SLEDAI-2K=0 in the entire follow-up; minimal disease activity (MDA): SLEDAI-2K=1 in one or more visits; chronic active disease (CAD): SLEDAI-2K≥2 in at least half of the follow up; relapsing-remitting disease (RRD): periods of SLEDAI-2K≥2 interspersed with periods of SLEDAI-2K=0.

The following factors were considered as possible predictors of damage accrual: sex, age at SLE onset, SLE duration, lag-time between SLE onset and diagnosis, anti-dsDNA antibodies, C3 and/or C4 low levels, immunosuppressive therapy, mean daily dose of prednisone or equivalent > 5 mg, number and type of SLE flares, pattern of disease activity including combined CAD and RRD (CAD/RRD).

The study was approved by the local ethical Committee.
Results: 165 patients, out of 356 diagnosed between 1970 and 2004, fulfilled inclusion criteria.

At T0, SLICC median (25°-75° percentiles) value was 0.78 (0-1), whereas at T1 it was 1.24 (0-2) ($p < 0.01$). A damage accrual during the follow-up (SLICC T1 > SLICC T0) was observed in 60 patients (36.4%); conversely, in 105 patients (63.6%) SLICC remained unchanged.

As reported in the table, musculoskeletal, cutaneous, renal, neurological and vasculitic flares were more frequent in patients with damage accrual compared with patients without.

An association between damage accrual and male sex (p=0.05), anti-dsDNA antibodies (p=0.003), immunosuppressive therapy ($p < 0.001$), mean daily dose of prednisone or equivalent > 5 mg ($p < 0.001$), number of flares ($p < 0.001$), and CAD/RRD patterns ($p < 0.001$) was observed. At the multivariate analysis, high dose of steroid therapy and the CAD/RRD patterns were independent predictors of damage accrual (R^2=0.33; OR 15.11, 95% CI 4.66-48.86, $p < 0.001$; OR 2.83, 95% CI 1.12-7.54, p=0.037, respectively).
Conclusions: At the end of the study, one third of SLE patients of this cohort had an increase in SLICC/ACR index. At the multivariated analysis, CAD/RRD patterns and high mean daily dose of prednisone were independent predictors of damage accrual.

P109

Pulmonary Hemorrhage in Systemic Lupus Erythematosus of Latin American Prospective Inception Cohort (GLADEL)

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Table

	SLE cohort, 165 patients Number (%)	*Patients with SLICC T1 > T0 60 (36.4) Number (%)*	*Patients with SLICC T1=T0 105(63.6) Number (%)*	*p*
Number of flares	221	138 (62.4)	83 (37.6)	< 0.001
Type of flare: Musculoskeletal	43 (19.5)	27 (62.1)	16(37.9)	< 0.001
Cutaneous	57 (25.8)	39 (67.4)	18 (32.6)	< 0.001
Renal	66 (30)	41 (60.7)	25 (39.3)	< 0.001
Nervous system	4 (1.8) 3	3 (75)	1 (25)	< 0.001
Haematologic	31 (14)	15 (48)	16 (52)	n.s.
Vasculitis	7 (3.2)	5 (71.4)	2 (28.6)	< 0.001
Serosal	13 (5.8)	7 (53.4)	6 (46.6)	n.s.

Introduction: Pulmonary hemorrhage (PHe) is an uncomon, potentially catastrophic complication of systemic lupus erythematosus (SLE), with frequency estimates ranging from 2 to 5.4% in cohorts of lupus patients and for 1.5 to 3.7% of hospital admissions due to SLE. The survival rate was quite variable from 50% to 100%.
Objectives: Establish the prevalence of PHe in patient with SLE. Analyze the socioeconomic-demographic, clinical and serological features, and mortality in patients with SLE and PHe.
Material and methods: Was included 1480 patients with a recent SLE diagnosis (≤2 years) and were followed for 4.5 years, from 34 centers of 9 Latin-American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela). We compared the socioeconomic-demographic, clinical and serological variables among patients with/without PHe. The statistical analysis included chi-square test for categorical variables and t test or Mann Witney test for continuous variables. Results with $p < 0.1$ were included for multivariate logistic regression analysis and significant $p \leq 0.05$. Kaplan Meier survival curve was examined.
Results: Sixteen patients had PHe, representing 1.1% of total (16/1480) and 3.2% of patients with pleuropulmonary manifestations (16/486), 14 (87.5%) were women, with a mean age (SD) at SLE onset of 30.1 (12.9) years. Four (25%) patients had PHe before the diagnosis of SLE, two patients had more than one episode of PHe.

Table 1 shows socioeconomic-demographic, clinical and serological feature the patients with /without PHe. In multivariate analysis the presence of PHe was associated with heart compromise ($p < 0.01$. OR: 6.1; 95%CI: 1.6-23.9) and presence of lupus anticoagulant ($p = 0.03$. OR: 4.4; 95%CI: 1.1-18.9)

Table 1. Socioeconomic-Demographic, Clinical and Serological Feature Patient with Systemic Lupus Erythematosus According to the Presence of Pulmonary Hemorrhage. Univariate Analysis

	With PHe (n 16)	*Without PHe (n 1464)*	*p*
Female n (%)	14 (87.5)	1316 (89.9)	0.6
Age of SLE onset m (DS)	30.1 (12.9)	28.1 (12)	0.4
Ethnicity Withe n (%)	5 (31.3)	601 (41.1)	0.1
Ethnicity Withe/Indian n (%)	11 (68.8)	634 (43.3)	0.1
Ethnicity African/Latin/ American n (%)	0	186 (12.7)	0.1
Ethnicity Others n (%)	0	43 (2.9)	0.1
SES High/Medium High n (%)	0	152 (10.4)	0.3
SES Medium n (%)	4 (25)	423 (28.9)	0.3
SES Medium Low/Low	12 (75)	889 (60.7)	0.3
Systemic Manifestations n (%)	15 (93.8)	1202 (82.1)	0.3
Musculoskeletal Manifestations n (%)	13 (81.3)	1362 (93)	0.09
Ocular Manifestations n (%)	2 (12.5)	257 (17.6)	1
Cutaneous Manifestations n (%)	15 (93.8)	1372 (93.7)	1
Heart Compromise n (%)	**11 (68.8)**	**311 (21.2)**	**< 0.001**
Ischemic Heart compromise n (%)	2 (12.5)	88 (6)	0.2
Renal Compromise n (%)	**16 (100)**	**860 (58.7)**	**0.001**
Neurologic Manifestations n (%)	9 (56.3)	516 (35.2)	0.08
Hematologic Compromise n (%)	15 (93.8)	1153 (78.8)	0.2
ANA positive n (%)	16 (100)	1377 (94.1)	0.6
Anti DNA positive n (%)	11 (68.8)	880 (60.1)	0.4
Anti RNP positive n (%)	3 (18.8)	319 (21.8)	1
Anti Sm positive n (%)	4 (25)	346 (23.6)	1
Anti Ro positive n (%)	3 (18.8)	340 (23.2)	1
Anti La positive n (%)	3 (18.8)	188 (12.8)	0.4
Lupus Anticoagulant positive n (%)	3 (18.8)	92 (6.3)	0.07
Anti cardiolipin IgG positive n (%)	6 (37.5)	357 (24.4)	0.2
Anti cardiolipin IgM positive n (%)	5 (31.3)	249 (17)	0.1
Anti BG1 positive n (%)	0	37 (2.5)	1
Hypocomplementemia n (%)	11 (68.8)	845 (57.7)	0.3
Pulmonary infections n (%)	3 (18.8)	98 (6.7)	0.09
Antiphospholipid syndrome n (%)	0	61 (4.2)	1
SLICC excluding respiratory M (min-max)	**3 (0-8)**	**1 (0-9)**	**< 0.001**
SLEDAI average M (min-max)	**7.5 (0.8-21.7)**	**3.5 (0-51)**	**0.02**

SES: Socioeconomic status SLICC:Systemic Lupus International Collaborating Clinics SLEDAI:Systemic Lupus Erythematosus Disease Activity Index

During the follow-up period 7 (43.8%) patients died with PHe vs. 83 (5.6%) patients without PHe ($p < 0.01$. RR: 13.1; 95%CI: 4.7-36.1).
Conclusions: The prevalence of PHe in this cohort of patients with SLE is 1.1%. The presence of PHe is associated with the presence of cardiac and renal manifestations, higher SLICC and SLEDAI. The PHe is independently associated with heart compromise and lupus anticoagulant. The presence of PHe increases the risk of death 13 times.

P110

Atherosclerosis and ischemic events in patients with Systemic Lupus Erythematosis – a cross sectional comparision with Systemic sclerosis patients and controls

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Introduction: Epidemiological studies demonstrate that patients with SLE have more CVD than controls, and accelerated atherosclerosis is thought to be a major underlying cause. Less is known about the frequency of atherosclerosis and CVD in comparison to other systemic autoimmune diseases. We studied the occurrence of CVD and ultrasound derived surrogate measures of atherosclerosis in the carotid arteries in patients with SLE and Systemic sclerosis (SSc) and in controls.
Materials and methods: From cohorts comprising 303 SLE patient and 111 SSc patients, 83 SLE patients were individually matched for age, gender and region of living with 83 SSc patients and with 161 population-based controls. The mean intima media thickness (mIMT) and the frequency of plaques (local IMT >1mm) were examined in the carotid arteries. History of CVD events were tabulated, defined as:

Results: Mean age was 58 ± 11 years for the two patient groups and controls. SLE patients had more CVD events than both SSc patients and controls (20%, 10% and 3% respectively) mainly due to more ICVD. Frequency of plaques and mIMT did not differ between SLE-patients, SSc patients and controls. But SLE-patients had more systemic inflammation than both SSc patients and controls.
Conclusion: Despite a higher prevalence of ischemic vascular event, especially cerebrovascular events, in patients with SLE, the frequency of plaques and the mIMT did not differ between SLE patients, SSc patients and controls. Our results suggest that other mechanisms than atherosclerosis are major contributors to the high prevalence of CVD in patients with SLE and possibly also in patients with other systemic autoimmune diseases such as SSc. The cross-sectional design limits our study to survivors of CVD. The older age at onset of SSc, is the reason why matched SLE patients were older in this study than in most SLE cohorts. Therefore we cannot generalize these results to younger patients with SLE.Ischemic heart disease (IHD): myocardial infarction (confirmed by electrocardiography and a rise in plasma creatine kinase, muscle and brain fraction (CK-MB) or troponin T) or angina pectoris (confirmed by exercise stress test)Ischemic cerebral

vascular disease (ICVD): cerebral infarction (confirmed by computer tomography) or transitory ischemic attacks (TIA, defined as transient

	Occurence of Atherosclerosis and ischemic event			***SLE vs SSc***	***SLE vs Controls***
	SLE (n=83)	*SSc (n=83)*	*Controls (n=161)*	*OR (95% CI)* P-value	*OR (95% CI)* P-value
Event % (n)	20 (17)	10 (8)	3 (5)	2.4 (1.0-5.9) *0.05*	8.3 (2.8-22.7 *<0.0001*
IHD % (n)	12 (10)	7 (6)	2 (3)	1.7 (0.6-5.1) *0.7*	7.2 (1.9-27.0) *0.0008*
ICVD % (n)	8 (7)	0 (0)	0.6 (1)	- *0.01*	14.6 (1.8-121.2) *0.001*
IPVD % (n)	4 (3)	4 (3)	0.6 (1)	1.0 (0.2-5.1) *1.0*	6 (0.6-58.6) *0.08*
Plaque % (n)	30 (25)	35 (29)	26 (41)	0.8 (0.4-1.5) *0.6*	1.2 (0.7-2.2) *0.5*
IMT mm	0.62 (0.5-0.7)	0.63 (0.6-0.7)	0.62 (0.5-0.7)	- *0.9*	- *0.6*

focal symptoms from the brain or retina with a maximum duration of 24 hours),Ischemic peripheral vascular disease (IPVD): intermittent claudication or peripheral arterial thrombosis/embolus (confirmed by angiogram or Doppler flow studies).

P111

Relationship between individual organ damage and mortality of systemic lupus erythematosus (SLE): a prospective cohort study of 679 patients

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Objectives: To study the relationship between damage in different organ systems and mortality in patients with SLE.
Methods: 679 patients who fulfilled >=4 of the ACR criteria for SLE (1995-2011) were prospectively followed. The cumulative survival rate was studied by Kaplan-Meier's plot. Organ damage was assessed by the SLICC damage index (SDI). Cox regression models were established to study the association between damage in individual systems and mortality.
Results: 679 Chinese SLE patients were studied (92% women; age of SLE onset 32.5+/-13.6 years; mean follow-up time 117+/-89 months). 67 (9.9%) patients died during the course of illness and 33 (4.9%) patients were lost to follow-up. 23 (3.4%) patients developed end stage renal failure (ESRF). The main contributing causes of death were: infection (51%), cardiovascular events (12%), cerebrovascular events (16%), cancer (9%), suicide (3%) and others (8%). Infective complications were the commonest causes of death both in patients with disease duration of less (55%) and more than 5 years (47%). In patients with SLE for less than 5 years, 19% of all deaths were caused by vascular events, which was lower than those with disease for more than 5 years (36%). The cumulative survival rate of the patients was 94.8% at 5 years, 91.3% at 10 years and 88% at 15 years. 301 (44%) patients had organ damage (SDI score >=1). Among patients who had organ damage, the frequency of damage in individual systems was, in decreasing order: neuropsychiatric (N=102, 15%), musculoskeletal (N=93, 14%), renal (N=78, 11%), ocular (N=46, 6.8%), cardiovascular (N=38, 5.6%), pulmonary (N=36, 5.3%), gonadal (N=32, 4.7%), endocrine (N=23, 3.4%), peripheral vascular (N=22, 3.2%), malignancy (N=19, 2.8%) and gastrointestinal (N=8, 1.1%). Within the first 5 years of onset of SLE, neuropsychiatric damage was most frequent (10%), followed by renal (7.9%) and dermatological (7%) damage. In patients with SLE duration of more than 5 years, the commonest cause of damage was in the musculoskeletal system (18.4%), followed by neuropsychiatric (17%) and renal damage (13.3%). The presence of any organ damage was significantly associated with mortality (HR 6.42[3.05-13.5]; p<0.001). Cox regression analysis revealed that damage in the neuropsychiatric system (HR 1.74[1.31-2.32]; p<0.001), renal (HR 1.97 [1.61-2.42]; p<0.001), cardiovascular (HR 1.75 [1.21-2.53]; p=0.03) and pulmonary (HR 2.63 [1.50-4.62]; p=0.001) systems was significantly associated with mortality.
Conclusions: In patients with SLE, organ damage predicts mortality, in particular damage in the renal, nervous, cardiovascular and pulmonary systems. Neuropsychiatric damage is commonest in early disease while musculoskeletal damage is most frequent in long-standing disease. Prevention of infective and cardiovascular complications, and minimization of renal damage is important in improving SLE survival.

P112

Repeat biopsy in lupus nephritis: a single-center experience in the 21st century

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Introduction: renal involvement in systemic lupus erythematosus (SLE) is an important cause of morbidity and even mortality. Lupus nephritis has diverse morphologic manifestations with varying clinical presentations and consequences. Treatment and prognosis accordingly range from excellent even with only observation with minimal mesangial deposits, to kidney failure despite aggressive immunosuppression in patients with severe proliferative disease. Renal biopsy plays a crucial role in the diagnosis of the specific form of lupus nephritis, and rebiopsy is often necessary during follow up in order to assess renal activity and guide treatment. We retrospectively reviewed patients with lupus nephritis who had more than one renal biopsy in our hospital and analized clinical, pathological and treatment changes after successive biopsies.
Methods: SLE patients (ACR criteria) who had a diagnosis of lupus nephritis and two or more renal biopsies were selected. Those with second biopsy after year 2001 were included. Electronic medical records were reviewed and clinical, laboratory and treatment data were obtained from each patient. Renal biopsy was evaluated according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis.
Results: we identified 45 lupus patients (40 females) with at least two renal biopsies. These patients had a total of 115 biopsies. Class IV (50.9%) and V (18.5%) were the most frequent findings. Treatments received are shown in table 1. Laboratory findings at the moment of biopsy are shown in table 2 and showed no significant differences between histologic patterns. 26 patients (57.8%) changed histology

classification between successive biopsies and 16 did not (35.6%). Those who did not change were mostly class IV (68.8%). 54 rebiopsies (85.7%) generated a treatment modification and 9 (14.3%) did not (insufficient data from 7). Seven patients (15.6%) had end stage renal disease (ESRD) (6 females). Having ever used cyclophosphamide was not protective for ESRD (p=0.66) and within this group similar number of patients received larger (more than 6 IV pulses) or lower doses of cyclophosphamide (p=0.77).

Table 1.

Induction treatment	*Maintenance treatment*
IV Cyclophosphamide >= 6 pulses (34.3%)	Mycophenolate (58.7%)
Mycophenolate (25.7%)	Azathioprine (20.7%)
IV cyclophosphamide < 6 pulses (13.3%)	Cyclophosphamide (9.8%)
Rituximab (5.7%)	Others (10.9%)
Others (21%)	

Table 2.

	Class II	*Class III*	*Class IV*	*Class V*	*Combination b/ III or IV + V*
Mean proteinuria (g/24 hs)	1.14	1.49	2.13	2.09	5.16
Mean creatinine (mg/dl)	1.03	1.1	1.2	1.6	0.95
Patients with hematuria, (>4 RBC), %	88.9%	55.6%	69%	40%	50%
Mean Albumin (g/dl)	3.23	3.47	2.6	2.88	2.7
Low C3, %	57.1 %	25%	71.8 %	64.3 %	60%
DNA +, %	66.7%	44.4%	69.2%	26.7%	40%

Conclusions: in this lupus nephritis cohort, 85.7% of repeat biopsies changed physician's treatment. Taking into account that histological findings did not correlate with laboratory parameters, rebiopsies were necessary to adjust treatment regimens properly and improve lupus patients' outcomes.

P113

Safety and efficacy of etanercept in systemic lupus erythematosus

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TNF is a strong mediator of inflammation with a controversial role in SLE. Whereas few open-label studies have shown efficacy of anti-TNFα agents in patients with SLE arthritis and renal disease, many others have reported its potential risk of autoantibody formation.
Objective: To evaluate the efficacy and safety of etanercept in patients with extra-renal active SLE.
Methods: In this open-label study, 42 patients with active SLE (10 with serositis, 6 with shrinking lung syndrome and 35 with arthritis refractory to other therapies) were given etanercept in addition to conventional immunosuppression therapy.
Results: Forty two lupus patients (34 female and 8 male, mean age 38.2 (18-60) received etanercept (50 mg/weekly). Patients were followed up for 24 months (3-6). Two of them withdrew from the study due to significant local reactions. Of the remaining patients, clinical improvement was observed in 38 of them (95%). Six patients had to be switched to adalimumab due to etanercept side-effects or lack of efficacy. Eight of the ten patients (90%) with pleuropericarditis achieved clinical remission in a mean period of 5.67±2.65 weeks. In four patients (80%) with SLS, FVC (%) rose from 43±12 to 58±16 ($p < 0.05$) at the end of treatment. Thirty-five patients (92%) with joint involvement achieved remission of arthritis. Relapse was frequent after stopping medication and occurred 8-11 weeks after stopping treatment. The main adverse effects were local reactions (14%) and urinary tract infection (5%). Levels of ANA and/or anti-dsDNA rose in 6 patients (14%), but were not associated with lupus flare.
Conclusions: Anti-TNF agents are safe and efficacious in SLE and did not lead to an increase SLE activity. In view of their anti-inflammatory properties they can be a therapeutical alternative for refractory serositis and SLS.

P114

Reduced olfactory function in SLE and NPSLE patients

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Objective: To evaluate the sense of smell in SLE patients aged less than 50 years old with and without CNS involvement and to compare the results with those obtained from a control population including both age-matched RA patients and age-matched healthy controls.
Methods: Olfactory function was evaluated in 50 SLE patients without CNS involvement, 25 NPSLE patients, 25 RA patients and 50 healthy controls. A Sjogren's Syndrome was excluded both in SLE and in RA patients. Levels of olfactory functions were assessed using the 3 stages of the Sniffin' Sticks Kit, which is based on a pen-like odor-dispensing device. In stage 1, threshold was valued using n-butanol as a single odorant at a certain diluition. The subject was then asked to identify the stick with the odorant. In stage 2, discrimination between 2 different odorants was assessed. The subject was presented with 3 pens; 2 contained the same odorant and 1 contained a different one. The subject was then asked to differentiate between pens. In stage 3, the ability of the subject to identify an odorant out of 4 options was evaluated. The maximum score in each stage was 16 points, with a maximum possible total score of 48 points for the stages of threshold, discrimination and identification (TDI) combined. Patients with a TDI score of > 30 are considered to have normal olfaction, patients with a score of 15-30 are considered to have decreased olfaction, and patients with a score of <15 are considered to have a loss of olfaction. Univariate comparisons between nominal variables were performed by chi-square test. P values less than or equal to 0.01 were considered significant.
Results: The mean age of the 4 studied groups were as follow: SLE population 35.9 ± 8.3 years; NPSLE population 38 ± 7 years; RA population 41 ± 6 years and healthy controls 28 ± 4 years. A young age was selected in order to avoid influence of age on olfactory function. A decrease in the sense of smell was documented in SLE and NPSLE (but not in RA patients) compared to healthy subjects. This difference appeared statistically significant (SLE TDI 31.6± 5.3, NPSLE TDI 29.6 ± 6.4 vs healthy controls TDI 35.7 ± 3.2; for both parameters p < 0,01) and was confirmed either considering TDI all together either taking into consideration threshold, discrimination and identification separately. Any statistically difference was noticed when comparing SLE vs NPSLE patients even if hyposmia and anosmia were more frequently documented in NPSLE patients (respectively 40% vs 26% and 4% vs 0).
Conclusions: Our study revealed significant olfactory deficits in SLE and NPSLE patients compared to age-matched healthy controls and compared to a population affected by RA. Preliminary results do not confirm, as previously stated by other authors, a major involvement of the olfactory function in NPSLE patients compared to SLE patients even if the first one showed more frequently hyposmia and anosmia.

P115

Metabolic syndrome and tumor necrosis factor in childhood-onset systemic lupus erythematosus

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Background: Patients with systemic lupus erythematosus (SLE) have a higher incidence of metabolic syndrome (MetS). Among the possible causes we may mention the inflammation associated with increased levels of triglycerides and cytokines such as tumor necrosis factor alpha (TNF-α), in addition to other factors that may cause the increase of cholesterol and its LDL fraction.
Objective: To analyze the association of MetS and TNF-α serum levels in cSLE patients according to age-adjusted criteria. Methods and Patients: We screened consecutive cSLE patients followed in a cohort at the pediatric rheumatology unit at the State University of Campinas. All patients had disease-onset before the age of 16. Controls were matched for age, sex and demographic background. cSLE patients were assessed for disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] both at study entry and over time. Total dose of prednisone was calculated in prednisone equivalent during the entire follow-up period. MetS was assessed using the definitions recommended by The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEPIII) definition adjusted according to age. We determined height, weight, waist circumference (WC) and hip circumference (HC), measurements and fractions of cholesterol and fasting glucose levels for each individual. TNF-α levels were measured by ELISA. Obesity was definite when Body Mass Index (BMI) was above 30kg/m2.
Results: We included 51 cSLE patients (47 women, mean age 17.6 years (SD±3.7; range) and 51 controls (47 females, mean age 18.2 years (SD±6.4; range). Disease duration was 12.47 years (SD±2.86; range 6-16 years). Thirty-seven (18.8%) patients were above the recommended average WC/HC, compared to 14 (7.14%) controls ($p < 0.05$). MetS was identified in 9 cSLE and 1 control (p=0.01). We observed higher TNF-α (p=0.036) levels in patients with obesity. The mean serum TNF-α level was 4.47±8.95pg/ml in cSLE, compared to 1.83±1.82pg/ml in healthy controls (p=0.004). No association between MetS criteria and serum TNF-α levels was observed. We observed a significant correlation between adjusted SLEDAI scores over time and the prevalence of MetS (r=0.68; p=0.01). In addition, TNF-α (p=0.001) levels were significantly increased in patients with active disease (SLEDAI≥3) when compared to patients with inactive disease. TNF-α levels correlated directly with SLEDAI scores (r=0.4; p=0.002). No correlation between cumulative corticosteroid dose, SDI scores and other clinical manifestations and prevalence of MetS was observed.
Conclusion: cSLE patients have a higher prevalence of MetS than the general population. Disease activity over time was the only disease characteristics associated with MetS. The higher risk of coronary disease and atherosclerosis makes the evaluation of MetS imperative in cSLE patients.
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P116

Abnormal sense of smell in systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disorder with heterogeneous clinical manifestations.Up to 75% of SLE patients suffer from a variety of neuropsychiatric manifestations (NPSLE patients), which are considered as a major cause for morbidity and mortality in SLE. Recently, links between the olfactory system, the immune system, and various diseases have been identified. The sense of smell is vital and has an important role in environment recognition. Olfaction is a complex process of the central nervous system (CNS) involving specific areas of the brain (e.g., the limbic system) and olfactory dysfunction has been confirmed in various CNS diseases, as well as in multiple sclerosis and SLE.
Objective: To assess the olfactory functions in SLE patients compared with age- and sex-matched healthy controls, and to examine the association between the sense of smell and disease activity, damage and CNS involvement (depression and anxiety).
Methods: Olfactory functions were evaluated using the Sniffin' Sticks test, the 3 stages of which are threshold, discrimination, and identification of different odors. All individuals were submitted to a standardized neuropsychiatric evaluation. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory (BDI and BAI). In SLE, disease activity was evaluated through SLE Disease Activity Index (SLEDAI), damage through Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC-SDI) and current drug exposures. We excluded patients with head injuries, nasofacial operations, or active nasal-sinus or allergic diseases. We use Kruskall-Wallis test, Fischer exact test and Spearman correlation. $p < 0.05$ was considered significant.
Results: We included 200 patients (92.0% women) mean age of SLE patients was 38.96 +- 12.06 years and 139 controls matched for age and sex. A decrease in the sense of smell was observed in SLE patients (56.0%) and controls (29.49%) ($p < 0.01$), while loss of smell (anosmia) was documented in SLE patients (2.5%) and controls (0.72%) ($p < 0.01$). Patients had an average of 28.94 +- 5.42 total points at the 3 stages of Sniffin' Sticks test while the controls had mean of 32.39 +- 5.53 points ($p < 0.001$). 9.5% of the patients smoked while of the patients smoked, while in controls this percentage was 6.43% (p=0.423), however, no observed significant difference was between olfactory alteration and smokers and nonsmokers (p=0.790). The olfactory alteration was correlated with depression (r=0.231; $p < 0.001$), anxiety (r=0.175; p=0.001) and SLICC (r=0.035; $p < 0.05$).
Conclusions: Comparing SLE patients and matched controls, we observed a significant decrease in the olfactory abilities in SLE patients, which was correlated with damage index and CNS manifestations. Based on the literature, smell deficiency has been suggest to be an early and predictive sign in several CNS diseases, and therefore, might be a useful and easy tool for the physician in early diagnosis of CNS involvement in autoimmune disease.
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P117

Partial and Complete Recovery From Proteinuria in Lupus Nephritis Patients Receiving Standard of Care Treatment

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Background: In the majority of clinical trials on lupus nephritis (LN), partial proteinuria recovery (PPR) is considered a secondary end point.

To determine: 1) the percentage of patients who achieve complete proteinuria recovery (CPR), PPR but incomplete proteinuria recovery and CPR or PPR in LN patients receiving standard treatment (SOC) at 6 months, 1 year and 2 years, and 2) determine if the initial level of proteinuria predicts recovery from proteinuria.
Methods: We studied all active LN patients at the Lupus Clinic (1970-2011). Proteinuria was defined as >0.5g/24 hours. Patients with proteinuria and at least one of the urinary sediments (hematuria, pyuria or casts) present at the entry of the study and persistent on 2 consecutive

visits were enrolled. Patients were grouped: group 1 as 0.51-0.99g/day, group 2 as 1-2g/day and group 3 as ≥2g/day.

Study end points: 1) CPR <0.5g/day based on SLEDAI-2K, 2) PPR a decrease of ≥ 50% in the level of proteinuria from baseline as defined by SLEDAI-2K Responder Index-50 (S2K RI-50), 3) CPR or PPR and 4) no response (<50% decrease in the level of proteinuria).

We determined:The percentage of responders who achieved PPR, CPR, PPR or CPR present on 2 consecutive visits at: 6 months, 1 year and 2 yearsThe percentages of responders were evaluated for each initial proteinuria levels using Kaplan-Meier curves

Results: 217 patients (83% F) were identified (age and duration of lupus at the start of the study was 34.2 ± 12.4 and 5.7 ±6.3 years). PPR was achieved by 19% of patients by 6 months, 21% by 1 year and 20% by 2 years. CPR was achieved by 7% of patients by 6 months, 25% by 1 year and 46% by 2 years. PPR or CPR was achieved by 26% of patients by 6 months, 46% by 1 year and 66% by 2 years. A Moderate (1-2g/day)-high (≥2g/day) level of proteinuria at baseline led to more responders with PPR as the outcome at 6 months, 1 year and 2 years ($p < 0.05$).

Conclusion: Complete proteinuria recovery is slow. High Level of baseline proteinuria leads to more responders with partial recovery. The percentage of responders increased when PPR or CPR is the end point. PPR or CPR should serve as the primary end point in research studies and clinical trials.

P118

Effect of renal disease on standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus

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Objectives: To study the effect of renal disease on standardized mortality ratio (SMR) and life expectancy (LE) of patients with systemic lupus erythematosus (SLE).

Method: Patients with >=4 ACR criteria for SLE who were prospectively followed in our unit from 1995 to 2011 were studied. The cumulative survival rate, SMR and LE was calculated, and the effect of renal involvement, histological classes, renal damage and end stage renal disease (ESRD) on these parameters was evaluated.

Results: 694 SLE patients were studied (92% women; age of onset 32.9+/-13.4 years). Renal disease occurred in 368(53%) patients and the ISN/RPS histological classes in 285 patients were: I (1%), II (6%), III (19%), IV (47%), III/IV+V (10%) and V (16%). Renal damage was present in 79(11%) patients and 24(3%) developed ESRD after 9.6+/-7.3 years. The age and sex adjusted hazard ratio(HR) of mortality in patients with renal disease, renal damage and ESRD compared with those without was 2.23[1.29-3.85] (p=0.004), 3.59[2.20-5.87] ($p < 0.001$) and 9.20[4.92-17.2] ($p < 0.001$), respectively. The proliferative types (adjusted HR 2.28[1.22-4.24]; p=0.01) but not pure membranous (adjusted HR 1.09[0.38-3.14]; p=0.88) type of lupus nephritis were associated with a significant increase in mortality. The age and sex adjusted SMRs of non-renal SLE patients, patients with lupus nephritis, proliferative nephritis, pure membranous nephritis, renal damage and ESRD were 4.8[2.8-7.5], 9.0[6.7-11.9], 9.8[6.5-14.1], 6.1[2.0-14.1], 14.0[9.1-20.5] and 63.1[33.6-108.0], respectively. Compared to the population, LE was reduced by 15.1 and 23.7 years, respectively, in SLE patients with renal disease and renal damage.

Conclusion: The presence of renal disease, in particular proliferative nephritis causing renal insufficiency, significantly reduces survival and LE of SLE patients.

P119

Assessment of sexual life in women with systemic lupus erythematosus

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Objectives: To evaluate the sexual life in women with Systemic Lupus Erythematosus (SLE).

Methods: A cross-sectional study including 165 consecutive SLE women was performed at the Rheumatology Unit of the State University of Campinas. Patients were asked to fill out the Short Personal Experiences Questionnaire (SpeQ) anonymously. One hundered and twenty five (75%) SLE women filled out the questionnaire. The control group consisted of 40 healthy women, matched by age, education and socio-economic status.

Results: We included 125 women with SLE (mean age 32 years; SD=11.93; range: 14 – 65) and 40 controls (mean age 30 years; SD= 11.09; range: 16-52). Regarding their marital status, 66/125 (52.8%) SLE and 11/40 (27.5%) controls ($p < 0.05$) were married, 41/125 (32.8%) patients and 29/40 (72.5%) controls were single ($p < 0.05$) and 18/125 (14.4%) patients and 1/40 (2.5%) controls were widows ($p < 0.05$). Absence of sexual activity (masturbation, excitation and/or penetration) within the last month was reported by 39/125 (31.2%) SLE and 5/40 (12.5%) ($p < 0.05$) controls, 70/125 (56%) patients and 34/40 (85%) controls ($p < 0.05$) had sexual activity up to 2 times/week, and 16/125 (12.8%) SLE and 2/40 (5%) ($p < 0.05$) had sexual activity > 2 times/week. Absence of sexual thoughts and fantasies was reported by 42/125 (33.6%) patients and 5/40 (12.5%) controls ($p < 0.05$), whereas 65/125 (52%) patients and 33/40 (82.5%) controls ($p < 0.05$) had sexual thoughts and fantasies up to 2 times/week and 18/125 (14.4%) patients and 2/40 (5%) controls ($p < 0.05$) had sexual thoughts and fantasies > 2 times/week. Absence of orgasm was reported by 84/125 (67.2%) and 9/40 (22.5%) controls ($p < 0.05$). Absence of stimulation or arousal during sexual activity was reported by 73/125 (58.4%) patients and 7/40 (17.5%) controls ($p < 0.05$) and absence of satisfaction in sexual activities was reported in 71/125 (56.8%) patients and in 7/40 (17.5%) controls ($p < 0.05$). Sexual partners were confirmed by 77/125 (61.6%) patients and 37/40 (92.5%) controls ($p < 0.05$). Problems with the partner were referred by 13/77 (16.9%) patients and 0/37 controls ($p < 0.05$); pain during sexual intercourse was reported as the most frequent problem by 16/77 (22.08%) patients and 2/37 (5.4%) controls ($p < 0.05$).

Conclusion: SLE patients had a worse sexual life than the control group, with less sexual activity, lower prevalence of sexual thoughts and fantasies and orgasm. The number of SLE patients with sexual partners was also significant lower and pain during sexual intercourse was the most frequently reported problem. With improvement of survival, physician should pay greater importance in evaluating quality of life of SLE patients and sexual life is directly related to it.

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P120

Role of early repeated renal biopsies in lupus nephritis

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Background: A renal biopsy is generally recommended for diagnosis and is necessary for classification of lupus nephritis (LN), but second biopsies after immunosuppressive therapy are seldom a routine procedure. We studied LN-patients in whom repeated biopsies were performed after induction treatment, regardless of clinical response. We

compared histopathological findings to clinical response and studied long-time renal outcome in order to evaluate if repeat biopsies may contribute to define treatment response as well as influence prognosis in LN.

Patients and Methods: Sixty-seven patients with active LN were included. Renal biopsies were performed at diagnosis and after induction immunosuppressive therapy (median 8 months). Clinical and laboratory data were collected at both biopsy occasions. Biopsies were evaluated according to the ISN/RPS classification and scored for activity and chronicity. Clinical response was defined as complete- (CR), partial- (PR) or non-response (NR) according to recent definitions. Histological response (HR) was defined as Class I, II or III/IV-C on repeat biopsies. Long-term renal outcome was determined after a median of 10 years in 55 patients.

Results: CR was demonstrated in 25%, PR in 27% and NR in 48% of patients. HR was shown in 42% and histopathological non-response (HNR) in 58% of patients. Twenty-nine percent of CR- and 61 % of PR-patients had active lesions on repeat biopsies, i.e. were HNR. A majority of these received intensified treatment. At long-term evaluation, 5 % of the patients had developed end stage renal disease (ESRD). Twenty-five % had a glomerular filtration rate (GFR) < 60 ml/min of which none had a doubling of serum creatinine. Poor long-term renal outcome was associated with high chronicity index at repeated biopsies, but not with clinical- or histological response.

Conclusions: Despite apparent clinical response, repeated biopsies revealed persisting active nephritis in a substantial proportion of the patients. Repeated biopsies thus provided information, which was not captured by routine laboratory parameters, and should be considered when treatment response is evaluated in LN. The long-term renal outcome was relatively good. Intensified treatment based on persistent inflammation in renal tissue may contribute to improve prognosis in LN.

Table 1. Clinical, laboratory and histopathological characteristics at first and second biopsies

	First biopsy	*Second biopsy*	*p-value*
Gender, female n (%)	58 (87)		
male	9 (13)		
Age	34 (18-61)		
Ethnicity, Caucasian (n)	59		
Hispanic	2		
Asian	3		
African	3		
Creatinine, μmol/l	84 (44-284)	76 (45-306)	0.003
Albuminuria, g/d	1.4 (0-8.4)	0.5 (0-3.6)	< 0.001
C3, g/l	0.5 (0.12-1.13)	0.79 (0.38-1.51)	< 0.001
C4, g/l	0.09 (0.02-0.51)	0.13 (0.02-0.45)	< 0.001
Anti-dsDNA ab, IE/ml	165 (< 5-300)	29.5 (< 5-300)	< 0.001
ISN/RPS, I-II		14	
III C		13	
III A - A/C	21	10	
IV C		1	
IV A - A/C	27	8	
III/IV + V	9	2	
V	10	19	
Renal activity index	5 (0-13)	2 (0-12)	< 0.001
Renal chronicity index	1 (0-6)	1.5 (0-8)	< 0.001
Induction treatment, n			
Cyclophosphamide	51		
Mycophenolate mofetil	12		
Rituximab	3		
Azathioprin	1		

Values are presented as median (range) unless otherwise indicated

Table 2. Laboratory and histopathological characteristics at repeat biopsies in CR/PR/NR

	CR (n=17)	*PR (n=18)*	*NR (n=32)*	*p-value*
Anti-dsDNA IE/ml	34 (10-120)	22 (7-250)	45 (5-300)	ns
C3, g/l	0.81 (0.38-1.31)	0.93 (0.6-1.38)	0.72 (0.45-1.51)	ns
C4 g/l	0.12 (0.06-0.28)	0.16 (0.1-0.45)	0.13 (0.02-0.29)	ns
Renal histology, ISN/RPS, n				
Class I-II	6	4	4	
Class III/IV (C)	6	3	5	
Class III/IV (A) or (A/C)	1	7	10	
Class III/IV (A)+ V	0	0	2	
Class V	4	4	11	
Renal activity index	1 (0-3)	2 (1-9)	2 (0-12)	0.001
Renal chronicity index	1 (0-6)	3 (0-8)	1.5 (0-8)	ns
Histological response				
HR, n (%)	12 (71)	7 (39)	9 (28)	
HNR, n (%)	5 (29)	11 (61)	23 (72)	

Values are presented as median (range) unless otherwise indicated

P121

Utility of TWEAK to assess neuropsychiatric disease activity in systemic lupus erhytematosus.

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Background/Purpose: TWEAK has been implicated in the physiopathology of CNS inflammation in multiple sclerosis. In SLE, a potential role in the pathogenesis and activity of nephritis has been suggested. The purpose of this study was to assess the utility of TWEAK in serum and CSF as biomarker of involvement, disease activity and remission in central neuropsychiatric SLE (cNPSLE).

Methods: In 36 patients with cNPSLE, 51 SLE patients without history of CNS involvement (non-NPSLE), 16 SLE patients who underwent elective surgical procedures (surgical-SLE), 5 SLE patients with septic meningitis, 4 patients with primary neuropsychiatric conditions, and 25 non-autoimmune patients without CNS symptoms, serum and CSF samples were drawn at hospitalization, except for the non-NPSLE group in whom only serum was studied. Six months later, serum/CSF samples were taken in 18 cNPSLE and serum samples were taken in 27 non-NPSLE patients. SLE activity was assessed at hospitalization in all patients, and six-months later in cNPSLE and non-NPLE. Serum and CSF TWEAK levels were measured by ELISA; values are expressed in pg/mL.

Results: The mean ± SD age of cNPSLE patients was 30.4 ± 12.4 years, which was similar across study groups (p=0.48). SLEDAI-2K scores among cNPSLE, Non-NPSLE, SLE-meningitis and SLE-surgical patients were 12.7 ± 7.8, 11.8 ± 7.7, 8.8 ± 4.4 and 3.8 ± 1.5 respectively. TWEAK levels in serum were not different in cNPSLE that non-autoimmune patients [169.4 pg/mL (10.2 -5495) vs 185.9 pg/mL (10.5 – 2656.9) p=0.94], and also were similar to all the other SLE, primary-NP and non-autoimmune groups. In CSF, TWEAK levels were higher in cNPSLE than in non-autoimmune patients [159.2 pg/mL (2–880) vs 122.1 pg/mL (0.5–456) p=0.04), but not different than SLE-surgical, SLE septic meningitis and primary-NP groups. Six

months later, when the cNPSLE manifestations were clinically in remission, serum levels of TWEAK did not vary from baseline values in cNPSLE and non-NPSLE patients, despite a significant decrease in SLEDAI-2K score, -9.8 and -5.6, respectively. CSF levels of TWEAK in cNPSLE also remained stable [146.9 pg/mL (66.7 – 880.5) vs 201.3 pg/mL (100.4 -622.5) p=0.47]. In cNPSLE and non-NPSLE patients, the correlation between serum TWEAK levels and SLEDAI-2K score were r=0.11 (p=0.41) and r= -0.037 (p=0.74), respectively. In cNPSLE patients, the correlation between CSF TWEAK levels and SLEDAI-2K score was r= -0.21 (p=0.12)
Conclusions: TWEAK levels in serum and CSF do not seem to be a useful biomarker of CNS involvement, disease activity and remission in SLE.

P122

Factors associated with lupus nephritis in a highly admixed population
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Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematous (SLE). Multiple clinical and serological risk and protective factors for LN have been identified in Caucasians. The aim of this study was to examine associated factors for LN in a new cohort of Latin American patients.
Patients and Methods: The study included 310 consecutive SLE patients (91% female, median age at onset: 38 years) followed at a single-center. The population means estimated autosomic Amerindian, European and African admixture are 26%, 63.5% and 10.6%, respectively, and the means estimated X-chromosome admixture are 43.5%, 45.3% and 11.2%, respectively. LN was defined by the presence of active urinary sediment or proteinuria, nephritic or nephrotic syndrome, or a positive renal biopsy (ISN/RPS). Data were examined by bivariate and multiple correspondence analyses. Environmental exposure (i.e., ever smoke, coffee consumption, silicone implants, organic solvents, hair dye, and pesticides exposure) and cutaneous involvement (i.e., photosensitivity, oral ulcers, malar rash, urticary, discoid lupus, subacute lupus, and skin and oral ulcers) were examined by latent trait analysis using two-parameters logistic model through item response theory. Logistic regression analysis was done to assess the factors associated with LN. Interaction among biologically plausible variables was also evaluated.
Results: Nephritis was present in 46.5% of patients. Environmental factors (AOR: 1.64, 95%CI: 1.02-2.71, p=0.04), dyslipidemia (AOR: 18.1, 95%CI: 4.58-89.2, p < 0.001), pleural effusion (AOR: 3.1, 95%IC: 1.45-6.99, p=0.004) and psychosis (AOR: 5.9, 95%CI: 1.40-31.4, p=0.02) were positively associated with LN. In contrast, the presence of Sjögren's syndrome (SS, AECG 2002) disclosed a protective factor (AOR: 0.23, 95%CI: 0.06-0.73, p=0.01). In addition, dyslipidemic patients with short duration of disease and those with pleural effusion with cutaneous involvement exhibited a higher risk for LN. The coefficient of determination was 27%, indicating the multifactorial causation of LN.
Conclusion: Risk and protective factors for LN were confirmed in this admixed SLE population. These results may serve to define public health policies aimed to tight control the modifiable risk factors for LN. The search for additional factors for LN including genetics and epigenetics will improve our knowledge of this critical condition. Admixed populations can be a powerful resource for elucidating those factors.

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Shrinking Lung Syndrome in Systemic Lupus Erythematosus of Latin American Prospective Inception Cohort (GLADEL)
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Introduction: Shrinking lung syndrome (SLS) is an infrequently reported manifestation of systemic lupus erythematosus (SLE), being its prevalence quite variable from 18-27%.
Objectives: Establish the prevalence of SLS in patient with SLE. Analyze the socioeconomic-demographic, clinical and serological features, and mortality in patients with SLE and SLS.
Material and methods: Was included 1480 patients with a recent SLE diagnosis (≤2 years) and were followed for 4.5 years, from 34 centers of 9 Latin-American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela). The SLE patients with SLS presented with dyspnea, orthopnea, radiological evidence of small lung fields and raised diaphragm, and/or a restrictive pattern of pulmonary function test.

Was compared the socioeconomic-demographic, clinical and serological variables among patients with/without SLS. The statistical analysis included chi-square test for categorical variables and t test or Mann Witney test for continuous variables. Results with p < 0.1 were included for multivariate logistic regression analysis and significant p≤ 0.05. Kaplan Meier survival curve was examined.
Results: Twenty-three patients had SLS, representing 1.5% of the total (23/1480) and 4.7% of patients with pleuropulmonary manifestations (23/486), 21 (91.3%) were female with a mean age (SD) at SLE onset of 30.2 (11.7) years. Eleven (47.8%) patients had SLS before the diagnosis of SLE

Table 1 shows socioeconomic-demographic, clinical and serological feature the patients with /without SLS. In multivariate analysis the presence of SLS was associated with positive DNA (p= 0.02. OR: 10.2; 95%CI: 1.3-77.4). During the follow-up period 5 (21.7%) patients died with SLS vs. 85 (5.8%) patients without SLS (p < 0.01. RR: 4.5; 95%CI: 1.6-12.4).

Table 1. Socioeconomic-Demographic, Clinical and Serological Feature Patient with Systemic Lupus Erythematosus According to whether they have or not Shrinking Lung Syndrome. Univariate Analysis

	With SLS (n 23)	*Without SLS (n 1457)*	*p*
Female n(%)	21 (91.3)	1309 (89.8)	0.8
Age of SLE onset m (SD)	30.2 (11.7)	26 (12)	0.3
Ethinicity White	9 (39.1)	597 (41)	0.03
n(%) White/Indian	9 (39.1)	636 (43.7)	
ALA	2 (8.7)	184 (12.6)	
Others	3 (13.1)	40 (2.7)	
SES High/MHigh	3 (13)	149 (10.2)	0.7
n (%) Medium	5 (21.7)	422 (29)	
MLow/Low	15 (65.2)	886 (60.8)	
Systemic Manifestations n (%)	21 (91.3)	1196 (82.1)	0.2
Musculoskeletal Manifestations n (%)	23 (100)	1352 (92.8)	0.1
Ocular Manifestations n (%)	7 (30.4)	252 (17.3)	0.1
Cutaneous Manifestations n (%)	21 (91.3)	1366 (93.8)	0.6
Heart Compromise n (%)	**9 (39.1)**	**313 (21.5)**	**0.04**
Ischemic Heart compromise n (%)	3 (13)	87 (6)	0.1

(continued)

Table 1. Continued

	With SLS (n 23)	*Without SLS (n 1457)*	*p*
Renal Compromise n (%)	15 (65.2)	861 (59.1)	0.5
Neurologic Manifestations n (%)	11 (47.8)	514 (35.3)	0.2
Hematologic Compromise n (%)	**22 (95.7)**	**1146 (78.7)**	**0.04**
ANA positive n (%)	23 (100)	1370 (94)	0.2
Anti DNA positive n (%)	**19 (82.6)**	**872 (59.8)**	**0.02**
Anti RNP positive n (%)	6 (26.1)	316 (21.7)	0.6
Anti Sm positive n (%)	7 (30.4)	343 (23.5)	0.4
Anti Ro positive n (%)	2 (8.7)	341 (23.4)	0.09
Anti La positive n (%)	2 (8.7)	189 (13)	0.5
Lupus Anticoagulant positive n (%)	0	95 (6.5)	0.2
Anti cardiolipin IgG positive n (%)	7 (30.4)	356 (24.4)	0.5
Anti cardiolipin IgM positive n (%)	6 (26.1)	248 (17)	0.2
Anti BG1 positive n (%)	1 (4.3)	36 (2.5)	0.5
Hypocomplementemia n (%)	**19 (82.6)**	**837 (57.4)**	**0.01**
Pulmonary infections n (%)	4 (17.4)	97 (6.7)	0.06
SLICC excluding respiratory M (min-max)	1 (0-5)	1 (0-9)	0.6
SLEDAI average M (min-max)	**7 (0.5-17)**	**3.5 (0-51)**	**0.01**

ALA: African/Latin/American SES: Socioeconomic status MHigh: Medium High MLow: Medium Low
SLICC: Systemic Lupus International Collaborating Clinics SLEDAI:Systemic Lupus Erythematosus Disease Activity Index

Conclusions: The prevalence of SLS in this cohort of patients with SLE is 1.5%. The presence of SLS is associated with the presence of cardiac and hematologyc manifestations, positive DNA, hypocomplementemia and higher SLEDAI. The SLS is independently associated with positive DNA. The presence of SLS increases the risk of death 4.5 times

P124

Occurrence and associations of atherosclerosis in SLE;-a cross sectional study of 281 patients with 281 individually matched population controls

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Background: Accelerated atherosclerosis, considered a feature of Systemic Lupus Erythematosus (SLE), is often recognized as the main cause of premature cardiovascular disease (CVD) among SLE patients. We investigated the prevalence of atherosclerosis in SLE patients and controls.
Patients and methods: 281 SLE patients and 281 population controls, individually matched for age, sex, and region of living were included. All were investigated clinically including CVD risk factors and inflammatory biomarkers. The same investigator performed B-mode ultrasonography of carotid arteries. Mean intima media thickness (mIMT) and plaque occurrence (local IMT > 1mm) were tabulated.
Results: Mean age was 48±14 years in both groups. Manifest CVD (ischemic heart, cerebro- and peripheral vascular disease) was more common in patients (12 % vs. 1 %, $p < 0.0001$). Patients had lower high (HDL)- and low density lipoprotein (LDL), higher triglycerides (TG) and apolipoprotein (apo)B/A. Patients had more antihypertensive- and lipid-lowering treatment, aspirin and warfarin ($p < 0.05$ for all). C-reactive protein, homocysteine, cystatin C, creatinine, albumine, tumor necrosis factor receptor (TNFR) 1 and 2, and vascular cell adhesion molecule-1 were higher in patients ($p < 0.005$ for all).

Patients had thicker mIMT than controls (0.59±0.01 vs 0.57±0.01, p=0.003), but plaque occurrence did not differ, 20% and 16% respectively.

After age-adjustment:

Manifest CVD was associated with plaques in patients ($p < 0.0001$), but not with mIMT (p=0.3).

In patients, mIMT was associated with smoking, sBP, HDL(negatively), LDL, TG, apoB/A, and glucose($p < 0.05$ for all). Plaques were positively associated with smoking, sBP, TG, albumine, cystatin C, nephritis, TNFR 1 and 2, SLICC > 1, and antihypertensive treatment, and negatively associated with leukopenia ($p < 0.05$ for all).

In controls, mIMT was associated with sBP, antihypertensive treatment, cystatin C, TNFR 1 and 2 and glucose ($p < 0.05$ for all). TG and apoB/A were associated with plaques ($p < 0.05$ for all).

Multivariable-adjusted models:

In patients age, sBP and apoB/A remained associated with mIMT ($p < 0.05$ for all). Age, sBP and manifest CVD remained for plaques ($p < 0.05$). In controls, age and sBP remained associated with mIMT and only age with plaques ($p < 0.05$ for all).

Stratified analyses:

Analysis of SLE subgroups (nephritis(112+112), dsDNA(141+141), SSA/SSB(131+131) and aPL(75+75)-positivity) compared to individually matched controls revealed that nephritis patients selectively had more plaques and thicker mIMT than their controls ($p < 0.05$).
Conclusions: This is, to our knowledge, the largest study of atherosclerosis in SLE patients/matched controls. Manifest CVD was more common among patients, but enhanced occurrence of atherosclerotic plaques was only confirmed among patients with nephritis, not in the whole patient group. mIMT was slightly thicker in patients, but not associated with manifest CVD. Since atherosclerosis measures did not differ convincingly between groups, other mechanisms, such as inflammatory and haemostatic factors, probably contribute more than atherosclerosis to SLE associated CVD.

P125

Cigarette smoking, disease activity, damage and anti-dsDNA antibodies in SLE

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Purpose: Cigarette smoking is linked with disease activity and damage in systemic lupus erythematosus (SLE) but the association with anti-dsDNA antibodies remains controversial. Most studies lack pack-years

data on smoking. Herein, we study the effects of smoking on ACR classification criteria, total and itemized disease activity (including anti-dsDNA antibodies) and damage assessments in a large ethnically heterogeneous SLE database which includes patients from the USA, Canada, Mexico, Argentina, Philippines and Turkey.

Methods: We used a large patient database including patients from various countries. Data from 424 SLE patients with self-report of smoking status (current, previous or never, including pack years) was available along with disease activity (SLEDAI), damage (SLICC/SDI-ACR) and anti-dsDNA antibody status (yes/no). ANOVA was used to compare disease characteristics across current, previous or never smokers. Odds ratios for the same variables were calculated based on comparison of (a) current smokers against never smokers and (b) ever smokers against never smokers. P value of ≤ 0.05 was set as significant (all are two-tailed).

Results: Fifty-four patients (12.7 %) were current smokers, 80 (18.9%) previous smokers while 290 (68.4 %) never smoked. Mean (SD) pack year history of current smokers was 10.8(13.3). Smokers (current or previous) were significantly older than never smokers. Mean (SD) age of current, previous and never smokers were 46.3 (15.1), 43.1 (13.4) and 37.3 (12.0) years (p=0.000).

Comparison for ACR classification criteria, itemized SLEDAI and SDI stratified by smoking status are shown in Table 1. Odds ratios for the disease variables that were significantly different among current and ever smokers as compared to never smokers are reported in Table 2. Current smokers had significantly greater odds of ACR hematologic and serositis manifestations, elevated anti ds-DNA antibody on SLEDAI than never smokers. Current smokers had greater risk of new rash on SLEDAI than previous smokers. Mean (SD) total SDI was higher among current smokers at 1.0 (2.0) than never-smokers at 0.0 (1.0), p= 0.006. Current smokers had greater prevalence of cataracts, cutaneous damage, malignancy and diabetes than never smokers.

Conclusions: Smoking is associated with greater odds of serologic (anti-dsDNA antibodies) and cutaneous activity, greater total damage (especially cataracts, cutaneous damage, malignancy and diabetes). SLE patients should be aggressively screened and counseled to quit smoking.

Table 1. Disease Characteristics by Smoking Status

	Never N=290	*Previous N=80*	*Current N=54*	*P-value*
Ethnicity (%)				<0.001
African American	0.7	0.0	5.6	
Caucasian	3.8	21.3	46.3	
Asian	26	21.3	1.9	
Hispanic	48.4	40.0	35.2	
American Indian	0.3	3.8	74.0	
Turkish	20.8	13.8	3.7	
ACR Criteria (%)				
Malar Rash	70.2	62.0	57.0	0.11
Discoid Rash	21.8	21.5	24.5	0.90
Photosensitivity	74.0	70.5	61.1	0.15
Oral Nasal Sores	49.3	50.0	53.7	0.84
Hematologic	54.1	60.0	81.5	<0.001
Arthritis	71.8	75.9	77.4	0.59
Neurologic	11.5	8.9	11.3	0.80
Lupus Nephritis	43.5	42.5	34.0	0.44
Serositis	19.7	34.2	32.1	0.01
Immunologic	77.6	80.5	79.6	0.89
ANA	97.2	97.5	98.1	0.93
SLEDAI (%)				
Seizure	0.0	0.0	0.0	NA
Psychosis	0.3	0.0	0.0	0.80
Organic Brain Synd.	0.7	0.0	3.7	0.07
Visual Disturbance	0.3	2.5	0.0	0.10
Cranial Nerve Disorder	0.0	0.0	0.0	NA
Lupus Headache	1.0	3.8	0.0	0.12
CVA	0.0	0.0	0.0	NA
Vasculitis	2.4	2.5	0.0	0.51
Arthritis	15.5	17.7	14.8	0.87
Myositis	2.1	2.5	0.0	0.53
Urinary Casts	2.4	2.6	0.0	0.52
Hematuria	9.3	10.4	9.6	0.96
Proteinuria	15.9	9.6	6.7	0.13
Pyuria	8.3	10.4	13.2	0.50
New Rash	13.2	5.1	22.2	0.01
Alopecia	10.0	10.1	11.1	0.97
Mucosal Ulcers	2.8	1.3	5.6	0.34
Pleurisy	0.7	2.5	1.9	0.36
Pericarditis	0.3	0.0	0.0	0.8
Low Complement	29.7	27.8	26.4	0.87
Anti-dsDNA Ab.	20.3	23.1	35.8	0.05
Fever	1.0	0.0	0.0	0.50
Thrombocytopenia	1.4	5.1	1.9	0.13
Leucopenia	4.8	3.8	0.0	0.23
SLEDAI-Total (Mean (SD)	4.1 (5.5)	4.0 (4.8)	3.8 (3.3)	0.90
SDI (%)				
Cataract	3.4	10.1	22.2	<0.001
Retinal Change/Optic Atrophy	2.1	1.3	5.6	0.23
Cognitive Impairment	4.1	6.3	11.1	0.11
Seizures	1.7	6.4	1.9	0.07
CVA $\geq$ 1 (%)	0.7	5.1	1.9	0.003
Cranial/Peripheral Neuropathy	1.4	1.3	1.9	0.96
Transverse Myelitis	0.3	1.3	0	0.49
Estimated or measured GFR <50%	2.8	1.3	5.6	0.34
Proteinuria $\geq$3.5gm/24hrs	8.3	8.9	1.9	0.23
ESRD (0,1)	3.1	3.3	3.0	0.85
Pulmonary Hypertension	1.0	1.3	0.0	0.73
Pulmonary Fibrosis	1.7	2.5	3.7	0.63
Shrinking Lung	0.0	0.0	0.0	NA
Pleural Fibrosis	0.3	1.3	1.9	0.39
Pulmonary Infarction	0.3	2.5	0.0	0.10
Angina/ Coronary Artery Bypass	1.0	1.3	1.9	0.88
Myocardial Infarction Ever	0.0	1.3	1.9	0.03
Cardiomyopathy	0.7	1.3	1.9	0.68
Valvular Disease	1.0	2.5	1.9	0.58
Pericarditis	1.4	0.0	5.6	0.04
Claudication for 6mo.	0.3	0.0	0.0	0.80
Minor Tissue Loss	0.3	0	0.0	0.80
Significant Tissue Loss Ever	0.6	0	0.0	0.96
Venous Thrombosis	3.1	1.3	0.0	0.30
Infarction/Resection of Bowel	0.3	3.8	1.9	0.04
Mesenteric Insufficiency	0.3	1.3	0.0	0.49
Chronic Peritonitis	0.0	1.3	0.0	0.11
Stricture/ Upper GI Track Surgery Ever	0.3	1.3	0.0	0.50
Muscle Atrophy/Weakness	2.8	6.3	5.6	0.26
Deforming/Erosive Arthritis	3.8	7.6	5.6	0.35
Osteoporosis with fracture	0.3	1.3	3.7	0.06
AVN	3.8	6.3	5.6	0.31
Osteomyelitis	0.0	1.3	0.0	0.11
Chronic scarring alopecia	3.4	8.9	16.7	0.001
Extensive scarring or panniculum	0.7	3.8	13.0	<0.001
Skin Ulceration >6mo.	1.4	1.3	0.0	0.69

Table 1. Continued

	Never N=290	*Previous N=80*	*Current N=54*	*P-value*
Premature Gonadal Failure	0.7	7.6	1.9	< 0.001
Diabetes	1.4	3.8	9.3	0.005
Malignancy ≥1	0.3	8.9	5.6	< 0.001
Total SLICC-ACR/SDI (Mean (SD)	0.67 (1.2)	1.3 (2.2)	1.5 (2.1)	< 0.001

Table 2. OR for Disease Characteristics by Smoking Status

	OR, 95% CI, P Current smokers vs. Never	*OR, 95% CI, P Ever smokers vs. Never*
ACR-Serositis (%)	1.4, 1.0 < -1.9, 0.05	1.7, 1.1 - 2.6, 0.02
ACR-Hematologic findings (%)	1.9, 1.3 - 2.8, 0.001	NS
SLEDAI-Organic Brain Synd. (%)	NS	NS
SLEDAI-New Rash (%)	NS	NS
SLEDAI-dsDNA (%)	1.5, 1.08 - 2.0, 0.02	1.9,1.2 - 2.9, 0.004
SDI-Cataract (%)	2.8, 1.8 - 4.4, < 0.001	3.9, 1.8 - 8.5, 0.001
SDI-CVA ≥ 1 (%)	NS	5.2, 1.1 - 26.2, 0.04
SDI-Pericarditis (%)	NS	NS
SDI-Infarction/resection of bowel (%)	NS	NS
SDI-Osteoporosis with fracture (%)	NS	NS
SDI-Chronic scarring alopecia (%)	2.4, 1.5 - 3.8, < 0.001	3.7, 1.7 - 8.1, 0.001
SDI-Extensive scarring or panniculum (%)	4.6, 2.1 - 10.3, < 0.001	9.9, 2.2 - 45.2, 0.003
SDI-Premature Gonadal Failure (%)	NS	7.1, 1.5 - 33.7, 0.01
SDI-Diabetes (%)	2.7, 1.4 - 5.3, 0.004	4.9, 1.5 - 15.7, 0.007
SDI-Malignancy (%)≥1	4.1, 1.3 - 12.9, 0.02	17.9, 2.3 - 141, 0.006

NS = not significant

P126

Cumulative Rate of Damage and Co-morbidities in Patients with Systemic Lupus Erythematosus Has Not Changed Over the Last Two Decades

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Objective: Co-morbidities are associated with a decline in many health outcomes, increased use of health care resources and mortality; this is of especial importance when managing chronic diseases such as SLE. The aim of this study is to compare the cumulative rate of damage and co-morbidities between SLE patients diagnosed during the 1990́s and those diagnosed during the first decade of the 21st century.

Patients and Methods: We retrospectively studied 172 SLE patients (as per the 1997 ACR criteria), 74 (43%) of whom were diagnosed during the 1990́s and 98 (57%) during the first decade of the 21st century. Damage was assessed using the SLICC/ACR Damage Index (SDI) and co-morbidities using the Charlson Index. Total SDI and Charlson Index were compared using the Student T test and the cumulative rate of damage and co-morbidities estimated by the Kaplan-Meier method.

Results: Patients were predominantly females (90%) with a median (IQR) age at diagnosis of 29.0 (17.8) years old. Median disease duration was 74.5 (91.3) months. Mean (SD) SDI and Charlson Index were higher among patients diagnosed during the 1990́s [0.95 (1.28) vs. 0.48 (0.80); p< 0.001 and 0.46 (0.98) vs 0.14 (0.45); p< 0.001, respectively]. However, neither mean (SE) time to first damage [139 (13) vs. 101 (7) months, log rank test= 0.20; p= 0.655] nor time to first co-morbidity [231 (15) vs. 150 (7) months, log rank test= 0.20; p= 0.658] were different between the two groups of patients. Table 1 depicts the cumulative rate of first and second item of the SDI and the Charlson co-morbidity Index

Table 1. Cumulative rate of first and second item of the SDI and the Charlson co-morbidity Index.

SDI	*Time (months)*	*Cumulative Rate (%) 1990́s*	*2000́s*
First item	0	8	9
	12	15	15
	60	36	34
Second item	0	1	1
	12	7	1
	60	14	9
Charlson			
First item	0	1	3
	13	4	4
	60	9	7
Second item	0	1	0
	12	1	0
	60	4	0

Conclusions: In this study, patients diagnosed during the 1990́s accrued more damage and co-morbidities compared to those more recently diagnosed, probably reflecting longer disease duration. However, the cumulative rate of both, damage and co-morbidities, did not differ between groups; the latter showing that in spite a better understanding of the disease and improvement of its management, patients still suffer co-morbidities in the same pace they did more than a decade ago. These findings may prompt the treating physicians to take active measures in other health outcomes not strictly related to the disease *per se*.

P127

Is vitamin d related to disease activity and antimalarials in systemic lupus erythematosus?

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Background: Role of Vitamin D deficiency in inflammation is being increasingly explored. Though vitamin D deficiency is commonly seen in Systemic Lupus Erythematosus (SLE), its association with disease activity has not been yet well established. Furthermore, conflicting reports suggest antimalarials (Hydroxychloroquine-HCQ) use in SLE may be associated with vitamin D insufficiency. Similarly corticosteroids may also decrease vitamin D levels. Herein, we look at the association between Vitamin D levels and (a) HCQ use, (b) disease activity, (c) damage.

Methods: Cross sectional data from our Lupus Data Repository of 308 SLE patients meeting the ACR classification criteria was utilized. Data included demographics, serum 25 hydroxy Vitamin D levels (Last visit), current use of HCQ (Yes/No) or corticosteroids (Yes/No). Disease activity (Physician Global Assessment PGA, Total

SLEDAI), damage (SLICC-ACR/SDI) data was available for 92 subjects. Descriptive statistics and spearman correlational analyses (including partial correlations after adjusting for HCQ, corticosteroid use) were performed. P value ≤0.05 was considered significant on two tailed tests.

Results: Mean (SD) age was 44.8 (14.8) years, 94% were women. Fifty percent were African American, 25% Caucasian, 17% Hispanic and 8% Asians. Seventy eight percent were taking HCQ, while 59% were currently on corticosteroids. Median (IQR) serum 25 hydroxy vitamin D levels in SLE patients were lower among HCQ users than non users (27 (18) vs 36 (22), p < 0.001). Correlation between HCQ use and 25 hydroxy Vitamin D levels was present (r=-0.22, p < 0.005). Current 25 hydroxy vitamin D levels were inversely correlated with PGA (r = -0.34, p=0.001), but not with total SLEDAI (r=-0.18, 0.09) or SDI (r=0.05, p=0.66). On controlling for HCQ use alone, 25 hydroxy vitamin D levels did not correlate PGA, SLEDAI or SDI. On controlling for current corticosteroid use alone, 25 hydroxy vitamin D levels did correlate PGA (r=-0.27, p=0.01), SDI (r=0.25, 0.02) but not with SLEDAI. However, on controlling for both current HCQ and corticosteroid use, current 25 hydroxy vitamin D levels correlated significantly with PGA (r=-0.30, p=0.007), total SLEDAI scores (r=-0.24, p=0.04) and damage (r=0.24, p=0.03).

Conclusions: HCQ use was associated with lower vitamin D levels in SLE patients. Furthermore, vitamin D deficiency was associated with disease activity (PGA and SLEDAI), even after accounting for both HCQ and corticosteroids use. This indicates the need for screening and treatment for vitamin D insufficiency among all SLE patients. Larger studies are indicated to confirm these results.

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Jaccoud's Arthropathy in Systemic Lupus Erythematosus: Clinical Presentation, Treatment, and Outcome: Data From a Multiethnic Latin American Cohort

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Background and Purpose: Jaccoud's arthropathy is characterized by the presence of easily reducible joint deformities, mainly affecting the hands, but also observed in other joints, such as the feet, knees, and shoulders amog others. This arthropathy may be barely symptomatic, and even completely painless and it may supervenewithout previous documented bouts of acute arthritis. The purpose of this study was to describe the clinical characteristics, laboratory features and outcome of SLE patients with Jaccoud's arthropathy.

Patients and Methods: SLE patients from 34 centers in nine countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela) with a recent diagnosis (≤2 years, ACR criteria fulfillment was not required) constitute this cohort.

The demographic, SLE related clinical manifestations (American College of Rheumatology, ACR criteria) prior to the event; disease activity (Systemic Lupus Erythematosus disease Activity Index, SLEDAI), auto-antibodies (cumulative), and mortality in SLE patients with and without Jaccoud's arthropathy were compared by Student's t-tests or Chi-squared tests; p-values < 0.05 were considered statistically significant.

Results: A total of 17 (1.1%) patients from this cohort (n-1480) patients with a median follow-up time of 56 months (quartiles: 54-59 months) develop Jaccoud's arthropathy and it ensued either prior to SLE diagnosis in 5 (29.4%) patients and after it in 12 (70.6%). Over the course of follow up rheumatoid arthritis, antiphospholipid syndrome and Sjögren's syndrome ensued in one patient each. Table 1 depicts the features of SLE patients as a function of the presence of Jaccoud's arthropathy.

Conclusions: In this SLE cohort, Jaccoud's arthropathy was associated with the presence of Raynaud's phenomenon, xerophthalmia and xerostomia, acute lupus pneumonitis as well as with higher SLEDAI scores over time The presence of anti-dsDNA antibodies was negatively associated with Jaccoud'sarthropathy but neither low complement levels nor other auto-antibodies were found to be associated with Jaccoud's arthropathy. Finally, the occurrence of Jaccoud's arthropathy seems to negatively affect the survival rates of these SLE patients.

Table 1. Socioeconomic-demographic, clinical manifestations (prior to diagnosis) and cumulative serologic characteristics of SLE patients as a function of the presence of Jaccoud's arthropathy

Features	*Jaccoud arthropathy Yes (n= 17)*	*Jaccoud arthropathy No (n= 1463)*	*p-value*
Age at diagnosis, years (mean + SD)	32.5+12.4	29.5+12.3	NS
Female, %	16 (94.1)	1314 (89.8)	
Ethnic group, (%)			
Caucasian (606)	10 (58.8)	596 (40.7)	
Mestizo (645)	5 (29.4)	640 (43.7)	NS
African-Latin American (186)	2 (11.8)	184 (12.7)	
Others (43)	0 (0)	43 (2.9)	
Residence			
Urban, (%)	17 (100.0)	1317 (90.8)	NS
Socioeconomic Status			
Upper/upper-middle (152)	3 (17.6)	149 (10.2)	
Middle (427)	5 (29.4)	422 (28.8)	NS
Lower-middle/lower (901)	9 (52.9)	892 (61.0)	
Education, years, (%)			
0-7 (469)	7 (41.2)	462 (31.6)	
8-12 (664)	9 (52.9)	655 (44.8)	NS
>12 (347)	1 (5.9)	346 (23.7)	
Medical insurance, (%)			
Public	14 (82.4)	1172 (80.1)	NS
Private	3 (17.6)	279 (19.9)	
Autoantibodies, (%)			
ANA	16 (100.0)	1377 (98.1)	NS
Anti-dsDNA antibodies	6 (42.9)	885 (73.3)	0.0280
Anti-Ro antibodies	5 (45.5)	338 (51.3)	NS
Anti-La antibodies	3 (27.3)	188 (30.9)	NS
aPL antibodies	11 (73.3)	468 (56.3)	NS
Low complement	12 (80.0)	844 (67.9)	NS
ACR Criteria, (%)			
Malar rash	8 (47.1)	771 (52.7)	NS
Discoid rash	1 (5.9)	143 (9.8)	NS
Photosensitivity	9 (52.9)	719 (49.1)	NS
Oral Ulcers	6 (35.3)	472 (32.2)	NS
Arthritis	13 (76.5)	1087 (74.3)	NS
Pleuritis	4 (23.5)	232 (15.9)	NS
Pericarditis	3 (17.6)	158 (10.8)	NS
Neurologic disorder	1 (5.9)	103 (7.0)	NS

(continued)

Table Continued

Features	Jaccoud arthropathy Yes (n= 17)	Jaccoud arthropathy No (n= 1463)	p-value
Renal diseorder	3 (17.6)	484 (33.1)	NS
Hematologic disorder	7 (41.2)	794 (54.3)	NS
Raynaud phenomenon	7 (41.2)	317 (21.7)	0.0530
Xerophthalmia and xerostomia	3 (17.6)	71 (4.9)	0.0490
Acute lupus pneumonitis	2 (11.8)	10 (0.7)	0.0080
SLEDAI average during follow up	12.2	9.4	NS
Death during follow-up	4 (23.5)	85 (5.8)	0.0160

P129

Validation of SLICC lupus criteria in a cohort in Argentina

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Introduction: The most widely used classification criteria for Systemic Lupus Erythematosus (SLE) are those developed by the American College of Rheumatology (ACR), revised in 1997. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) developed a new set of classification criteria. Our objective was to validate and compare SLICC and ACR criteria in a cohort of patients with rheumatic diseases in a single center from a country not represented in SLICC.

Patients and methods: 607 patients seen at the Rheumatology Section with diagnoses of SLE (n=299), Inflammatory Myositis (IM) (n=17), Systemic Sclerosis (SS) (n=154), Rheumatoid Arthritis (RA) (n=92) and Sjogren syndrome (n=45) were included for analysis. Electronic medical records were reviewed in order to determine fulfillment of ACR and SLICC criteria. Physician's diagnosis was considered as the gold standard.

Results: SLICC classification criteria had 89.9 % sensitivity (95% CI: 86-93) and 99.3 % specificity (95% CI: 97.6-99.9) compared with 75.6% (95% CI: 70-80) and 100 % respectively for the ACR criteria. Fewer patients were misclassified with SLICC criteria (32 versus 73 patients).

	LUPUS (n=299)	MYOSITIS (n=17)	SCLERO-DERMA (n=154)	RHEUMATOID ARTHRITIS (n=92)	SJOGREN (n=45)
Females, %	89.6	82.4	95.5	92.4	100
Age at diagnosis, y mean (SD)	31.5 (15.2)	56.6 (20.4)	59.6 (13.8)	51.3 (13.3)	56.8 (16.1)
Patients fullfiling lupus ACR criteria, n (%)	226 (75.6)	0 (0)	0 (0)	0 (0)	0 (0)
Patients fullfiling lupus	269 (89.9)	1 (5.9)	1 (0.6)	0 (0)	0 (0)

(continued)

Table Continued

	LUPUS (n=299)	MYOSITIS (n=17)	SCLERO-DERMA (n=154)	RHEUMATOID ARTHRITIS (n=92)	SJOGREN (n=45)
SLICC criteria, n (%)					

Conclusions: in this cohort SLICC lupus criteria showed better sensitivity than 1997 ACR criteria, with similar specificity. Fewer misclassifications were seen with SLICC criteria and these seem to be useful in daily clinical practice.

P130

Musculoskletal Ultrasonography Findings in SLE Arthritis and Relationship with 2010 ACR/EULAR RA Criteria

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Objective: To determine sonographic abnormalities in the wrist and hand of patients with SLE and to determine relationship with the 2010 ACR/EULAR RA criteria.

Methods: Forty eight patients with the diagnosis of SLE fulfilling the ACR criteria were screened and patients with a history of arthritis were recruited to the study. Thirteen patients whom enrolled to the study was evaluated for 2010 ACR/EULAR RA criteria at their first presentation to the clinic from the patients charts retrospectively. Sonographic evaluation was performed to the patients from the wrist, metacarpal and proksimal interphalangeal joints and periarticular structures of both hands in dorsal and volar sides. Erosive changes were evaluated from the lateral longitudinal and transvers view of the 2nd MCP, 5th MCP, 2nd PIP and ulnar styloid of the both hands. The presence of synovitis (synovial hypertrophy and/or joint efffusion), tenosynovitis, erosions and Doppler signal were investigated. Changes according to definitions of OMERACT group study were recorded (Wakefield 2005). My Lab 70 (Esaote Biomedica, Italy) sonography machine was used with a 6-18 mHz probe for the sonographic evaluation.

Results: Median disease duration and median age were 6.5±5.8, 44±12 years respectively. Seven of 13 (58%) patients fullfilled 2010 ACR/EULAR RA criteria. The median SLEDAI score was 2 (range 0-11). Clinical examination revealed arthritis only in 2 of the patients during recruitment to the study.

Synovitis of the carpal recesses were found in 6 of the 26 evaluated wrists. In 4 of the 6 wrists with synovitis had PDS. Synovitis has been observed in 15 of 130 MCP joints and 3 of them had PDS. Synovitis has been found in 4 PIP joints, 2 of them with PDS.

Joint abnormalities in sonography were found in 7 patients. Flexor and extensor tenosynovitis was detected in 1 and 1 patients respectively. Only two patients had erosive disease.

More than half of the patients with SLE arthritis fullfilled the new RA criteria but correlation between sonographic findings and score of 2010 ACR/EULAR RA criteria was not significant. Only patients with tenosynovitis tended to have higher 2010 ACR/EULAR RA score than patients without tenosynovitis (7 vs 5.8, p=0.089). No correlation has been observed between the incidence of clinical involvement and presence of sonographic pathologies. Younger patients (33 vs 48, p=0.008) and patients with short disease duration(4.5 vs 8, p=0.067) had higher sonographic findings of synovial proliferation in the wrist.

Conclusion: Sonography may be a useful method to detect and categorize musculoskeletal pathologies since joint and tendon involvement can be silent in patients with SLE. There were a tendency to have

tenosynovitis in SLE patients whom fulfilled 2010 ACR/EULAR RA criteria.

P131

Pulmonary hypertension in systemic lupus erythematosus: a 6-year follow-up study cohort.

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Introduction: Systemic lupus erythematosus (SLE) may present hemodynamic alterations including pulmonary hypertension (PH); however, this information is still scarce and varies depending on the ethnic group studied. Echocardiography (ECHO) is a noninvasive imaging technique useful to classify pulmonary hypertension (PH) as unlikley (sPAP ≤36 mmHg), possible (37-50 mmHg), or likley (>50 mmHg).

End points: Describe clinical associations, performance of several biomarkers and survival of PH in a long-term follow-up cohort of Mexican patients with SLE.

Methods: Study cohort with 6-year follow-up including 139 SLE patients. At baseline, demographics, organ involvement, disease activity (SLEDAI-2K), cumulated organ damage (SLICC/ACR), and laboratory analyses including antibody profile were obtained. Serum samples were stored in standard conditions. Clinical follow-up was performed ~3 months.

For the present study, SLE patients who had an ECHO for any reason by the time of recruitment (±6 months) were included. From stored sera, levels of endothelin 1 (ET1) and monocyte chemotactic protein 1 (MCP1) were measured by ELISA.

Discrete variables are described as percentages and continuous variables as medians (interquartile range). Analyses were performed by either chi-square test for trends or Kruskal-Wallis with Dunn's post-test as correspond. Spearman's rank correlation coefficient (ρ) was used to assess associations. Survival was assessed by the Kaplan-Meier method with log-rank test for trends.

Results: 55 SLE patients were included. According to ECHO, patients were classified in 3 groups: unlikely, possible, likely PH..

There were no differences in demographic or serologic features between groups, whereas organ damage was higher in patients with PH (SLICC/ACR index of 1 (1-2), 3 (1.7-4), 3 (2-6), respectively; P=0.0009). Active arthritis was present in 12%, 13%, 38% (P=0.05); history of pulmonary thromboembolism in 8%, 13%, 46% (P=0.005).

Differences in ECHO: interventricular septum thickness of 9 (9-10), 10.5 (9-12), 10 mm (9-12; P=0.04); right ventricular diastolic diameter 27.5 (27-30.2), 37 (35.5-39), 41 mm (35.5-45.7; P=0.004), respectively. Serum levels of ET1 and MCP1 were similar between groups.

The sPAP showed a positive correlation with age (ρ 0.29), disease duration (ρ 0.32), serum creatinine (ρ 0.26), SLEDAI-2K (ρ 0.26), SLICC/ACR (ρ 0.55), left atrium diameter (ρ 0.45), interventricular septum thickness (ρ 0.33), and right ventricular diastolic diameter (ρ 0.71).

Rates of survival for each SLE group in the first year were: improbable PH 92%, possible PH 94% and probable PH 90%. After three years, these were 92%, 89% and 77%, respectively. After six years 88%, 87% and 68%, respectively.

Conclusions: In SLE, PH (sPAP >50 mmHg) is associated with decreased survival in the medium term. It is related to cumulated organ damage and history of pulmonary thromboembolism. Validated biomarkers in idiopathic PH such as ET1 and MCP1 are not useful to distinguish PH in patients with SLE.

P132

Correlation of spot urine protein/creatinine ratio and 24-hour proteinuria in patients with Systemic Lupus Erythematosus

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Background: Spot urine protein/creatinine (Pr/Cr) ratio has shown a good correlation with 24-hour proteinuria in patients with several types of nephropathy. However, in Systemic Lupus Erythematosus (SLE), information about it is scarce and controversial.

Aim: To determine the correlation between Pr/Cr ratio and 24-hour proteinuria in SLE patients.

Methods: In a cross-sectional study, SLE patients consecutively seen in our Rheumatology Department from January to November 2012 were evaluated. An interview, chart review, physical examination and laboratory tests were performed. SLE was defined using the ACR criteria. Spot urine Pr/Cr ratio was obtained by dividing the urinary protein concentration by the urinary creatinine concentration, both expressed in mg/dl; and 24-hour proteinuria was reported as mg/d. Difference between 24-hour proteinuria and Pr/Cr ratio was also calculated. The correlation was determined using the Pearson correlation coefficient and the intraclass correlation coefficient (ICC); these analyses were calculated for the whole population and according to the creatinine clearance rate (more than 90, between 60 and 90, between 30 and 60 and less than 30 ml/min). Also, patients were divided according to the level of proteinuria (less than 500, between 500 and 1000, between 1000 and 2000, between 2000 and 3000, and more than 3000) and the concordance between categories was evaluated using kappa index. Statistical analyses were performed using SPSS v16.0.

Results: 129 patients were evaluated, with an average age of 42.3 (SD: 12.4) years, 122 (94.6%) were female and almost all of them were mestizo. Disease duration was 7.8 (SD: 6.4) years. The SLEDAI was 5.7 (SD: 4.6), the SDI was 0.7 (SD: 1.0). The creatinine clearance rate was 98.7 (SD: 38.4) ml/min. The median of 24-hour proteinuria was 162.4 (interquartil rank (IQR): 113.1; 309.1), and the median of Pr/Cr ratio was 167.0 (IQR: 107.0; 359.0). The median of the difference between 24-hour proteinuria and Pr/Cr ratio was -8.6 (IQR: -67.9; 24.8). There was a good correlation between 24-hour proteinuria and Pr/Cr ratio (R: 0.98, ICC: 0.98, $p < 0.01$), and this correlation was similar after dividing the patients according to the creatinine clearance rate ($R > 0.95$ and $ICC > 0.94$, $p < 0.01$ in all the categories). A good concordance between categories of proteinuria was present in 116 (89.9%) patients (kappa: 0.67, $p < 0.01$).

Conclusions: Spot urine Pr/Cr ratio accurately correlated with 24-hour proteinuria in SLE patients, independently of the level of the creatinine clearance rate. Spot urine Pr/Cr ratio should be validated for the follow-up of SLE patients.

P133

Comparative evaluation of cumulative damage in adult and childhood onset systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a chronic, multisystemic disease affecting predominantly woman in reproductive age. Previous studies have reported childhood-onset (c)SLE to be more severe than adult-onset (a)SLE.

Objectives: The aim of this study was to compare the prevalence and types of cumulative damage in SLE according to age of disease onset.
Patients and methods: We conducted a cross-sectional study including 247 aSLE and 63 cSLE patients matched for disease duration and followed at Rheumatology and Pediatric Rheumatology Unit of the State University of Campinas. Damage was analyzed according to Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) and data were extracted from patients charts.
Results: We included 247 aSLE patients (234 women; mean age 38.7 years (SD = 12.4) and 63 cSLE patients (61 women; mean age 18.6 years (SD = 5.6). SDI scores ≥1 were observed in 166 aSLE and 28 patients cSLE ($p < 0.001$). The mean SDI in aSLE (mean = 2; SD= 1.2) was similar to cSLE (mean = 1.5, DP = 0.7) ($p > 0.05$). In aSLE we observed the following frequency of damage: musculoskeletal 66/166 (37.3%), premature gonadal failure 55/166 (33.1%), cardiovascular in 44/166 (26.5 %), ocular 29/166 (17.5%), neuropsychiatric 28/166 (16.7%), vascular 19/166 (11.4%), pulmonary 17/166 (10.2%), renal 15/166 (9%), diabetes with 14/166 (8.4%), gastrointestinal 12/166 (7.2%), skin 7/166 (4.2%) and malignancy in 1/166 (0.6%) patient. In cSLE we observed the following prevalence of damage: musculoskeletal 13/28 (46.4%), cardiovascular 7/28 (25%), ocular 6/28 (21.4%), neuropsychiatric 5/28 (18%), pulmonary 3/28 (11%), diabetes 2/28 (7.1%), renal 1/28 (36%), gastrointestinal 1/28 (3.6%), skin 1/28 (3,6%), malignancy 1/28 (3.6%). The prevalence of cardiovascular damage was high in our cSLE cohort and was due mainly to valvular stenosis and diastolic dysfunction. Although the types of damage was similar among groups, aSLE patients had significantly more premature gonadal failure and cSLE patients had more cardiovascular damage($p < 0.05$).
Conclusion: aSLE have more damage than cSLE. However when present, the types of damage are similar between groups except for gonadal failure that is more frequently observed in aSLE and cardiovascular damage more frequently observed in cSLE. cSLE patients have a greater life expectancy and have therefore a greater tendency to present more damage later in life. Close follow-up for permanent damage is necessary in SLE.
Grants: FAPESP (2010/13636-2 and 2008/02917-0), CNPq (471343/2011-0, 300447/2009-4)

P134

Reduction of cerebral and corpus callosum volumes in childhood-onset systemic lupus erythematosus. A volumetric magnetic resonance imaging analysis

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Background: Cerebral atrophy has been described to occur in SLE with variable frequency. Aging, systemic diseases, corticosteroid use and central nervous system (CNS) involvement may lead to cerebral atrophy. However, studies evaluating the prevalence of cerebral atrophy in childhoodonset

systemic lupus erythematosus (cSLE) using magnetic resonance imaging (MRI) volumetric measurements are rare.
Objectives: To determine the frequency of cerebral and corpus callosum atrophy in cSLE and to determine the possible relationships between atrophy and clinical, laboratory and

treatment features of the disease.
Methods: A total of 51cSLE patients (48 female; mean age=17.0; SD=3.9) and 50 healthy age and sex matched volunteers (37 women; mean Age=18.4; SD=5.7) followed at the pediatric rheumatology unit of the State University of Campinas were enrolled in this study. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological

manifestations were analyzed according to the ACR classification criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity (SLEDAI), damage (SDI) and current drug exposures. Total dose of corticosteroids and other immunosuppressant

medications used since the onset of disease were calculated. MRI scans were performed in a 3T Phillips scanner using a standardized protocol. Sagittal T1 weighted images were used for semiautomatic volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Non-parametric tests and correlation were used for

statistical analysis.
Results: In cSLE, cerebral (mean volume=1077.1 cm3; SD=94.5) and corpus callosum (mean volume=11.8 cm3; SD=1.8) volumes were significantly smaller when compared to cerebral (mean volume=1191.7; SD=122.1; $p < 0.001$) and corpus callosum (mean volumes=10.8; SD=1.6;

p=0.005) volumes of healthy volunteers. Corpus callosum atrophy were identified in 4 (7.8%; p=0.005) and cerebral atrophy 7 (14%; p=0.003) cSLE and in none of the controls. The presence of corpus callosum atrophy was associated with positive anti-dsDNA antibodies (p=0.018). An indirect correlation between age and corpus callosum volume (r=0.88; p=0.001) was observed. The presence of cerebral atrophy was associated with the presence of depression (p=0.007), vasculitis (p=0.001) and disease activity (p=0.04). No relationships between cerebral and corpus callosum volume and disease duration, the presence of CNS manifestations, total corticosteroid

dose, and the presence of antiphospholipid antibodies were observed.
Conclusion: Cerebral and corpus callosum atrophy is observed more frequently in cSLE when compared to controls. The presence of immunological and clinical features are associated with the presence of atrophy. Depression was the only neuropsiquiatric manifestation associated with

cerebral atrophy.
Grants: FAPESP 2008/02917-0; CNPq 300447/2009-4

P135

Comparison of the LupusQol and SF-36 Scores As Valid Measures of Change in Health Related Quality of Life

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Background: The LupusQoL questionnaire is a disease-specific questionnaire for adults with lupus while SF-36 is a generic questionnaire. To determine if the LupusQoL and the SF-36 questionnaires are comparable measures of change in patients with SLE on standard of care (SOC) treatment.
Methods: We analyzed the results of SF-36 and LupusQoL questionnaires available from a group of lupus patients who were followed at the Lupus Clinic. Patients were studied if they had at least one follow-up visit within 6 month period while receiving SOC treatment.

Each of the questionnaires, SF-36 and LupusQoL, includes 8 domains and its scores ranges from 0 (worst possible) to 100 (best possible) quality of life. The SF-36 subscales can be further summarized into 2 component scores: the physical component summary (PCS) and the mental component summary (MCS).

The mean change in the domains scores for both questionnaires was determined by subtracting the scores of the follow-up visits from the score of the baseline visit.

We determined the correlation (Pearson) of the change in scores of LupusQoL and the change in scores of SF-36. The correlation of the comparable domains of LupusQoL was determined with the corresponding domains of SF-36. For each of the non-comparable domains of the LupusQoL questionnaire the correlation was determined with PCS and MCS individually.

Results: 99 patients (91% F) had baseline and at least one follow-up visit available. 44% were Caucasian, 33% Black, 10% Asian and 12% others. For the 99 patients 251 observations were identified for which both SF-36 and LupusQoL questionnaires were available. Age at lupus diagnosis and lupus duration at first visit were 27.2 ± 12.4 and 11.9 ±7.7 years. The mean SLEDAI-2K on all visits was 7.49 ± 5.21.

The correlation of the change in scores of the comparable LupusQoL and SF-36 domains ranged from 0.38-0.65. For the non-comparable domains the correlation of the LupusQoL domains with SF-36 MCS and PCS ranged from 0.25-0.33 (Table 1).

Conclusion: The correlation of the change in the scores of comparable domains of Lupus QoL and SF-36 ranged from moderate to large. The correlation of the change in the scores of non-comparable domains of Lupus QoL and SF-36 was insubstantial to small. Thus these questionnaires measure different aspects of quality of life and the changes should be correlated with a gold standard such as a patient global assessment.

Table 1. Correlation of change in SF-36 and LupusQoL for comparable and non-comparable domains

	Lupus QoL domains	*SF-36 Domains*	
Comparable domains	Pain	Bodily Pain	0.65(<0.0001)
	Physical Health	Physical Functioning	0.38 (<0.0001)
	Emotional Helath	Mental health	0.56 (<0.0001)
	Fatigue	Vitality	0.48 (<0.0001)
Non-Comparable domains	Body Image	PCS	0.09 (0.28)
	Body Image	MCS	0.28 (0.0007)
	Planning	PCS	0.33 (<0.0001)
	Planning	MCS	0.29 (0.0004)
	Intimate Relationships	PCS	0.27 (0.01)
	Intimate Relatioinships	MCS	0.02 (0.89)
	Burden to others	PCS	0.25 (0.002)
	Burden to others	MCS	0.29 (0.0004)

P136

Early disease onset in SLE. Grupo de Estudio de Lupus de la Sociedad Argentina De Reumatología.

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Systemic lupus erythematosus (SLE) is a chronic, multiorgan, autoimmune disease that is more common in women of reproductive age, but occurs in people of all ages. Kidney involvement and damage has been reported to have a higher prevalence in patients with SLE with disease onset during childhood.

Objective: To explore the prevalence of early- onset Lupus and the relationship with the diverse manifestations of the disease.

Methods: Our study included 649 patients enrolled in a consecutive way between February and November 2012. Age of disease onset was determined as the age at which the fourth American College of Rheumatology SLE criterion had been met.

Early onset of the disease was considered in people who were diagnosed before the age of 18.

The clinical manifestations were compared between patients with and without early SLE onset.

Results: 103/649 (16%) met the criteria for early –onset SLE. The female to male ratio was 8:1.

The mean age at SLE diagnose was 15 years (7-17) and mean age of adult onset was 33 (18-76).

The mean SLE criteria classification was 7±1.4 vs. 6±1 (p=0.0001). The SLEDAI score was 5.41 (0-26) vs. 5.45 (0-26) (NS). The SLICC/ACR index was 1.09 ±1.86 vs. 0.97 ±1.98 (NS).

Early onset patients had more frequently malar rash: 77% vs. 64% (OR: 1.81, p=0.01, CI: 1.09-3.10) and renal disease: 65% vs. 45% (OR: 2.24, p=0.0003, CI: 1.41-3.57).

They also had more often cumulative anti-dsDNA antibodies: 70% vs. 51% (OR: 2.20, p=0.001, CI: 1.33-3.71).

At the time of entering to the study early onset patients had more active proteinuria (>500mg/24 hours): 25% vs. 13% (OR: 2.17, p=0.002, CI: 1.25-3.69).

They received more treatments with antimalarics: 73% vs. 60% (OR: 1.70, p= 0.02, CI: 1.05-2.83) and low-dose cyclophosphamide: 46.6% vs. 31% (OR: 1.93%, p=0.002, CI: 1.23-3.03).

Conclusion: In a multi-centric Lupus study, 16% were early-onset disease patients. They represent a more severe phenotype of the disease, characterized by malar rash and renal disease with active proteinuria. Furthermore they presented more frequently anti-dsDNA antibodies as well as treatments with antimalarics and low-dose cyclophosphamide.

P137

Disease activity and clinical features in recent-onset systemic lupus erythematosus (SLE): gender differences

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Introduction: Approximately 4-22% of lupus patients are male according with the published literature. Although these patients may develop the same clinical manifestations as females, some differences have been observed with regard to certain key clinical manifestations and disease outcomes. The objective of this study was to determine the influence of gender in disease manifestations and disease activity in patients with recent-onset SLE.

Patients and methods: This is a matched (male-female) cross-sectional study. Patients presenting for the first time to the Rheumatology Section of our University Hospital between January 2000 and December 2011, meeting four ACR criteria for SLE, ≥ 16 years were assessed. Each male was age- (± 5 years) and ethnicity-matched to 3 female. Disease activity was assessed with the SLEDAI. Patients were stratified according to SLEDAI scores as having low (≤ 4), moderate (5-11) and high disease activity (≥12).

Disease and patient characteristics were examined by the Chi-square and Student's t-tests for categorical and continuous variables, respectively; variables with $p \leq 0.05$ in these analyses were considered statistically significant and were entered into multivariable regression analysis in which disease activity was the dependent variable; time to diagnosis (≤1 month, 1-6 months, 6-12 months, >12 months) was adjusted for this regression.

Results: Forty male were matched with 120 female patients for age and ethnicity (87.5% mestizos, 10% African-descents and 2.5% whites). The median age for men was 32 years (IQR 22-41) and for women 30.5 years (IQR 23-42).

Alopecia was more frequent in women than in men (52.5% vs. 17.5%; $p < 0.0001$) while some manifestations (pleuritis, 35% vs. 25%, pericarditis, 17.5% vs. 14.2%, cutaneous vasculitis, 17,5% vs. 7,5%), were numerically more frequent in men than in women but statistical significance was not reached. Lupus nephritis occurred with comparable frequency in men and women (55% vs. 51%) and so was the frequency of proliferative lupus nephritis. Anti-Ro antibodies were more frequent in women than in men (53.6% vs. 33.3%; p=0.034) but other autoantibodies occurred with similar frequency in both genders.

Ninety percent of the men and 78 % of the women exhibited a SLEDAI score >12 at presentation. By multivariable analyses male gender was associated with higher of disease activity as noted in Table below.

*Variables**	*OR*	*95% CI*	P
Gender (male vs female)	3,27	1,17-9,15	0,024
Time delay to SLE diagnosis			
<1 month(reference)	1		
1 a 6 months	0,981	0,36-5,08	0,971
6 a 12 months	1,486	0,55-4,05	0,438
>12 months	1,37	0,37-5,08	0,636

*Age and ethnicity were controlled from study design

Conclusions: Independent of age and ethnicity, male gender was associated with higher disease activity at the time of disease diagnosis in this cohort of patients with relatively early disease. However, with the exception of a higher frequency of alopecia and anti-Ro antibodies in women, we could not find any other notable difference in other clinical and immunological parameters.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 7 Pregnancy & Contraception"

Atlantico A+B+C

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Pathologic characteristics of placentas in Systemic Lupus Erythematosus patients

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Introduction: SLE pregnancy is associated with intrauterine growth retardation, prematurity, fetal loss and neonatal morbidity. Antiphospholipid antibodies (aPL ab), are associated with thrombosis and/or circulatory compromise of the maternal-fetal-placental unit, and an increased risk of fetal loss. The placentas have a higher incidence of low birth weight, stroke, bleeding and decidual vasculopathy. Nodes, calcifications and fibrin deposits are associated with placental maturity and should be present at term.

Our **objectives** were 1- to describe anatomical and pathological characteristics of the placentas of SLE patients; 2- to correlate the presence of placental changes in patients with positive aPL antibodies; 3- to estimate the rate of prematurity and low birth weight in this cohort.

Patients and methods: This is a retrospective, controlled, descriptive and observational study. We reviewed pathologic preparations of placentas from SLE patients (ACR 1997) admitted to the Obstetrics Department between 2008 and 2011 and we compared with a healthy control group. Medical history and serology were obtained from medical records. The data were analyzed by SPSS 17.0 Chicago IL.

Results: We analyzed 20 lupus placentas vs. 14 controls. Average age of patients: 27.2 years (SD 5.83) (no statistical differences with controls). Median evolution of SLE 49.5 months (0-184), 6/20 (30%) had positive aPL, 7/20 (35%) had gestational hypertension

Median gestational age in SLE: 34 weeks (25-38.4), 17/20 (85%) were premature vs control group 0% (p=0,001). Deliveries: cesareans 18/20 (90%) vs. 5/1 (36%) control group. (p=0,002)

Placentas characteristics

	SLE N: 20 (%)	*Control N: 14 (%)*	*P*
Median gestational age (weeks)	34 (25-38.4)	38.1 (37-40)	p=0,001
Nodes syncytial	19 (95)	14 (100)	NS
Fibrin deposits	18 (90)	14 (100)	NS
Calcifications	15 (75)	11 (78)	NS
Decidual vasculopathy	12 (60)	0	p< 0,0001
Chronic villitis	1 (5)	0	NS
Low weight	5 (25)	4 (28)	NS
Decidual thrombosis	1 (5)	0	NS
Infarction >20% of the surface	3 (15)	0	NS

There were no statistically significant differences in the groups with and without aPL.

Treatment during pregnancy: 17/20 (85%) 8-40 mg corticosteroids. In 8/20 (40%) who did not receive HCQ was a trend toward lower gestational age ($p = 0.087$).

Conclusions: Decidual vasculopathy is an anatomo pathological expression of placental hypoperfusion. It was statistically significant in our patients and could be involved in the development of syncytial nodes, calcification and fibrin deposits as premature placental aging signs. In our SLE patients, most with preterm deliveries, findings of

placental maturity were abnormal, showing the possible impact of autoimmune inflammatory process on this organ.

The lack of statistically significant difference between the placentas of patients with and without aPL could be related to the small sample number.

P139

Fetal outcome in systemic lupus erythematosus treated with azathioprine during pregnancy

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Background: Lupus patients, especially those with major organ involvement, frequently need to go under immunosuppressive therapy during pregnancy in order to avoid disease flares or maintain remission state. Azathioprine is one of the main drugs used in this disease during this period, but there is still more to know about relevant outcomes during pregnancy with the use of this drug.
Objective: To evaluate the effect of Azathioprine intake during the pregnancy period on the obstetric outcomes.

Patients and Methods. We reviewed medical records from pregnant women with diagnosis of SLE (ACR criteria) seen at our outpatient clinic from January 2005 to June 2010. Patients were divided in two groups: 1. Azathioprine exposed (AZA-Group) and 2. Non azathioprine exposed (NON-AZA group). Exposure to azathioprine was considered before conception or from the first trimester.

Fetal outcomes recorded were: rate of liveborns, premature rupture membranes (PRM), preterm birth (< 37 weeks), fetal loss (spontaneous abortion and stillbirth), term delivery, neonatal death, low birth weight (< 2,500 g), and congenital malformations. Statistical analysis: Student t-test, Mann Whitney U test, for non-parametric data, Fisher's exact test, multivariate logistic regression model and odd ratios were calculated, with 95% confidence intervals (CI).
Results: Information on a total of 114 pregnancies was collected. The maternal characteristics at pregnancy of the AZA-group (n=58) and NON AZA-group (n=56) differed with regard to maternal age (27.8±4.9 vs 25.3±4.9 years, p=0.01), first pregnancy (62.0% vs. 30.3%, p=0.01), and previous renal involvement (53.4% vs 19.6%, p=0.0002). Mean daily dose of AZA-group was 75 mg (range, 50-150 mg). Nephritis class IV (WHO) was the more common type of renal involvement. Fetal outcomes were similar in both groups (table 1), except for a lower proportion of term deliveries in AZA-group (31% vs 50%, OR 0.4, CI 0.20-0.96, p=0.03). In the multivariable analysis, preeclampsia was associated with preterm birth (OR 10.1, CI 2.5-39.9, p=0.001) and first pregnancy with low birth weight (OR 2.7, CI 1.1-6.8, p=0.02). Only one malformation was observed in a live borne exposed to azathioprine (congenital torticolis).
Conclusions: This study suggests that azathioprine can be used in SLE pregnancy without association with poor fetal outcome. Pre-eclampsia and first pregnancies were associated with preterm birth and low birth weight respectively.

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Prolactin and Dendritic Cells in systemic lupus erythematosus and pregnancy

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Introduction: Dendritic cells (DCs) are antigen presenting cells with the ability to induce primary immune responses and preserve immunological tolerance during normal pregnancy. Prolactin (PRL) plays an important role as an immunostimulator hormone-cytokine and it is considered to be associated with fetal loss and systemic lupus erythematosus (SLE) activity during pregnancy. However, the interaction between DCs and PRL in the gestational period of SLE patients is unknown.
Objective: To determine the PRL and DCs levels in pregnant patients with SLE and its relationship with lupus activity and clinical course of pregnancy.
Patients and Methods: Pregnant patients with SLE from the Pregnancy and Autoimmune Rheumatic Diseases Clinic of our hospital, and healthy pregnant women (controls) were included. Peripheral blood was drawn for the PRL analysis by chemiluminescent (IMMULITE 2000 Prolactin) and DCs: CD1 (monocytoid, immunogenic cells) and CD2 (plamocytoid, tolerogenic cells), by flow cytometry. These determinations were made each trimester of pregnancy using specific antibodies. The PRL results were expressed in ng/dL and the DCs in percentages. The m-SLAM scale was used to measure the SLE activity during pregnancy (score $\geq$ 4). For the statistical analysis we used Student's t-test and Pearson correlation. The significant level was considered as $p < 0.05$.
Results: We included 13 pregnant women with SLE and 11 healthy pregnant women. The mean age of SLE patients was 25.67 $\pm$ 3.84 and 29.2 $\pm$ 5.3 years old in the control group. The m-SLAM was 0.62 (0-3). All SLE patients were in clinical remission. The mean CD1 for the SLE patients was 11.42 $\pm$ 9.4 vs. 56.15 $\pm$ 22.32 in healthy pregnant women ($p < 0.01$). The mean CD2 in SLE was 10.5 $\pm$ 8.7 vs. 20.49 $\pm$ 14.4 for the control group ($p < 0.02$). PRL levels in SLE patients were 166 $\pm$ 23.24 ng/dl vs. 148.5±69.8 (p=ns) in the controls. Linear analysis showed a trend of positive correlation between PRL and CD1 ($r = 0.36$, $p = 0.1$) in patients with SLE. The analysis of the third trimester showed the same trend of positive correlation ($r = 0.42$, $p = 0.12$) between CD1 and PRL. No correlation was found between CD1, CD2 and SLE activity. To date, seven patients have had normal deliveries.
Conclusions: This study shows a significant decrease in DCs (CD1/CD2) in SLE patients compared with healthy pregnant women. We did not found a significant correlation between PRL and CD1 (immunogenic) in SLE. These results are directly related to the absence of SLE activity in pregnancy. There is a close relationship between SLE clinical remission, positive obstetric outcome, and normal PRL levels.

P141

Improving Outcomes for Pregnant Lupus Patients: Is There a Rural Penalty?

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Introduction/background: Systemic lupus erythematosus (SLE) results in excess miscarriages, preterm births, and other complications of pregnancy. This is especially true for young women of African-American or Hispanic origin because they may lack necessary resources to effectively manage their illness. Some of these results may be due to geographic disparities. We analyzed this possibility through the process of

geocoding patient zip codes to identify rural versus urban patients by correlating this with the Medically Underserved Areas.
Patients and Methods: We performed a secondary data analysis of an existing multicenter, multiethnic USA cohort of SLE patients. Analyses were performed using the STATA statistical software package to analyze the following variables: zip code, age, race/ethnicity, income, education, preterm birth of fetus, miscarriage/spontaneous abortion frequency, mode of delivery (vaginal or c-section) and corticosteroidamount (re: dosage). Continuous variables, such as age and dosage amounts, were analyzed via descriptive statistics whereas dichotomous variables were analyzed via logistic regression. We compared the statistically significant variables with US Census-designated, Medically-Underserved Areas.
Results: A total of 108 patients experienced pregnancy during the duration of observation, 44 of these patients were rural and 64 were urban. Adverse pregnancy outcomes were common. A total of 65 patients out of the 108 had at least one adverse pregnancy complication including, miscarriage, abortion, moderate to severe prematurity, and stillbirth. Of the adverse outcomes examined, there was a disparity between rural and urban patients with 25% of rural patients experiencing a miscarriage versus 16% of urban patients; likewise, moderate to severe prematurity was more common in rural patients (23%), than in urban patients (14%). Lastly, stillbirth was also more common in rural patients, 7%, versus 3% in urban patients. However, in each case the p-value was

> . 05.

Conclusions: Women with lupus have a high frequency of adverse outcomes of pregnancy. Those lupus patients living in rural areas appear to have more frequent and more severe pregnancy outcomes than urban patients. Other comorbid factors such as age, race/ethnicity, educational level, and income, may play a role contributing to this disparity and further research will be necessary to identify the contributions of each of these possible confounders.

P142

Predictors of flare during pregnancy in women with systemic lupus erythematosus

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Introduction: Woman with systemic lupus erythematosus (SLE) have 2 to 3 times higher risk of reactivation during pregnancy. However, the predictive factors of lupus flare in pregnancy are not completely elucidated.

Objective. To identify predictors of flare in pregnant women with SLE.
Patients and methods: We reviewed clinical records of a cohort of pregnant women with SLE (ACR 1982, 1997) treated in our Clinic of Pregnancy and Rheumatic Diseases in a tertiary referral center for the period January 2005 to June 2011. Patients were evaluated at least once during each trimester and once postpartum. Primary endpoint was lupus flare including specific skin lesions, arthritis, hematological, neurologic, cardiopulmonary and renal manifestations. We analyzed 15 clinical and laboratory variables that potentially have predictive value for lupus flare during pregnancy, including age, duration of disease, activity of SLE before pregnancy, renal function, organic involvement, parity, drug use and immunological parameters. For analysis each pregnancy was included as an independent event and these were divided into 2 groups: those of mothers who relapsed and those who did not. Statistical analysis included descriptive statistics, chi square, Student t test, bivariate and multivariate analysis; odds ratios (OR) with confidence intervals (CI) 95% were also calculated.
Results: We studied 124 pregnancies in 120 women with a mean age of 26.5±5.1 years at time of pregnancy, with an mean of SLE evolution 5.2±4.1 years, 45 (36.2%) patients had lupus nephritis before pregnancy, 16 (12.9%) women had SLE activity before pregnancy, 47 (37.9%) women had at least one episode of flare during pregnancy. The significant variables associated with lupus flare during pregnancy in the multivariate analysis were primiparous (OR 2.3, 95% CI 0.99-5.52, p=0.05) and hypocomplementemia (OR 2.2, 95% CI 0.94-6.84, p=0.06).

The live birth rate was similar in both groups (80.9% vs 87%, p=0.35); on the other hand, the rate of prematurity was higher (55.3% vs 35.1%, p=0.02) with fewer weeks of gestation (34.6±3.9 vs 35.8±3.4, p=0.009) in women who relapsed.
Conclusions: According to the experience of our center, primiparous woman with SLE and hypocomplementemia before conception (lupus subclinical activity data) have a higher risk of relapse during pregnancy.

P143

Contraceptive Methods in Women with Systemic Lupus Erythematosus and Rheumatoid Arthritis in Turkey

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Introduction: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that is 10 times more prevalent in women, particularly those of reproductive age. The varying effects of pregnancy on this disease and the differences between available SLE treatments make pregnancy timing and contraceptive methods significant. We aimed to determine the contraceptive methods used by SLE patients in Turkey, and compared them with those used by rheumatoid arthritis (RA) patients and healthy controls.
Patients and methods: The study was comprised of 113 sexually active SLE patients (mean age 39±9 years), 84 RA patients (mean age 41±8 years) and 92 healthy control group (mean age 38±9 years). The data was collected through individual (face to face) interviews.
Results: Twenty-three (20.3%) out of 113 SLE patients, 18 (21.4%) out of 84 RA patients and 17 (18.6%) out of 92 healthy controls did not use any contraceptive methods. Use of the withdrawal and condom methods was more common among SLE patients, accounting for 61% (withdrawal 32.7%, condom 28.3%). Only 6 patients in the SLE group used oral contraceptive (OC) although all OCs used contained estrogen, no patients had a history of thrombosis, and four of the six patients were antiphospholipid antibody positive. The prevalence of intra uterine device (IUD) use in SLE patients is between 10% and 15% according to current literature. Although this rate is in line with the results of our study, the number of patients with SLE using IUD was lower than that of the healthy controls. Whereas the rate of patients with SLE using tubal ligation was only 4%, the corresponding rate was higher among healthy controls (12%). None of the women in any of the study groups used a diaphragm and/or a spermicide. The numbers of normal pregnancy, unplanned pregnancy and miscarriage were also evaluated, and no difference was found between SLE, RA and healthy control patients in terms of unplanned pregnancy and miscarriage. Moreover, 52% of SLE and 50% of RA patients were neither given information about contraceptive methods nor offered a suggested method compared to 34% in the health control group.
Conclusion: Although pregnancy timing is of great importance for SLE patients, necessary information and recommendations concerning contraceptive methods have been ignored and the use of effective methods is not a priority in such groups of patients. The prevalence of OC use is low in Turkey; notwithstanding the withdrawal and condom methods, which are frequently used despite their high failure risk. No patients in our study used progestin-only pills, diaphragm and/or spermicide.

Although there is no limitation concerning types of contraceptive methods used by SLE patients, estrogen-containing preparations should be avoided in patients with a history of thrombosis and APS. Since contraceptive methods vary between countries even in healthy populations, results of the present study are essential in terms of revealing contraceptive methods used by SLE and RA patients in Turkey.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 8 Pediatric Lupus"

Atlantico A+B+C

P144

Systemic lupus erythematosus – cause of death: a study evaluating multiple cause-of-death in deaths before and after 20 years of age.

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Introduction: The mortality in systemic lupus erythematosus (SLE) patients is about 2-3 times greater than in general population. The knowledge of multiple causes of death in SLE may support better disease management.
Objective: To compare the main associated causes of deaths in SLE occurred at age until 19 years and ≥ 20 years in the state of São Paulo.
Methods: Data were obtained from the official databank of Sao Paulo state which contains all data of death certificate (DC). We analyzed all DC issued from 1985 to 2007, in which SLE was selected as the underlying cause of death. Deaths were divided into 2 age groups: GI: 0-19 years and GII ≥ 20 years. We compared the associated cause of deaths between groups, using Qui-square or Fisher exact test. $P < 0.05$ was considered significant.
Results: A total of 3,133 DC were analysed and 440 of them occurred at age lower than 20 years. Among deaths before 20 y.o. 388 (88%) were female and the female/male ratio was 7.5 F: 1 M. For deaths ≥20 years the ratio was 9.5 F: 1 M. Renal failure was the main cause of death in both age groups. The second cause in GI was infection while in GII was circulatory system diseases (CSD). CSD included the group of cerebrovascular diseases, hypertensive diseases, pulmonary embolism, primary pulmonary hypertension, heart failure, acute myocardial infarction (AMI) and other ischemic heart disease. From among CSD, cerebrovascular disease (cerebral hemorrhage, stroke and cerebral infarction) was proportionally more mentioned in deaths in GI than GII ($p < 0.001$). On the other hand, hypertensive diseases were less frequent in GI than in GII ($p < 0.001$). AMI and other ischemic heart diseases were not mentioned in GI ($p=0.002$).
Conclusions: Renal failure was the main associated cause of death in SLE. The high frequency of infections in all age groups is worrying. Regarding the circulatory system diseases, in young age the cerebrovascular diseases and not ischemic heart diseases are important cause of death. Therefore aggressive treatment for renal involvement is necessary but with cautions to avoid infections. Rigorous control of cardiovascular risk factors must be done to decrease fatal outcomes.

Associated cause of death	*GI (< 20 y.o)*	*GII (≥20 y.o)*	*p*
Renal failure	124 (28.19)	808 (30.00)	0.438
Pneumonia	98 (22.28)	707 (26.25)	0.076
Circulatory System Disease	72 (16.36)	731 (27.14)	< 0.001
Septicemia	100 (22.73)	614 (22.80)	0.973
Hipertensive Diseases	15 (3.41)	230 (8.54)	< 0.001
Cerebro vascular Diseases	30 (6.82)	156 (5.79)	0.399
Heart failure	16 (3.64)	160 (5.94)	0.052
nephrotic/nephritic syndrome	37 (8.41)	113 (4.20)	< 0.001
Cerebro vascular hemorrage	19 (4.32)	86 (3.19)	0.224
Pulmonary embolism	9 (2.04)	82 (3.04)	0.247
Acute myocardial infarction	0	57 (2.12)	0.002
Stroke (hemorrhage or infarction)	6 (1.36)	46 (1.71)	0.600
Gastrointestinal hemorrhage	5 (1.14)	44 (1.63)	0.436
Disseminated intravascular coagulation	9 (2.04)	31 (1.15)	0.121
Cerebral infarction	5 (1.14)	24 (0.89)	0.591*

(continued)

Table Continued

The percentages correspond to the number of mentions among death in each age group.
*Fisher's Exact Test.

P145

Pediatric Automated Neuropsychological Assessment Metrics As a Screening Tool for Neuropsychiatric Childhood-Onset Systemic Lupus Erythematosus

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Background: Neuropsychiatric involvement appears to be common in childhood-onset systemic lupus erythematosus (cSLE), with neurocognitive dysfunction (NCD) identified in as many as 59%. NCD is typically detected via formal neuropsychological testing but it is costly, time intensive, not readily available, and requires specialized advanced training. Recently, computerized tests have been explored as more feasible screening tools of NCD such as the Pediatric Automated Neuropsychological Assessment Metrics (PedANAM), a library of automated tasks assessing various aspects of cognitive status.

The objective of this ongoing study is to determine the feasibility of the PedANAM to monitor cognitive status in cSLE in a clinical setting.
Methods: cSLE patients were recruited from 5 pediatric rheumatology centers. Demographic and disease relevant information was recorded. 12 cognitive subtests of the PedANAM were administered to each patient. Patient were observed for at least part of the testing to document effort (motivation) and technical difficulties. Mean reaction time for correct responses (MNc; msec) and accuracy (AC; % of correct responses) were measured for each subtest.
Results: Baseline data for 84 of an expected 200 patients were analyzed (88% females, mean age of 14.95 years; White 34%, African American 30%, Asian 16%, Hispanic 14%, Other 6%). Patients' grade level ranged from 4th through the 12th grade; 8% of patients had repeated a grade, and 17% received special school services. PedANAM completion required 35-55 minutes. All patients completed testing. 20 patients

responded randomly and unusually quickly on at least one subtest. Racial/ethnic groups tended to perform similarly on most test variables. Parent ratings of cognition based on PCF-43 were not related to objectively measured MNc but were related to decreased AC, with statistically significant differences on the Code Substitution Delayed (CDD) and Continuous Performance (CPT) subtests, tests that measure the recognition and working memory. Patients with at least one NPSLE symptom performed less accurately on the CDD and CPT subtests (p's < .05). Disease activity, as measured by the SLEDAI was associated with slower performance overall. Using Pearson correlations, significantly slower MNc were seen on the CDD, Matching to Sample (M2S), CPT, and SPD subtests (respectively, r= 0.258, 0.354, 0.289, 0.304; p = 0.037, 0.004, 0.017, 0.012).
Conclusion: This study demonstrated acceptable feasibility of the PedANAM to monitor cognitive status in a clinical setting. Some patients responded randomly and unusually quickly on at least one subtest particularly on the CPT and CDD, which may indicate difficulty complying with test requirements or reduced motivation. These data demonstrate that slower performance on the CDD, CPT, M2S and SPD are related to greater disease symptomatology. Further research is needed to explore the relationship between cognition and cSLE activity.

P146

Biologically Based Recurrent Intravenous Methylprednisolone Induction Therapy Allows Rapid Steroid Tapering

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Background: Our group has previously reported that high dose intravenous methylprednisolone (IVMP) is the only medication that acutely affects the interferon signature in active pediatric lupus (pSLE). The interferon signature returns within a week due to regeneration of the plasmacytoid dendritic cells (pDC). This observation drove a protocol in our center of frequent IVMP pulsing during induction therapy. Herein we review our experience with this protocol.
Patients/Methods: Retrospective chart review of all newly diagnosed pediatric SLE patients fulfilling ACR classification criteria between 2000-2009 who received IVMP during induction therapy and followed at least 6 months Standardized information is routinely collected at each clinic visit and standardized outcome measures prospectively collected. All patients were consented as part of a longitudinal gene expression study in pSLE. The treatment protocol for induction therapy typically consists of IVMP at 30 mg/kg/dose (maximum-1000 mg) given as an infusion 3 consecutive days weekly for 3 weeks then spaced to every 2 weeks and then to every 3-4 weeks depending on disease activity. Daily prednisone is usually limited to 5-10 mg/day.
Results: 125 patients met study criteria. Median age 13 years (5-17), 81% female, 48% Hispanic, 74% nephritis, 63% Class III/IV, 41% received cyclophosphamide (CYC), 9% mycophenolate (MMF). Subjects demonstrated excellent clinical response to therapy with a significant decrease in the median SLEDAI score from initial visit to the end of the 6 month period (16 vs. 6) (p < 0.0001). Seventy-eight percent were steroid naïve at baseline assessment, 22% had received varying doses of steroids prior to referral. Median number of IVMP doses during first 6 months of disease: 27 (2-39). Sixty-five percent received 3 consecutive doses for 3 consecutive weeks. Sixty-nine percent of patients were on 10 mg/day or less of prednisone by 3 months, 77% by 6 months. Hypertension occurred during at least 1 IVMP infusion in 78% but did not result in discontinuation of IVMP therapy in any patient for this indication. There were 15 documented infections (6 cases of Herpes Zoster, sepsis, septic joint, pneumonia and dental abscess). Seven of the infections occurred during the initial 3 doses. Forty-eight percent of patients were described as Cushingnoid but the median increase in weight was only 5.3 kg. IVMP was discontinued in 2 patients: 1 with steroid induced psychosis, 1 with posterior reversible encephalopathy syndrome. There was 1 bone infarct and no vertebral compression fractures over the long-term.
Conclusions: IVMP recurrent pulsing during induction therapy of pSLE was well tolerated and efficacious.

P147

Interleukin-10 Promoter Polymorphisms and Expression in Juvenile Systemic Lupus Erythematosus

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Introduction: *Interleukin (IL)-10* has become a potential candidate gene for SLE susceptibility as single nucleotide polymorphisms (SNPs) at positions -1082A/G, -819T/C and -592A/C of the promoter were shown to increase susceptibility to SLE in adults. IL-10, the gene product, plays a substantial role in the pathogenesis of SLE as the cytokine facilitates antibody production by stimulating B-lymphocytes. IL-10 expression is regulated by the promoter gene and correlated with SLE activity in adult patients. As the pathogenesis of juvenile SLE (JSLE) may differ from adult-onset SLE, we evaluated SNPs at positions -1082A/G, -819T/C and -592A/C of *IL-10* promoter and serum IL-10 levels in JSLE.
Patients and Methods: 71 patients aged < 18 years with JSLE were recruited. Demographic data were obtained by medical record review. Disease activity was evaluated using the SLE Disease Activity Index (SLEDAI) and active SLE was defined as the SLEDAI of more than 6. SNPs at the positions -1082A/G, -819T/C and -592A/C of *IL-10* promoter were identified by the polymerase chain reaction and restriction fragment length polymorphism technique. Serum IL-10 levels from patients with JSLE and 15 healthy children (controls) were measured by ELISA.
Results: There were 8 males and 63 females. The mean age was 14.5 ± 2.8 years. Nephritis occurred in 57 patients (80%). The mean SLEDAI was 5 ± 6.8 (range 0 - 29). Twenty-one patients (30%) had active SLE while 50 patients (70%) had inactive SLE. Serum IL-10 levels were significantly higher in patients with active SLE (24.11 ± 21.12 pg/mL) than in patients with inactive SLE (8.3 ± 12.67 pg/mL) and controls (6.12 ± 4.47 pg/mL) ($p < 0.01$). Serum IL-10 levels did not differ in patients with nephritis when compared to patients without nephritis (13.96 ± 18.32 vs.7.86 ± 8.22 pg/mL). In JSLE, -819 CC and -592 CC were identified with higher frequencies than in the general population with the odds ratio (OR) of 2.75 (95% CI 1.11 - 6.81, $p = 0.04$). GCC increased the susceptibility to nephritis in patients with JSLE (OR 2.16, 95% CI 1.07 - 4.35, $p = 0.03$). There was no correlation observed between serum IL-10 levels and genotypic variants of the *IL-10* promoter in patients with JSLE.
Conclusion: Genetic variants of the *IL-10* promoter are a predisposing factor to JSLE susceptibility and nephritis although a single genetic variant of the promoter may not explain the entire pathogenesis of JSLE. As a starting point, this study has shown that IL-10 plays a crucial role in the pathogenesis of JSLE and correlated with disease activity as IL-10 expression was upregulated in patients with active JSLE. The -819 CC and -592 CC genotypes increased the susceptibility to JSLE and GCC increased the susceptibility to JSLE nephritis.

P148

Prevalence and clinical significance of white matter lesions in childhood systemic lupus erythematosus (cSLE)

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Background: Magnetic resonance imaging (MRI) is the method of choice for evaluating systemic lupus erythematosus (SLE) patients with central nervous system (CNS) manifestations. Imaging findings in SLE patients are very diverse. Atrophy, diffuse or regional, enlarged ventricles and hyperintense white matter hyperintensities (WMH) have been described in variable frequency. However the prevalence and clinical significance of WMH in patients with disease onset before the age of 16 (jSLE) is still unknown.
Objectives: The aim of this study was to analyze the frequency and clinical significance of WMH in both symptomatic and asymptomatic cSLE patients by a visual and semi-automatic segmentation method.
Methods: We included consecutive cSLE patients followed in a cohort at the pediatric rheumatology unit at the State University of Campinas. All patients had disease-onset before the age of 16. Controls were matched for age, sex and demographic background. A complete clinical, laboratory, and neurologic evaluation was performed in all individuals. MRI scans were obtained through a standardized protocol (3Tessla Philips). FLAIR images were used for visual and semiautomatic volumetric measurements. We compared jSLE patients with controls using the 2-sample t-test. Analysis of variance was used to test for differences between groups. Linear regression was used to analyze the association between WMH and age, disease duration, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)]and total corticosteroid dose
Results: The study included 51 patients (47 women) with mean age 16.96 years (SD $\pm$ 3.58) and 56 controls with mean age 17.25 years (SD $\pm$ 4.23). The white matter lesions were identified in 44 (86.2%) patients and in 4 (7.1%) controls ($P < 0.001$). In cSLE predominantly subcortical lesions were identified (72%), followed by periventricular (12%), deep white matter (10%) and cortical lesions (6%). In the controls predominantly subcortical lesions (62%) were observed, followed by deep white matter (36%) and periventricular (2%) lesions. Both the number (n=1029 vs n=44) and volume of lesions (v=35796.4 vs v=1870.5 mm3) were significantly higher in cSLE patients when compared to controls ($p < 0.001$). cSLE patients with WMH were significantly younger than controls with WMH ($p < 0.001$). In cSLE, the presence of WMH was associated with the presence of cutaneous vasculitis ($p < 0.001$). No other clinical and laboratory manifestation was associated with WMH in cSLE.
Conclusions: The vast majority of cSLE patients presented WMH.The presence of small WMH was associated with vasculitis in cSLE patients, suggesting that these lesions are a result of the CNS involvement of the disease and not an incidental finding. Furthermore the quantitative MRI evaluation allowed us to determine better objective evaluation.
Grants: FAPESP (2010/13639-1, 2008/02917-0), CNPq 300447/2009-4; 471343/2011-0)

P149

Abnormal sense of smell in childhood systemic lupus erythematosus.

Peres FA, Longhi BS , Peliçari KO, Sinicato NA, Postal M, Gomes CC, Pereira FC, Silva GK, Marini R, Appenzeller S
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Background: Childhood Systemic Lupus Erythematosus (cSLE) is a chronic and multisystemic autoimmune disease. Neuropsychiatric involvement in cSLE has a prevalence ranging from 20 to 50.9% and results in significant morbidity and mortality. The most common clinical manifestations of childhood neuropsychiatric SLE (NPSLE) are headache, cognitive dysfunction, mood disturbances and seizures. Childhood NPSLE manifestations are often difficult to diagnose. Involvement of the limbic system (e.g., atrophy of the hippocampus and amygdala) in SLE patients was recently documented utilizing magnetic resonance imaging Recently, links between the olfactory system, the immune system, and various diseases have been identified. Decreased olfaction was observed in patients with several CNS diseases in which immune-mediated mechanisms have been implicated (e.g., Parkinson's disease, schizophrenia, Alzheimer's disease, and multiple sclerosis).
Objective: To assess the olfactory functions in cSLE patients compared with age- and sex-matched healthy controls, and to examine the association between the sense of smell and disease activity, damage and CNS involvement (depression and anxiety).
Methods: Olfactory functions were evaluated using the Sniffin' Sticks test, the 3 stages of which are threshold (TDI), discrimination, and identification of different odors. All individuals were submitted to a standardized neuropsychiatric evaluation. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory (BDI and BAI). In SLE, disease activity was evaluated through SLE Disease Activity Index (SLEDAI), damage through Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC-SDI) and current drug exposures. We excluded patients with head injuries, nasofacial operations, or active nasal-sinus or allergic diseases. We use Kruskall-Wallis test, Fischer exact test and Spearman correlation. $p < 0.05$ was considered significant.
Results: We included 61 patients (91.8% women) mean age of SLE patients was 17,51+- 3.42 years and 61 controls matched for age and sex (p=0.701). Smell deficit correlated with duration of disease (r=-0.295; $p < 0.05$) and anxiety (r=0.279; $p < 0.05$). A decrease in the sense of smell was observed in cSLE patients (31.14%) and controls (27.87%) (p=0.697). Not observed anosmia in both the cSLE and control groups. Patients had an average of 31.26 +- 4.47 total points at the 3 stages of Sniffin' Sticks test while the controls had mean of 33.28 +- 5.28 points ($p < 0.05$). The olfactory alteration was not correlated with depression (r=0.055; p=0.678), SLICC (r=0.777; $p < -0.042$) or SLEDAI (r= -0.118; p=0.419).
Conclusions: Comparing cSLE patients and matched controls, we observed a significant decrease in the olfactory abilities in cSLE patients, which was correlated with duration of disease and CNS manifestations. Based on the literature, smell deficiency has been suggest to be an early and predictive sign in several CNS diseases, and therefore, might be a useful and easy tool for the physician in early diagnosis of CNS involvement in autoimmune disease.
Grants: FAPESP (2011/15422-2; 2008/02917-0) CNPq: (471343/2011; 300447/2009-4)

P150

Impact of Disease Duration on Vascular Surrogates of Early Atherosclerosis in Pediatric-Onset Systemic Lupus Erythematosus

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Introduction: Cardiovascular disease is a leading cause of morbidity and mortality in adults with systemic lupus erythematosus (SLE). Exposure to atherogenic risk factors in pediatric-onset SLE (pSLE) likely leads to accelerated atherosclerosis. The aim of the study was to determine the effect of disease duration on vascular surrogates of early atherosclerosis in pSLE. We hypothesized that longer disease duration would negatively impact vascular measurements.

Patients and Methods: A cross-sectional analysis of a prospective longitudinal pSLE cohort was performed. All subjects fulfilled ≥ 4/11 American College of Rheumatology classification criteria for SLE. Disease activity and medications were recorded. Fasting lipid, glycemic and inflammatory profiles were performed. Carotid intima-media thickness (CIMT), flow-mediated dilation (FMD) and pulse wave velocity (PWV) were measured using standardized protocols. Data from the last set of vascular studies were used. Vascular data of pSLE patients were compared to those of 138 healthy controls.
Results: 149 pSLE patients participated in the study (Table). Disease duration at the most recent study visit ranged from 1 month to 14.9 years. Seventy percent of pSLE subjects had inactive disease with a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≤2. CIMT, FMD and PWV were not worse in pSLE patients when compared to controls. Gender, a history of lupus nephritis, levels of proteinuria and inflammatory markers did not significantly impact on vascular data. We observed a negative correlation between disease duration and FMD (r=-0.2, p=0.02) but not with CIMT or PWV. In univariate analysis, disease duration was significantly associated with FMD (β=-0.219, p=0.01).
Conclusion: In this large single-center pSLE cohort, longer disease duration was associated with worse FMD, suggesting progressive endothelial dysfunction over time. CIMT and PWV in pSLE were similar to control and independent of disease duration.

Table. Characteristics of pSLE patients and controls.

	pSLE (n=149)	*Controls (n=138)*
Male:female ratio	25:124	69:69
Age at vascular study (years)	16.1±2.6	14.4±2.3
Age at diagnosis (years)	12.8±3.2	-
Disease duration (years)	3.3±2.5	-
Lupus nephritis*	53 (36)	-
Class III, IV, IV + V	45 (85)	
Class V	8 (15)	
SLEDAI	2±3	-
Body mass index (kg/m^2)	23.4±5.0	20.6±3.7
Systolic blood pressure (mmHg)	112±12	109±9
Diastolic blood pressure (mmHg)	63±9	58±7
Vascular measurements†:		
CIMT (mm)	0.041±0.006	0.043±0.005
FMD (% change)	8.9±4.3	5.1±0.9
PWV (m/s)	5.3±0.9	7.5±3.1
Laboratory measures:		-
C3 (g/L)	0.99±0.23	
C4 (g/L)	0.18±0.08	
ESR (mm/h)	20±23	
CRP (mg/L)	2.2±5.9	
LDL-cholesterol (mmol/L)	2.10±0.69	
HDL-cholesterol (mmol/L)	1.38±0.40	
Triglyceride (mmol/L)	1.1±0.6	
Urine protein/creatinine ratio (mg/mmol)	24.6±58.8	

Numbers are presented as mean ± standard deviation unless otherwise specified;
* Number (percentage);
†CIMT (n=148), FMD (n=137), PWV (n=146).

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Cognitive impairment associated with s100β protein in childhood-onset systemic lupus erythematosus

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Objectives: To determine clinical and laboratorial manifestations associated with S100β protein in childhood-onset systemic lupus erythematosus (cSLE) patients
Methods: We included consecutive cSLE patients with disease onset before the age of 16 and healthy controls and age and healthy age and sex matched controls. All subjects underwent a standardized neuropsychological evaluation assessing the following: simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, and executive functions. Individual results were converted into standard scores and compared to normative data. Subjects with a total score in any of the 8 domains ≤-2 SD below the normative value were considered impaired. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory (BDI and BAI) in all subjects. cSLE patients were assessed for disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. S100β protein levels were measured by enzyme-linked immunosorbent assay using commercial kits. Clinical/laboratorial manifestations, disease activity, cumulative damage and drugs undertaken were assessed at time of blood withdrawal.
Results: We included 42 cSLE patients (mean age 16.56±3.68) and 20 healthy controls (mean age 19.9±5.31). Cognitive impairment was observed in 25 (60%) cSLE patients and in 3 (15%) healthy controls ($p < 0.05$). Patients with cognitive impairment presented significantly higher levels of the S100β protein (median 38.64) compared to patients without cognitive impairment (median 25.49; p=0.001) and controls (median 23.62; $p < 0.001$). No other clinical/laboratorial manifestations and drugs undertaken were associated to S100β protein levels in cSLE.
Conclusions: Cognitive impairment was associated with higher levels of the S100β protein, suggesting the presence of neuronal lesions in this cSLE patients cohort.
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P152

Analysis of growth in female patients with pediatric-onset Systemic Lupus Erythematosus

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Background: Systemic Lupus Erythematosus (SLE) is a lifelong disease characterised by multi-organ involvement and autoantibodies. It is assumed that growth impairment is common in pediatric-onset SLE (pSLE), but only few studies are available that report on the frequency and characteristics of growth abnormalities in pSLE.
Aim: To analyse growth in female patients with pSLE and examine its relationship to disease characteristics and treatment.
Patients and Methods: Prospectively collected digital growth curves and menarche status of an inception cohort of 196 female patients with pSLE diagnosed < 16 years and a minimal disease duration of 3 years were analysed. Abnormal growth was defined as i) one or more periods of growth arrest (< 2 cm) lasting minimal 6 months, ii) more than one growth curve percentile difference between height at diagnosis and at any follow up visit, or iii) < 2 cm growth after menarche. 67 patients were not further analyzed as they had reached final height prior to diagnosis of pSLE.
Results: 58/129 (45%) pSLE patients with growth potential had abnormal growth. The median growth curve percentile at diagnosis (50th) was significantly different from the percentile at last follow up (10th) in these patients with abnormal growth ($p < 0.001$). Patients with abnormal growth were diagnosed significantly younger than patients with normal growth (9.4±2.8 versus 11.6±2.6 years, $p < 0.001$). 90% of

these patients showed period(s) of growth arrest, whereas 10% showed a gradual decline in growth only. The median height of the 36 patients with abnormal growth having reached age 16 years (presumed final height) was significantly lower compared to the height of patients diagnosed after 16 years (154.8±8.6 versus 161±6.1cm, $p < 0.001$). Ethnicity, disease activity over time and cumulative medication use are currently being tested for their potential relation to growth impairment.

Conclusion: Growth was impaired in approximately half of female pSLE patients and may lead to abnormally low final height. Abnormal growth was characterized by periods of normal growth and growth arrest rather than gradual decline in growth, likely related to disease flares and/or treatment.

P153

Low Bone Mass in Juvenile Onset Systemic Lupus Erythematous (JoSLE): the Role of Bone Microarchitecture and Vitamin D Status

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Introduction: Young women with Systemic Lupus Erythematosus (SLE) have high risk of low bone mass and fractures mainly associated with reduced bone density. The influence of bone microarchitecture alterations in this condition has not been investigated in these patients. The objective of this study was to analyze in juvenile onset SLE (JoSLE) patients with and without low bone mineral density (BMD) the effect of bone microarchitecture, other clinical risk factors and vitamin D concentration.

Patients and Methods: Forty two JoSLE female patients (age 10-25 years) were evaluated. Demographic, antropometric and clinical data including disease duration, disease activity score (SLEDAI) and glucocorticoid (GC) use were recorded by interview and chart review. BMD at lumbar spine, hip and whole body were analyzed by DXA. Bone microarchitecture and density at distal radius and tibia were measured using High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT). 25-hydroxyvitamin D levels were measured by immunoassay. Patients were divided in two groups: 22 patients with low lumbar spine BMD (Z-score≤-2.0) and 19 patients with normal lumbar spine BMD for chronological age (Z-score > -2.0).

Results: No difference was found between groups regarding age, body mass index, disease duration, previous year mean SLEDAI, maximum and previous year cumulative GC dose ($p > 0.05$). Patients with low lumbar BMD presented lower vitamin D levels (21±5vs. 27±5ng/ml, p=0.004) and lower BMD in the other sites compared to patients with normal BMD [femoral neck (0.683±0.084vs. 0.791±0.098g/cm^2, p=0.001), total femur (0.75±0.08vs. 0.8±0.10g/cm^2,$p < 0.001$) and whole body (0.94±0.08vs. 1.01±0.06g/cm^2,p=0.009)]. Regarding HR-pQCT, patients with low lumbar spine BMD had lower values of bone microarchitecture parameters in distal radius and tibia, as described below:

Table 1. Distal Radius HR-pQCT in JoSLE patients with and without low lumbar spine BMD

	BV/TV	*TbSp (mm)*	*Dtrab (mgHA/cm^3)*	*Dmeta (mgHA/cm^3)*	*Dinn (mgHA/cm^3)*	*CtTh (mm)*
Low BMD	0.117±0.02	0.390±0.05	141.49±28.9	195.28±97.21	104.22±30.31	0.395±0.13
Normal BMD	0.147±0.02	0.469±0.09	177.66±35.64	235.01±35.42	138.08±36.49	0.495±0.19
p	0.001	0.005	0.001	0.001	0.003	0.071

Table 2. Tibia HR-pQCT in JoSLE patients with and without low lumbar spine BMD

	BV/TV	*TbSp (mm)*	*Dtrab (mgHA/cm^3)*	*Dmeta (mgHA/cm^3)*	*Dinn (mgHA/cm^3)*	*CtTh (mm)*
Low BMD	0.127±0.02	0.476±0.09	153.47±32.14	216.93±37.23	110.28±30.84	1.026±0.18
Normal BMD	0.149±0.02	0.521±0.09	179.07±34.38	243.06±30.45	135.54±39.83	1.182±0.13
p	0.023	0.131	0.022	0.021	0.035	0.004

Data expressed in mean±SD. BV/TV: bone volume to total volume ratio; TbSp: trabecular separation; Dtrab: trabecular volumetric density; Dmeta: meta trabecular density; Dinn: inner trabecular density; CtTh: cortical thickness

Conclusion: Low lumbar spine BMD in JoSLE patients was associated with generalized bone alterations in trabecular and cortical microarchitecture and hypovitaminosis D. Further studies are necessary to assess the contribution of these factors to increased fracture risk in these patients.

P154

Condyloma acuminatum by human papilloma virus infection in childhood-systemic lupus erythematosus patients

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Introduction: Infections are frequent in childhood-systemic lupus erythematosus (C-SLE) patients, including genital infections, as human papillomavirus (HPV). HPV infection may cause genital and anal warts, namely condyloma acuminatum (CA) in adult SLE. However, to our knowledge, no cases were reported and the prevalence of CA in pediatric lupus population was not performed.

Patients and Methods: From January 1983 to May 2012, 5,682 patients were followed at the Pediatric Rheumatology Unit, Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo and 289 (5%) of them met the American College of Rheumatology classification criteria for SLE. Pap smears were evaluated by the same cytopathologist blinded to gynecology examination in our University Hospital. The identification of the organisms (Trichomonas vaginalis, Candida spp, bacterial vaginosis, Actinomyces spp and herpes simplex

virus) was also evaluated. Colposcopically guided biopsies of the worst visible lesions were also obtained. HPV infection was confirmed according to DNA testing, Hybrid Capture 2 (HC2 high-risk; Digene Corporation, currently QIAGEN, Gaithersburg, MD, USA), using DNA of oncogenic group (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68)

Results: Four (1.4%) of our female C-SLE patients had CA. The median age at C-SLE diagnosis was 13 years (8-15) and the median interval between diagnosis of C-SLE and CA was 35 months (1-108). Three of them were sexually active and the median interval of sexual debut was 16 years (14-16) with median interval of menarche 10.5 years (10-12). The median Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was 16.5 (6-20). All of them had anogenital warts and the confirmation of high risk HPV was performed by HPV DNA testing using Hybrid Capture 2. Pap smears were carried out for all sexually active patients according to the 2001 Bethesda Classification and showed low-grade squamous intraepithelial lesion (LSIL). Colposcopically guided biopsies of the worst visible lesion identified chronic cervicitis and vulvar, vaginal, anal and/or cervix intraepithelial neoplasia. All of them were receiving corticosteroids and immunosuppressive drugs at CA diagnosis (azathioprine or intravenous cyclophosphamide) and were treated with loop electrosurgical excisional procedure, CO2 laser vaporization or surgical removal. None of our male C-SLE patients had condyloma acuminatum.

Conclusion: CA by high-risk HPV infection was rarely observed in C-SLE population, occurred in sexually active and virgin patients with disease activity and under immunosuppressive agents. Our patients require rigorous gynecologic follow-up due to the severe anogenital dysplasia. HPV vaccine should be recommended for all C-SLE patients, particularly before sexual intercourse, however immunogenicity and safety of this vaccine should be evaluated in pediatric population.

P155

Exercise Training in Childhood-Onset Systemic Lupus Erythematosus: A Controlled Randomized Trial

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Introduction: Exercise training has emerged as a promising therapeutic strategy to counteract physical dysfunction in adult systemic lupus erythematosus. However, no longitudinal studies have evaluated the effects of an exercise training program in childhood-onset systemic lupus erythematosus (C-SLE) patients.

Objective: To evaluate the safety and the efficacy of a supervised aerobic training program in improving the cardiorespiratory capacity in childhood-onset systemic lupus erythematosus (C-SLE) patients.

Methods: Nineteen physically inactive C-SLE patients were randomly assigned into two groups: trained (TR, n=10, aerobic exercise program) and non-trained (NT, n=9). Gender-, BMI- and age-matched healthy children were recruited as controls (C, n=10) for baseline (PRE) measurements. C-SLE patients were assessed at PRE and after 12 weeks of training (POST). Main measurements included exercise tolerance and cardiorespiratory measurements in response to a maximal exercise (i.e.: peak VO2, chronotropic reserve [CR], and the heart rate recovery [ΔHRR] (i.e. the difference between HR at peak exercise and at both the first [ΔHRR1] and second [ΔHRR2] minutes of recovery after exercise).

Results: The C-SLE NT patients did not present changes in any of the cardiorespiratory parameters at POST ($p > 0.05$). In contrast, the exercise training program was effective in promoting significant increases in time-to-exhaustion (p=0.01; ES=1.07), peak speed (p=0.01; ES=1.08), peak VO2 (p=0.04; ES=0.86), CR (p=0.06; ES=0.83), and in ΔHRR1 and ΔHRR2 (p=0.003; ES=1.29 and p=0.0008; ES=1.36, respectively) in the C-SLE TR when compared with the NT group. Moreover, cardiorespiratory parameters were comparable between C-SLE TR patients and C subjects after the exercise training intervention, as evidenced by the ANOVA and the Z-score analysis ($p > 0.05$, TR vs. C). SLEDAI-2K scores remained stable throughout the study.

Conclusion: A 3-month aerobic exercise training was safe and capable of ameliorating the cardiorespiratory capacity and the autonomic function in C-SLE patients.

P156

Atmospheric pollution: influence on disease activity in childhood-onset systemic lupus erythematosus patients

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Introduction: Environmental factors, such as atmospheric pollution, may trigger the inflammation in adult systemic lupus erythematosus (SLE) patients. However, the role of atmospheric pollution and disease activity in childhood-onset systemic lupus erythematosus (C-SLE) population was not reported at the moment. Therefore, the objective of the present study was to investigate the association between changes in daily concentrations of air pollutants in Sao Paulo metropolitan region and disease activity in C-SLE patients.

Methods: This was a longitudinal panel study including 410 consecutive medical visits in 22 C-SLE patients (ACR criteria). They were followed at the Pediatric Rheumatology Unit, Children's Institute, Faculdade de Medicina da Universidade de Sao Paulo, Brazil, between 2005 and 2010. Disease activity was evaluated according to Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and the patients were divided arbitrarily in two groups: with disease activity (SLEDAI > 8) and without disease activity (SLEDAI < 8). The Sao Paulo State Environmental Agency (CETESB) provided daily concentrations of inhaled particulate matter (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), ozone (O3) and carbon monoxide (CO). Meteorological variables, such as the minimum temperature and relative humidity, were obtained from the Institute of Astronomy and Geophysics of the University of Sao Paulo. Generalized estimation equation (GEE) model were used for binomial distribution to assess the impact of these measurements in the SLEDAI 2K score, considering the fixed effects for repetitive measurements, and adjusted for erythrocyte sedimentation rate, C-reactive protein, prednisone and/or immunosuppressant use, presence of infection 20 days before the medical appointment, minimum temperature and relative humidity. The results were expressed in relative risk (RR) and confidence interval (CI) of 95%.

Results: 410 consecutive medical visits were evaluated in 22 C-SLE patients (20 girls), with a mean of 19 visits/patient (4-30). The mean current age at the time of evaluation was 15.3 years (10.8-19.0). The mean age at C-SLE diagnosis was 10.3 years (6-12) and the mean age at disease duration was 5.3 years (7months-11years). Interquartile range increases of PM10 (25.2 $\mu g/m^3$), CO (0.8 ppm), and NO2 (102 $\mu g/m^3$) were associated with increases of 1.74 (95% CI 1.28-2.39), 1.37 (95% CI 1.12-1.67) and 1.11 (CI 95% 1.02-1.21) in the risk of SLEDA-2K score > 8, respectively, 13 days after the exposure to these pollutants. The four days PM10 cumulative effect (from lag13 to lag16) increased

the risk of outburst of SLE in 65% (CI 95% 1.06- 2.75). In contrast, ozone and SO2 did not show a significant effect on the SLEDAI-2K score.
Conclusion: Variations in air pollution may influence disease activity in C-SLE patients. Therefore, oxidative stress may be an important trigger of inflammation in this systemic autoimmune disease.

P157

Age of Onset of Systemic Lupus Erythematosus in Children in an International Cohort

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Background/Purpose: Based on the literature, children with systemic lupus erythematosus (SLE) are diagnosed at around 11-12 years of age; however, some evidence suggests that childhood-onset SLE (cSLE) is more frequently diagnosed at a younger age in non-White patients. The objective of this study was to explore the average age of onset of cSLE across different continents and ethnicities.
Methods: In a cross-sectional international multicenter cohort of cSLE patients, geographic location, ethnicity, and age of onset of symptoms (patient/parent reported) were examined. Descriptive analysis and comparison of median ages were performed.
Results: Out of the 454 patients, 403 had an onset of disease between 2-16 years of age. For these patients, the median age of onset was 11 years (range 2-16years). Children were of the following ethnicities: White non-Latino (33%); Black non-Latino (24%), Asian (16%), Latino (18%), and Other (9%). They were from the following continents: North America (41%), South America (25%), Europe (16%) and Asia (17%). Ages of onset were significantly different

across continents (p=0.009, Kruksal Wallis test) (please refer to table 1 below).

There was no difference found between the median ages of onset across different ethnicities. However, when we examined a subset of patients (n=70) with lower age of onset of cSLE (age of onset of 8 years or younger), 48 were non-Whites (48/70-69%); 14 were Whites (14/70-20%) and 8 had unconfirmed ethnicities.
Conclusion: As shown previously, a younger age of onset is seen more often in non-Whites. The mean age of onset was lowest in South America and Asia in our study. It is possible that due to racial intermixing, there was no difference in the median age of onset across ethnicities. Larger population-based studies with listing of detailed ethnicities of ancestors are needed.

Addendum: In addition to the above authors- the International SMILEY (SImple Measures of Impact of Lupus Erythematosus in Youngsterds) collaborative group has been involved and their names will be listed in the poster if accepted.

Table 1. Median age of onset of SLE in children from different continents

Continent	*Number of subjects*	*Median age (years)*	*Range of ages (years)*
North America	166	11.9	2-16
Europe	65	11.7	3-16
Asia	70	11	5-16
South America	102	10.7	2-15

19/04/13
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Poster Sessions & Tours 1
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Atlantico A+B+C

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Antiphospholipid syndrome associated to systemic lupus erythematosus during a 10-year period: Analysis from the "Euro-phospholipid Project".

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Introduction: The antiphospholipid syndrome (APS) was first recognized in patients with systemic lupus erythematosus (SLE). The objective of this study is to evaluate the morbidity and mortality in APS associated to SLE after a 10-year follow-up and to determine whether there are differences in comparison with primary APS.
Methods: The clinical and immunological features of a cohort of 1000 patients with APS from 13 European countries, who had been followed up from 1999 to 2009 (Euro-Phospholipid project), were analyzed.
Results: The cohort included 531 (53.1%) patients with primary APS and 362 (36.2%) with APS associated to SLE. During the 10 year

prospective study, some patients were reclassified and 230 patients with APS associated to SLE were lost (mean, 2.3% every year). Finally, 132 patients with APS associated to SLE and 432 with primary APS were followed for 10 years. Of those patients with APS associated to SLE, 84% were females and 16% males. The mean age (SD) at inclusion was 46 (10) years, and this age was lower in comparison with the mean age of those with primary APS (50 (12) years, $p < 0.002$). Table 1 shows the frequencies of the main APS clinical manifestations during the period analyzed and compares APS associated to SLE with primary APS. Both groups had similar profiles, with some exceptions: APS associated to SLE developed more arthralgias and arthritis, leucopenia, anemia, livedo reticularis, epilepsy, glomerular thrombosis and myocardial infarction. On the other hand, primary APS had more superficial thrombophlebitis and pregnancies with more premature births and intrauterine growth restriction. During the observational period, 6.8% of patients with APS associated to SLE and 7.1% with primary APS died. Table 2 shows the main causes of death.

Conclusions: The Euro-Phospholipid project, which covers an APS population that is representative of Europe, identified the main causes of morbidity and mortality in patients with APS associated to SLE as well as several differences in comparison with patients with primary APS.

Table 1. Main clinical manifestations related to the antiphospholipid syndrome (APS) associated to systemic lupus erythematosus (SLE) and primary APS that appeared during the 10-year follow-up (1999–2009) of the ''Euro-phospholipid'' cohort.

*Clinical manifestations**	*APS associated to SLE (n=132)† No. (%)*	*Primary APS (n= 420)† No. (%)*	*p-value‡*
Arthralgia	41 (31.1)	34 (8.1)	$p < 0.0001$
Arthritis	28 (21.2)	12 (2.8)	$p < 0.0001$
Livedo reticularis	25 (21.2	29 (6.9)	$p < 0.0001$
Skin ulcers	2 (1.5)	10 (2.4)	
Leukopenia	19 (14.4)	10 (2.4)	$p < 0.0001$
Autoimmune haemolytic anaemia	21 (15.9)	9 (2.1)	$p < 0.0001$
Thrombocytopenia ($< 100{,}000$ /μl)	16 (12.1)	31 (7.4)	
Amaurosis fugax	6 (4.5)	7 (1.7)	p 0.057
Superficial thrombophlebitis	0	8 (1.9)	p 0.036
Deep vein thrombosis	4 (3.0)	18 (4.3)	
Stroke	9 (6.8)	20 (4.8)	
Transient ischaemic attacks	8 (3.1)	13 (3.1)	
Epilepsy	9 (6.8)	5 (1.2)	$p < 0.0001$
Myocardial infarction	5 (3.8)	5 (1.2)	p 0.050
Valve thickening/ dysfunction	9 (6.8)	19 (4.5)	
Unestable angina	4 (3.0)	10 (2.4)	
Pulmonary embolism	4 (3.0)	9 (2.1)	
Glomerular thrombosis	4 (3.0)	1 (0.2)	p 0.003
Obstetric manifestations§	*(No.=14)*	*(No.=65)*	
Pre-eclampsia/eclampsia	1 (7.1)	3 (4.6)	
Early pregnancy loss (< 10 weeks)	3 (21.4)	10 (15.3)	
Late pregnancy loss (≥ 10 weeks)	0	2 (2.4)	
Live birth	10 (71.4)	47 (72.3)	
Live birth with prematurity¶	4 (40.0)	34 (72.3)	p 0.045
Live birth with intrauterine growth restriction¶	1 (0.1)	24 (51.1)	p 0.017

**Some patients had several associated presenting manifestations.*
† Number of patients that continued in the study until 2009
‡ Pearson Chi2
§ Related to number of pregnancies (No.)
Some women had more than one pregnancy.
¶ Percentage related to number of live births.

Table 2. Causes of death related to antiphospholipid syndrome (APS) associated to systemic lupus erythematosus (SLE) and primary APS that appeared during the 10-year follow-up (1999–2009) of the ''Euro-phospholipid'' cohort.

*Causes of death**	*APS associated to SLE (No.=9)† No.(%)*	*Primary APS (No.= 30)† No. (%)*
Myocardial infarction	0	3 (0.7)
Stroke	1 (0.8)	3 (0.7)
SLE renal involvement	1 (0.8)	10 (2.4)
SLE haematologic involvement	1 (0.8)	10 (2.4)
Bacterial infection	3(2.3)	9 (2.1)
Viral infection	0	3 (0.7)
Haemorrhage	2 (1.5)	7 (1.7)

*Several patients had more than one cause of death.
† Number of death (No.)
APS, antiphospholipid syndrome;
SLE, systemic lupus erythematosus.

P159

Antiphospholipid Syndrome. Clinical and Laboratory Expression in Multiethnic Latin American GLADEL Cohort.

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Background: Antiphospholipid Syndrome (APS) may have serious clinical manifestations in Systemic Lupus Erythematosus (SLE) patients. We reviewed APS expression in SLE patients from a large multicenter and multiethnic cohort from nine Latin America countries, associated in the GLADEL consortium

Methods: Clinical and laboratory variables in 1480 SLE patients were collected in ARTHROS database. Fulfilment of ACR 1982 SLE criteria at diagnosis was not mandatory, although 95.6% complet 4 criteria during the course of the disease. Standard statistically test were performed evaluating demographic and clinical manifestations in SLE and APS patients.

Results: Most of SLE patients ware female, 1330 (89.8%), mean age at diagnostic of disease was 29.5 ±12.3 years, with a mean follow-up of 55 months (range 1-102).

Positivity for antiphospholipid antibodies test (APLa) in SLE patients was: false VDRL 31%, Lupus Anticoagulant (LA) 30%, Anticadiolipin IgG (ACLG) 49%, Anticardiolipin IgM (ACLM) 38%, and B2Glicopotein (B2GP) 55%.

Only 61 (4.1%) patients in the cohort were diagnosed as having APS by the attending physicians. In 29 of them, (47.5 %) APS was diagnosed before SLE diagnosis. Demographic characteristics of this

group were: female 54 (88.5%), mean age at APS diagnosis was 28.3 years. Regarding ethnicity 23 (37.7%) were white, 33 (54.1%) mestizos, 3 (4.9%) and african latin american (ALA).

The relative risk of APS in SLE population by different ethnic group was: white RR 0.9 (95% CI 0.5 – 1.5) p = 0.59, mestizos RR 1.5 (95% CI 0.9 – 2.5) p = 0.09, and ALA RR 0.4 (95% CI 0.1 – 1.1) p = 0.06.

Relative risk for clinical complications in APS positive or APS negative patients was: pulmonary thromboembolism RR 7.8 (95% CI 2.9 – 20.6) p < 0.05, myocardial infarction RR 3.9 (95% CI 0.5 – 31.7) p = 0.3, combined arterial and venous thrombosis: RR 10.2 (95% CI 7.2 – 14.6) p < 0.05, ischemic cerebral vascular attack: RR 13.1 (95% CI 7.0 – 24.7) p < 0.05, abortion: RR 2.8 (95% CI 1.7 – 4.6) p < 0.05, fetal loss: RR 6.5 (95% CI 3.4 – 12.4) p < 0.05.

Conclusions: Positivity for APLa in this group, ranging between 30% and 55%, is similar to the reported in the literature for SLE patients.

The reported APS frequency in this group (4.1%) seems to be lower than expected, probably by different clinical criteria used in the diagnostic definition of APS, and the change of APS diagnostic criteria along the last years.

No significant differences were observed in APS relative risk among different ethnics groups.

Major clinical manifestations associated to APS in SLE patients were: pulmonary thromboembolism, combined arterial and venous thrombosis, ischemic cerebral vascular attack, abortion and fetal loss, but not myocardial infarct, maybe because the increased cardiovascular risk in all SLE populations.

P160

Antibodies against domain I of beta2 glycoprotein in anti-phospholipid antibody syndrome

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Background: anti-phospholipid antibodies (aPL) target PL-binding proteins, mainly β2glycoprotein-I (β2GPI). Antibodies against β2GPI (aβ2GPI) represent a risk-factor for clinical manifestations of anti-phospholipid syndrome (APS). However, some aβ2GPI-positive subjects never develop APS-related clinical manifestations. This observation may be explained by the heterogeneity of aβ2GPI population, with autoantibody subgroups targeting different β2GPI epitopes. Antibodies anti-domain I (aDI) but not domains IV and V (aDIV/V) of β2GPI have been associated with thrombotic events.

Patients and Methods: 58 patients with a diagnosis of primary APS (PAPS) have been included. 38 subjects (65.5%) presented with venous and/or arterious thrombothic events while 20 (34.5%) had obstetric manifestations only. 15 aPL asymptomatic carriers were also recruited. All samples had been tested for anti-cardiolipin antibodies (aCL) and aβ2GPI with home-made assays and for lupus anticoagulant (LA). Most patients displayed a triple positivity (n=48, 66%); positivity in two aPL tests was detected in 16% of cases (2 subjects were LA/aCL+, 5 LA/aβ2GPI+, aCL/aβ2GPI+); 18% of patients presented a single aPL test (9 were LA+, 3 aβ2GPI+, 1 aCL+). In the thrombotic PAPS group, 35/38 subjects (92.1%) were aβ2GPI-IgG positive; aβ2GPI-IgG positivity rate was 85% in the obstetric PAPS group (17/20 women); 80% of asymptomatic aPL carriers displayed aβ2GPI-IgG. Specificities against whole β2GPI and DI were evaluated with a novel solid-phase chemiluminiscent assay (BioFlash, INOVA Diagnostics) while aDIV/V were detected using an ELISA kit not yet commercially available (INOVA Diagnostics).

Results: The rates of reactivity against different β2GPI epitopes in our cohort are listed in Table 1.

Table 1.

Positive patients n (%)	*Whole β2GPI*	*DI*	*DIV/V*
15/73 (21%)	+	+	+
30/73 (41%)	+	+	-
15/73 (21%)	+	-	-
3/73 (4%)	+	-	+
3/73 (4%)	-	-	+
7/73 (9%)*	-	-	-

*5 patients LA+ only, one aCL/aβ2GPI+, one LA/aCL/aβ2GPI+.

aDI prevalence was 74% among patients with thrombotic PAPS, 60% among women with obstetric manifestations. 40% of asymptomatic carriers were aDI-positive. We tested aDI in both vascular and obstetric PAPS patients differently from previous reports not considering pure obstetric APS.

aβGPI-IgG detected by BioFlash well correlated with aβ2GPI-IgG performed using our home-made ELISA (r=0.907;p< <0.01). We observed a strong correlation between aβ2GPI and aDI (p< <0.01, r=0.836) but not with aDIV/V (p=0.07, r=0.216). In our cohort, a significant correlation between aDI and thrombotic events was detected (p=0.02, OR 4.2, 95%CI 1.2-14.7).

Conclusions: The occurrence of aDI in the majority of APS patients suggests that DI is the immunodominant β2GPI epitope compared to DIV/V. A consistent proportion of samples resulted positive for whole β2GPI molecule being negative for the investigated domains, suggesting the presence of antibodies against additional epitopes in APS patients.

P161

Auditive dysfunction as an expression of atherosclerosis in primary antiphospholipid syndrome patients.

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Introduction: Microvascular oclussion may occur as part of the manifestations of the Antiphospholipid syndrome (APS), beeing sensorineural hearing loss(SHL) one of the associated neurological syndromes.

Objetive: To determine the prevalence of auditive dysfunction in patients with primary APS and its association with carotid intima-media thickness (IMT).

Patients and Methods: From a cohort of 50 patients with primary APS we investigated the presence of auditive dysfunction based on the following symptoms: unilateral or bilateral sudden or progressive hearing loss, tinnitus and recurrent vertigo. All patients presenting for evaluation of the above-described symptoms were evaluated with audiometric assessment and balance function testing (in patients with vestibular symptoms). Auditive dysfunction was defined as hearing loss below normal values (mild hearing loss: audition loss <35dB; moderate hearing loss: audition loss ranging from 35to 60dB;and severe hearing loss >60 to 90dB or presence of labyrinthine affection). Cardiovascular risk factors such as dyslipidemia, diabetes mellitus, arterial hypertension and carotid IMT were assessed. For the statistical analysis we employed descriptive statistics and chi square test.

Results: We detected 15 patients with hearing loss (30%) with a men age of 51.6 years, APS disease evolution 12.7 years, treated with oral anticoagulants (INR between 2-3),3 with arterial hypertension, 2 with diabetes mellitus, 6 con dyslipidemia, 8 had history of ischemic stroke. One patient presented sudden SHL that improved with corticosteroids, another one had left vestibular paresis as a stroke sequelae. Twelve patients were diagnosed with mild to moderate bilateral SHL and 3 with unilateral SHL. Three patients also had conductive hypoacusis by otosclerosis,5 had tinnitus and vertigo and were diagnosed as

labyrinthine affection improving with vestibular rehabilitation therapy. Three patients required hearing aid. Interestingly 12/15 patients (80%) with bilateral hearing loss presented carotid IMT with a mean of 1.2 mm ±0.2 (range from 1 a 2.9mm). In contrast, 14/35 (40%) with carotid IMT did not have hearing loss ($p < 0.002$).
Conclusions: Auditive dysfunction is present in primary APS patients and its associated with carotid IMT. SHL may be an atherosclerosis expression. These new findings in primary APS indicate the necessity of other alternative therapies, besides the strict control of risk factors for atherosclerosis. Auditive assessment must be performed at least once a year in order to identify and delay the presence of sequelas.

P162

Non-valvular cardiac manifestations in antiphospholipid syndrome (APS). Long-time echocardiographic follow-up study.

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Introduction: The non-valvular cardiac manifestations in APS are scanty known.
Patients and methods: We performed a controlled prospective echocardiography study assessing its prevalence and evolution in a cohort of APS patients. A total of 53 patients and 20 controls were included, with mean echocardiography follow-up time of 12 years.
Results: Pericardial effusion presented a prevalence in patients of 3,8%, not different from controls (P=0,12) and without changes along echo follow-up. Left myocardial disease occurred with a prevalence of 3,8%, not different from controls (P= 0,12). Both cases were diastolic dysfunction with altered relaxation without morphological changes in myocardium, not showing progression in echo follow-up. Prevalence of pulmonary hypertension was 13,2%, statistically superior respect to control group (P=0,04). All three patients with mild pulmonary hypertension in baseline echo stayed stable along echo follow-up. Intracardiac thrombi presented a prevalence of 1,8%, not different from controls (P=0,4).
Conclusion: Our results indicate that pulmonary hypertension is the only non-valvular cardiac manifestation that is increased in frequency in patients with APS respect to healthy controls being the rest rare manifestations in APS, in some cases once eliminated confounding risk factors, normally of mild clinical significance and stable along time.

Table 1. Patient characteristics

Characteristic	*Value*
Patients, n (%)	53 (100)
Sex, n (%)	
Male	20 (38)
Female	33 (62)
Mean age at diagnosis (SD), and	37 (15)
Mean follow-up (SD), and	12 (6)
Primary APS, n (%)	34 (64)
APS associated to lupus, n (%)	19 (36)
Type of thrombosis, n (%) a	
Arterial	25 (47)
Venous	35 (66)
Pregnancy morbidity	18 (34)
Thrombotic risk factors, n (%)	
None	15 (28)
Arterial	25 (47)
Venous	13 (25)
Livedo reticularis, n (%)	18 (34)
Migraine, n (%)	15 (28)
Raynaud, n (%)	9 (17)
Assays, n (%) b	
Positive IgG anticardiolipin antibodies	39 (73)
Positive IgM anticardiolipin antibodies	6 (11)
Positive lupus-anticoagulant test	49(92)
Positive anti-nuclear antibodies	36 (68)
Treatment regimens, n (%) c	
Anticoagulant	41 (77)
Anti-aggregant	30 (56)
Corticoids	22 (41)
Chloroquine	12 (22)

a Patients presenting one or more thrombotic-type episodes between diagnosis and during follow-up.
b Results of assays at diagnosis of patients.
c Received by patients from diagnosis and throughout follow-up.

Table 2. Cardiac abnormalities at baseline and follow-up echocardiograms in our cohort of patients with APS.

	BASELINE ECHO APS PATIENTS n= 53	*FOLLOW-UP ECHO APS PATIENTS n=53*	*P value**
Pericardial effusion	2 (3,8%)	2 (3,8%)	NS
Myocardial disease a	1 (1,9%)	2 (3,8%)	NS
Diastolic dysfunction	1 (1,9%)	2 (3,8%)	NS
Systolic dysfunction	0	0	
V Hypertrophy	0	0	
V Dilatation	0	0	
Ejective Fraction b	62,5 %	61%	NS
Pulmonary hypertension	3 (5,7%)	7 (13,2%)	0,04
Mild	3	3	
Moderate	–	2	
Severe	–	2	
Intracardiac thrombi	1 (1,9%)	1 (1,9%)	NS

*Comparison with controls. NS: no significant difference.
aNot attributable to hemodynamically significant valvular disease (moderate to severe), hypertension, diabetes, myocardial infarction or myocarditis.
bMean.

P163

DNA methylation pattern analyses in patients with antiphospholipid syndrome:screening study

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Introduction: Antiphospholipid syndrome (APS) is a immune, thrombotic disorder of unknown etiology, characterized by the association of arterial or venous thrombosis and/or pregnancy morbidity, with the presence of antiphospholipid antibodies (aPL): anticardiolipin antibodies (aCL) and/or lupus anticoagulant (LA) and/or anti-β2-glycoprotein 1 antibodies (anti-β2GP1). In recent years, epigenetic modification has been studied in many autoimmune, immune disorders to elucidate its pathophysiologic correlation, along with genomic, epigenomic profiling. Among them, aberrant DNA methylation (hypo-, or hypermethylation) and its impact on gene expression have been implicated in diverse spectrum of diseases, including immune disease or cancer. The objective of this study is to investigate a global DNA methylation

status of antiphospholipid syndrome patients with CpG microarray, and compared it with healthy controls.

Materials and methods: Human peripheral whole blood samples were obtained from 6 APS (2 primary APS and 4 secondary APS, which were 3 systemic lupus erythematosus and 1 Behçet's diseae) and from 6 age, sex-matched healthy controls. Total genomic DNA extracted using the QIAamp DNA mini and blood kit protocol (Qiagen, Hilden, Germany). To discover aberrantly methylated genes in APS by genome-wide search, we introduce Illumina Infinium Human Methylation 450K BeadChip (Illumina Inc, San Diego, USA) for directly identifying differentially methylated regions of the genomes in each pooled whole blood between APS patients and healthy controls. Immunologic profiles of the patient group including aPL, aCL, LA, anti-2GβP1 were obtained. This study was reviewed by the institutional ethical board and written informed consent was completed.

Results: All patients and the control groups were female and there was no statistical difference in age distribution (age of patients=35.26 ±10.34 year). The fluorescent signal intensities were extracted using GenomeStudio Methylation module (1.8.5) software. One-hundred and thirty two CpG sites were filtered by criteria of delta mean (difference of average β value from patients and controls) > 0.2, and p value < 0.05 after the quantile normalization to reliably compare data from multiple samples by minimize non-biologic differences. Seventy nine CpG sites (KNDC1, ABHD8, CDK2AP1, MX1, IL16, ROCK2, SNTG2, SORCS2, mi518, mi662, NLRC5, PARP9, etc) were hypermethylated and 53 sites (CYP2E1, BTNL2, DTX2, GCC2, SLC9A3, PLOD1, PXDN, PROZ, ATP4B, etc) were hypomethylated. All differentially methylated CpG sites were located in 5'UTR, TSS1500, TSS200, Exon, intergenic body, 3'UTR. Hierachical clustering (figure1) and the functional classification analysis using DAVID was done.

Conclusions: Hundreds of candidate genes were screened by BeadChip microarray of peripheral blood in APS patients. High-throughput, next generation sequencing of the individual patients for validation will be underwent and the correlation with immunologic profile and thrombotic features will be investigated.

Disclosure of interest:This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education, Science and Technology(2011-0007659)

P164

Evidence of premature atherosclerosis in primary antiphospholipid syndrome (APS) without traditional risk factors using non-invasive methods

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Background: Atherosclerosis has been recognized as an immune-mediated inflammatory disease with an early onset in auto-immune diseases. Primary Antiphospholipid Syndrome (PAPS) patients could be at risk to develop early atherosclerotic vascular damage after thrombosis. The aim of this study was to evaluate the vascular wall stiffness as an indirect measurement of early vascular wall lesion in APS using non-invasive Pulse Wave Velocity (PWV) and Echo-Tracking (ET) device.

Patients and Methods: 28 female patients with primary PAPS (Sidney criteria) and 28 controls age-matched were consecutively selected. All PAPS patients were anti-coagulated and subdivided according to the vascular involvement: exclusive arterial (n=12), exclusive venous (n=11), and both events (n=5). Exclusion criteria were: black race, hypertension, dyslipidemia, smoking, diabetes, pregnancy, menopause, and obesity (BMI > 30 m/kg2). Demographic and clinical data were obtained during visits and by extensive chart review. PWV in femoral-carotidal bed (Complior) and echo-tracking in carotidal bed (Wall Track System) was performed in all subjects to analyze vascular wall mechanical and functional properties.

Results: Age (41.5 ± 9.3 vs. 41.2 ± 10.2 years; p=0.92) and BMI (25.3 ± 3.6 vs. 25.8 ± 3.2 kg/m2; p=0.55) were comparable in PAPS and control groups. PAPS patients had similar mean PWV values (9.07 ± 1.08 vs. 9.34 ± 1.48 m/s; p=0.21) and mean intima-media thickness (650 ± 152 vs. 612 ± 109 μm; p=0.29) compared to controls. In contrast, PAPS patients with exclusive Arterial thrombosis demonstrated higher PWV values than PAPS patients with exclusive Venous thrombosis (9.56 ± 0.94 vs. 8.55 ± 0.70 m/s, p=0.01) but comparable intima-media thickness (683 ± 171 vs. 636 ± 140 μm, p=0.52), as well as carotideal diameter (p=0.26), distensibility (p=0.40), compliance coefficients (p=0.92), and elastic modulus (p=0.83). Moreover, PWV had a positive significant correlation with age (r=0.584, p=0.001) and blood vessel diameter (r=0.407, p=0.04), and also with total cholesterol (r=0.507, p=0.01), LDL (r=0.402, p=0.05), and triglycerides (r=0.583, p=0.003).

Conclusion: Our study provides clear evidence of premature atherosclerosis in PAPS patients without traditional risk factors, particularly those with arterial events.

P165

Antiphospholipid and antioangiogenic activity in women with recurrent abortion and autoimmune diseases

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterial/venous thrombosis or recurrent abortion associated to the presence of antiphospholipid antibodies (Ab). APS may be either primary or associated to another autoimmune disease, most frequently systemic lupus erythematosus (SLE). They are directed to phospholipids, such as cardiolipins, or to complexes formed between phospholipids and different protein cofactors, such as β2 glycoprotein 1 (β2GP1), prothrombin, C and S proteins and annexin V. It is assumed that these autoAb constitute a family involved in thrombotic events that would participate in antiphospholipidic activity (APA). The probability of abortion in patients bearing these Ab, without treatment, is of 91% and those pregnancies that do not have an abortion outcome, have a high risk of preeclampsia, low weight of the newly born, prematurity and fetal distress. On the other hand, there are proangiogenic factors involved in the normal development of placental vasculature, such as the vascular endothelial growth factor (VEGF) and the placental growth factor (PlGF). These factors exert their actions through interaction with a tyrosine kinase-like receptor of the placenta. Overexpression of VEGF receptor in its soluble form (sVEGF-R1) has been associated to a higher antiangiogenic activity, thus generating vasoconstriction and endothelial disfunction. This fact prompted a postulated pathogenic role of sVEGF-R1 in the development of preeclampsia. Our aim was to analyze the association between the plasmatic levels of APA activity [a-cardiolipins (ACA), lupus anticoagulant (LA), a-β2GP1 and a-annexin V] and those of sVEGF-R1 with recurrent abortion in women with autoimmune diseases. We studied 24 women with SLE and or APS, who were divided into two groups: women with recurrent abortion [A; n= 12; age (mean ±

SD)= 37 ± 9] and women with no history of abortion [NA; n= 12; age (mean ± SD)= 32 ± 9]. ACA (IgG and IgM), total a-β2GP1, a-annexin V (IgG and IgM) and sVEGF-R1 levels were assessed in both groups by EIA methods. LA was evidenced by recommended screening and confirmatory tests (ISTH 2009). APA was positive in 92% of group A (ACA: 67%; LA: 50%; a-β2GP1: 50% and a-annexin V: 8%) and high levels of sVEGF-R1 were only found in 8% of the same group. APA was positive in 58% of group NA (ACA: 58%; LA: 8%; a-β2GP1: 8% and a-annexin V: 8%) and high levels of were found in 17% of the same group. No significant association was obtained between recurrent abortion and the presence of ACA, a-annexin V and sVEGF-R1 ($p > 0.05$). Contrarily, LA and a-β2GP1 were significantly associated to the belonging group ($p < 0.05$). Through estimation of the odds ratio with a confidence interval of 95%, we found that the chance to belong to group A for patients with positive LA or a-β2GP1 is 11.5 times higher than when they are negative. We conclude that LA and a-β2GP1 Ab would be better markers of recurrent abortion in women with autoimmune diseases.

P166

Livedo Reticularis: Association with Hypertension and Stroke in Patients with Primary Antiphospholipid Syndrome

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Introduction: Livedo reticularis is the most common cutaneous manifestation in patients with Antiphospholipid Syndrome (APS) and its presence is associated with recurrent arterial events and central nervous system manifestations. However, previous studies did not evaluate associated cardiovascular risk factors. The aim of this study was to evaluate the association of livedo reticularis, cardiovascular risk factors and thrombotic events in patients with primary APS (PAPS).
Patients and Methods: Twenty six PAPS patients with livedo and 39 PAPS patients without livedo, matched for age, gender and disease duration, were enrolled. All patents fulfilled APS Sydney criteria and were followed in a single APS outpatient clinic. Data were obtained from an ongoing electronic database protocol, established in January 2000, which was carried out for all patients at 1- to 6-month intervals and consisted of an extensive clinical and laboratory evaluation. The variables analyzed were: thrombotic events and obstetric morbidity, APS related autoantibodies anticardiolipin (aCL), anti-b2 glycoprotein 1 (aB2GP1) and lupus anticoagulant (LA) and the traditional cardiovascular risk factors including hypertension, diabetes, dyslipidemia, obesity and smoking.
Results: PAPS patients with and without livedo had similar mean age (48±11 vs. 47±11 years, p=0.868), age at diagnosis (35±12 vs. 37±13 years, p=0.468), disease duration (13±6 vs. 10 years, p=0.137) and frequency of female gender (88 vs. 87%, p=1.0). Both groups had similar frequency of positive aCL (58 vs. 54%, p=0.804), aB2GP1 (57 vs. 38%, p=0.612) and LA (76 vs. 69%, p=0.579). Patients with and without livedo also had comparable frequencies of venous thrombosis (46 vs. 61%, p=0.309), non-stroke arterial thrombosis (23 vs. 18%, p=0.754), obstetric morbidity (42 vs. 56%, p=0.317) and thrombocytopenia (15 vs. 26%, p=0.373). PAPS patients with livedo had higher frequency of stroke (65 vs. 26%, p=0.002) than patients without livedo. Regarding cardiovascular risk factors, patients with livedo had higher frequency of hypertension (57 vs. 26%, p=0.018), but not diabetes (3 vs. 10%, p=0.640), dyslipidemia (23 vs. 26%, p=1.0), obesity (11 vs. 12%, p=1.0) or smoking (19 vs. 20%, p=1.0). In addition, a subanalysis of patients with and without stroke confirmed statistic significant association with livedo and hypertension ($p < 0.05$).
Conclusion: The present study demonstrated that the association of livedo reticularis with stroke in PAPS patients is independent of age and gender. In addition, our data reinforces the relevance of identification and treatment of hypertension in PAPS patients, especially in those with livedo.

19/04/13

08:00 - 19:30

Poster Sessions & Tours 1

"Area 10 Lupus Treatment"

Atlantico A+B+C

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Clinical Experience In Latin America With Blisibimod Amongst Subjects with Active, Moderate-to-Severe Systemic Lupus Erythematosus: Data From The Phase 2b PEARL-SC Study

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Introduction: The PEARL–SC study evaluated the safety and efficacy of 24weeks treatment with subcutaneous blisibimod, a B–cell activating factor (BAFF) inhibitor, in subjects with SLE from Latin America, North America and Asia/Pacific countries.
Patients and Methods: 547 subjects with anti–dsDNA or anti–nuclear antibodies and SELENA–SLEDAI score ≥6 were randomized to receive placebo or blisibimod (200 mg every 4 weeks, 100mg weekly [QW], or 200mg QW). Randomization was stratified by baseline SELENA–SLEDAI score (6-9 vs ≥10) and race. The primary endpoint was a comparison at Week 24 of the percentage of subjects in the pooled blisibimod and placebo groups who achieved an SLE Responder Index–5 (SRI–5: ≥5 point improvement in SELENA–SLEDAI, no new BILAG A or ≥2B organ domain scores, and no worsening in Physician's Global Assessment).
Results: A total of 388/547 (70.9%) subjects were enrolled from Argentina (n=51), Brazil (n=102), Chile (n=16), Colombia (n=102), Mexico (n=62) and Peru (n=55). The commonest SELENA–SLEDAI organ descriptors amongst Latin American subjects were: arthritis 18.7%; rash 16.3%; increased dsDNA binding 17.3%; low complement 16.5%; alopecia 15.5%; mucosal ulceration 5.9% and proteinuria 2.9%.

The primary endpoint of the study was not met due to the lack of efficacy in the two lowest dose groups. However, higher SRI response was observed with blisibimod 200mg QW, particularly when compared with regimen-match placebo, and in SRI analyses requiring clinically–meaningful SELENA–SLEDAI improvements of ≥7 and ≥8 (Furie 2012).

Amongst Latin American subjects, no SRI–5 improvement was observed with blisibimod treatment. However, when compared with pooled placebo, SRI–8 improvements were observed at 24 weeks in both the pooled blisibimod group (ΔSRI–8=4.9%) and the 200mg QW blisibimod group (ΔSRI–8=12.3%, p=0.026).

Blisibimod treatment was even more effective when compared to pooled placebo in those Latin American subjects with SELENA–SLEDAI≥10 and receiving corticosteroids (N=211): pooled blisibimod ΔSRI–8=8.8%; 200mg QW blisibimod ΔSRI–8=22.1%, p=0.016. Statistically–significant treatment differences were also observed with 200mg QW blisibimod at Week 16 (ΔSRI–8=18.9%, p=0.022) and Week 20 (ΔSRI–8=20.6%, p=0.016). When compared with regimen-matched placebo, the treatment effects of blisibimod 200mg QW were still more pronounced: Week 16 ΔSRI–8=23.3%; Week 20 ΔSRI–8=34.1% and Week 24 ΔSRI–8=39.3%.

In the mITT population, blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Amongst the commonly-reported adverse events in the study, imbalance was observed only with injection site reactions (200mg QW blisibimod=15%, matched placebo=7%), but never serious or severe.

Conclusions: These data indicate that blisibimod 200mg QW may be an effective adjunctive treatment for SLE in Latin American subjects with high disease activity treated with standard–of–care and corticosteroids.

References

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Sustained Disease Improvement and Safety Profile Over 1745 Patient-Year Experience (7 years) With Belimumab in Patients With Systemic Lupus Erythematosus

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Introduction: The safety/efficacy of belimumab were assessed over 7y in patients with active SLE.

Patients and Methods: 449 SLE patients with SELENA-SLEDAI scores ≥4 were enrolled in a phase 2 study of belimumab 1/4/10mg/kg vs placebo, plus standard therapy, for 52wk (NCT00071487). All placebo patients switched to belimumab 10mg/kg at wk56; prior belimumab patients continued on the same dose or switched to 10mg/kg. At wk80, all patients electing to enter a continuation study received belimumab 10mg/kg (NCT00583362). Adverse events (AEs) were assessed in all patients at each visit. Analyses of disease activity: SLE Responder Index (SRI; posthoc), BILAG A/B flares, SELENA-SLEDAI Flare Index (SFI), and biomarkers. Efficacy assessments were limited to patients who were autoantibody+ at baseline.

Results: Of the original 449 patients, 296 (66%) entered the continuation trial; at the end of the 7y interval, 190 patients remained. Total belimumab exposure was over 1745 patient-y. Belimumab was generally well tolerated; rates of AEs/100 patient-y remained stable/decreased over 7y (table). Seven patients treated with belimumab died over 7y: no single cause predominated; etiologies included aspiration pneumonia with subsequent sepsis and respiratory failure, infection, cardiovascular disease, suicide, osteomyelitis with subsequent respiratory failure, and B-cell lymphoma. SRI rate with belimumab: 46% at wk52 (vs 29% with placebo; $p < 0.05$), increasing to 55%-65.2% through 7y. Frequency of 1 new BILAG A/2 new B flares with belimumab: 38% at 1y (vs 44% with placebo), decreasing to 7.7% at 7y. Frequency of all SFI flares with belimumab: 84% (severe 17%) at 1y (vs 85% [19%] with placebo), decreasing to 40.4% (2.1%) at 7y. Over 7y, an increasing percentage of previously positive patients were no longer anti-dsDNA+ (45.8%) and had normalized complement (66.0% with C3, 71.4% with C4). Of the 118 remaining patients on corticosteroids at baseline, corticosteroid use decreased over 7y (reduction: median 55%, absolute 3.7mg/d).

Conclusions: Belimumab plus standard SLE therapy was generally well tolerated in SLE patients over 7y treatment. Autoantibody-positive patients treated with belimumab showed sustained improvement in SRI and disease activity, and declines in BILAG and SFI flares, accompanied by reductions in autoantibody levels and corticosteroid use.

AE Incidence (/100 pt-y) With Belimumab	*Interval 1 (0-1y)*	*Interval 2 (1-2y)*	*Interval 3 (2-3y)*	*Interval 4 (3-4y)*	*Interval 5 (4-5y)*	*Interval 6 (5-6y)*	*Interval 7 (6-7y)*
Patients, n (pt-y)	336 (320.1)	339 (299.1)	274 (258.1)	248 (234.2)	223 (215.8)	208 (197.6)	190 (167.0)
Overall AEs	326 (101.8)	322 (107.7)	260 (100.8)	237 (101.2)	211 (97.8)	191 (96.7)	172 (103.0)
Serious AEs	55 (17.2)	52 (17.4)	49 (19.0)	31 (13.2)	41 (19.0)	32 (16.2)	30 (18.0)
Overall infections	254 (79.4)	237 (79.2)	192 (74.4)	181 (77.3)	145 (67.2)	126 (63.8)	128 (76.6)
Serious infections	17 (5.3)	14 (4.7)	8 (3.1)	8 (3.4)	6 (2.8)	8 (4.0)	5 (3.0)
Malignancies[a]	0	3 (1.0)	2 (0.8)	1 (0.4)	3 (1.4)	2 (1.0)	1 (0.6)
Mortality	3 (0.8)	0	1 (0.4)	1 (0.4)	0	0	2 (1.2)

aExcluding nonmelanoma skin cancer; including unspecified lung malignancy.

Disclosures: JTM: consulting, HGS/GSK; RAF/DJW: research support/consulting/speakers bureau, HGS/GSK; WS: research support, HGS; WWC/MAP: research support/consulting, HGS/GSK; AW: research support, HGS, consulting/speakers bureau, HGS/GSK; JDM: stock, HGS; EMG: research support, HGS/GSK; WWF: employment, HGS.

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Medium or high doses of prednisone in the induction treatment of lupus nephritis?

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Introduction: Treatment of lupus nephritis (LN) consists of induction and maintenance phases. Induction therapy usually includes high-dose glucocorticoids and immunosuppressive agents. The basis for dosing prednisone is essentially empirical, and glucocorticoids have many serious adverse effects. Due to these facts, our group has been working in lowering doses of prednisone.

Patients and methods: A comparison between two groups was performed: 'the historic cohort' (HC), and 'the Cruces-protocol cohort' (CPC). Patients were paired 2 (HC):1 (CPC). All patients had biopsy-proved lupus nephritis (LN). The HC was treated with a classical scheme, high-dose cyclophosphamide (National Institute of Health scheme) and high-dose prednisone (1 mg/kg/day with variable duration and no defined tapering scheme). The CPC was treated with a protocolized scheme, cyclophosphamide (Eurolupus scheme, up to 3-6 g, depending on the achievement of remission), medium doses of prednisone (20-30 mg/day, quickly tapered to 5 mg/day), methylprednisolone pulses, hydroxychloroquine and angiotensin inhibitors. Partial and complete remission rates and glucocorticoid-related side effects were assed at six and twelve months.
Results: 30 HC and 15 CPC patients were studied. Table 1 shows pretreatment demographic and clinical characteristics. Median initial dose of prednisone: 50 mg vs. 20 mg in the HC and CPC groups, respectively ($p < 0.001$); median cumulative dose of prednisone at six months: 4.2 g (average daily dose = 25 mg) in the HC vs. 1.65 g (average daily dose = 9.3 mg) in the CPC ($p < 0.001$); median cumulative dose of cyclophosphamide at six months: 5 g in the HC vs.3 g in the CPC ($p < 0.001$); 10 (33%) patients in the HC were treated with hydroxychloroquine vs. 15 (100%) patients in the CPC ($p < 0.001$). At six months, 14/30 (47%) patients in the HC were in partial or complete remission vs.12/15 (80%) patients in the CPC (p=0.03). At 12 months 19/30 (63%) patients in the HC were in complete remission vs. 13/15 (87%) in the CPC (p=0.1). Ten cases of osteonecrosis/osteoporotic fractures were seen in the HC vs. no cases in the CPC (p=0.019). Thirteen patients presented metabolic disorders (hyperglycemia, hypercholesterolemia, overweight) in the HC vs. one in the CPC (p=0.012). Corticosteroid-related toxicity was associated with the cumulative dose of prednisone at six months (OR = 2.1; CI 95%: 1.3 – 3.5).
Conclusion: Our results support that a protocolized treatment including medium doses of prednisone combined with methylprednisolone pulses, lower doses of cyclophosphamide and hydroxychloroquine is at least as effective as those including higher doses of prednisone in achieving complete or partial remission of lupus nephritis. Toxicity is undoubtedly less frequent.

Table 1.

	Cruces-protocol cohort (CPC) (n = 15)	*Historic cohort (HC) (n=30)*	*p value*
Sex (female)	11	27	0.15
Age SLE (mean +/- SD)	37 (13.9)	32 (12.9)	0.3
Age LN (mean +/- SD)	39 (13.8)	35 (13.2)	0.9
Race:	12	27	0.44
– White	2	1	
– Black	1	2	
– Others			
Lupus nephritis:	1	2	0.85
– Type II	3	5	
– Type III	9	21	
– Type IV			
– Type V	2	2	
Proteinuria g/day (mean +/- SD)	2.4 (2)	3.7 (3.1)	0.08
CrCl ml/min (mean +/- SD)	76 (26.8)	71.5 (22)	0.65
C3 (mg/dl) levels (mean +/- SD)	52.5 (19.3)	47.3 (22.7)	0.2
C4 (mg/dl) levels (mean +/- SD)	7.7 (4.9)	9.4 (8.1)	0.87

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Anti-malarial drugs reverses IFN-α elevation through TLR-9 recognition of nucleotides which could not be suppressed by glucocorticoid.
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Backgroud/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by chronic stimulation of the innate immune system by endogenous nucleic acids, which results in the activation of interfron-α (IFN-α) pathway. Glucocorticoids have be widely used to treat autoimmune diseases due to their strong anti-inflammatory effects. A recent research has found that toll-like receptor (TLR) recognition of self nucleic acids hampers glucocorticoid activity in lupus. Although the mechanisms are still unkown, most of experts agree that anti-malarial drugs block TLR. We are going to explore whether glucocorticoid and/or anti-malarial drugs influence the activation of IFN-α in human peripheral blood mononuclear cells (PBMC) and whether anti-malarial drugs could improve glucocorticoid effects in lupus.
Methods: Freshly isolated PBMCs of healthy donors were stimulated with the TLR-9 agonist CpG oligodeoxynucleotides (CpG-A ODN)-2216, then incubated with different kinds of anti-malarial drugs (hydroxychloroquine (HCQ), quinacrine(Qn) or both) and/or different doses of glucocorticoid (hydrocortisone). The changes in the expression of IFN-α were detected by real time PCR.
Results: A. HCQ or Qn alone or combined together significantly reversed the elevation of IFN-α caused by ODN 2216 (Qn (p=0.047), HCQ (p=0.047), Qn and HCQ (p=0.046)), and in low and middle doses of glucocorticoid (low dose: Qn (p=0.034), HCQ (p=0.032), Qn and HCQ (p=0.036), middle dose: Qn (p=0.028), HCQ (p=0.024), Qn and HCQ (p=0.028)). B. The low dose (10^{-5} M) and the middle dose (10^{-4} M) of glucocorticoid had no effects on the IFN-α expression in PBMCs with or without ODN 2216 stimulated ($p > 0.05$, respectivrly), while the high dose (10^{-3} M) of glucocorticoid could significantly promote the expression of IFN-α ($p=0.032 < 0.05$), showing a negative influence in the depression of IFN-α, even when added with anti-malarial drugs (Qn ($p < 0.001$), HCQ ($p < 0.05$), Qn and HCQ ($p < 0.005$)).
Conclusions: 1. Anti-malarial drugs hamper the critical pathogenesis of lupus that TLR-9 recognition of nucleotides (ODN 2216) elevates the IFN-α expression in PBMCs. 2. The Combination with anti-malarial drugs seems to be a good choice to help glucocorticoid to achieve a better disease control by inhibiting IFN-α, which cannot be decreased by glucocorticoids alone.

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Low baseline complement levels, autoantibody persistence and delayed thymic reactivation are risk factors for development of relapses after hematopoietic stem cell transplantation (HSCT) for refractory SLE
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Objective: Our previous research has provided the evidence that an autoreactive immune system can be "reset" into a healthy, tolerant state by immunoablative treatment to eradicate pathogenic effector cells, followed by transplantation of hematopoietic progenitor cells

(HSCT). Nevertheless, disease flares may occur in a subset of these patients post-transplantation. Here, we longitudinally analyzed the immune reconstitution of these patients to identify predictive cellular or serologic markers for favorable long-term responses.
Patients and Methods: Since 1998, 10 patients with refractory SLE received a CD34+-selected autologous stem cell transplantation after immunoablation with antithymocyte-globulin (ATG) and cyclophosphamide as part of a monocentric phase I/II clinical trial. Autoantibody titers were evaluated with ELISA, peripheral T- and B lymphocyte subsets immunophenotyped using multicolor flow cytometry.
Results: Clinical remission (SLEDAI $\leq$ 3) could be achieved in all patients, despite immunosuppressive drug withdrawal, associated with disappearance of anti-dsDNA antibodies and marked reduction of protective antibodies in serum. Unfortunately, two patients died due to transplant-related infections. From the remaining eight patients, five patients are in long-term clinical remission for up to 14 years after HSCT, while three patients suffered a relapse of SLE at 18, 36 and 80 months post-transplantation, respectively. Patients with early relapses ($\leq$ 36 months) had lower baseline complement levels (C3 $\leq$ 67 mg/dl), showed persistence of antinuclear antibodies, less significant reduction in protective antibody levels and had slower repopulation of $CD31^+$ $CD45RA^+$ thymic-derived $CD4^+$ T cells after HSCT ($< 100/\mu l$ at 18 months) when compared to long-term responders. In addition, flow cytometric analyses revealed an expansion of peripheral blood plasmablasts and increased coexpression of Siglec-1 on monocytes (as surrogate marker for type-I interferon signature), preceding the clinical flares by $\sim$ 6 months.
Conclusion: Low baseline complement levels, persistence of antinuclear antibodies and delayed thymic reactivity post-transplantation could be identified as risk factors for development of lupus flares after HSCT. Since ATG-mediated cell lysis is complement-dependent, we conclude that low serum complement is directly associated with incomplete depletion of immunologic memory cells in these patients and may provide a rationale for complement substitution before immunoablation with ATG. Moreover, lupus flares may be predicted individually by flow cytometry with plasmablast expansion and recurrence of type-I interferon signature.

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Immunologic Response to Short-Term and Long-Term Treatment with Epratuzumab in Patients with Systemic Lupus Erythematosus

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Background: Epratuzumab, a monoclonal antibody targeting CD22, is in phase III clinical trials for SLE. CD22 is a B-cell surface molecule that regulates B-cell adhesion and B-cell receptor (BCR) signaling. We report immunologic response in short-term (EMBLEM, ALLEVIATE) and long-term (SL0006) SLE clinical trials.
Patients and Methods: ALLEVIATE 1 and 2 were randomized, double-blind trials, terminated because of interrupted drug supply. Patients received placebo (n=37), 360 (n=42) or 720mg/m2 (n=11) epratuzumab in 12-week cycles for up to 48 weeks. SL0006 was an open-label extension of ALLEVIATE in which 29 patients received 360mg/m2 epratuzumab. EMBLEM was a 12-week phase IIb study in which 227 patients (37–39 per arm) received either: placebo, epratuzumab 200mg cumulative dose (cd) (100mg every other week [EOW]), 800mg cd (400mg EOW), 2400mg cd (600mg weekly), 2400mg cd (1200mg EOW), or 3600mg cd (1800mg EOW). Absolute peripheral blood CD19+ B-cell and CD3+ T-cell counts and serum levels of IgG, IgA and IgM were measured.
Results: Table 1 shows absolute B-cell counts and changes from baseline during treatment with epratuzumab. At week 12, median (range) percentage changes in B-cell counts from ALLEVIATE baseline (BL) were –35.5% (–92 to 145) and 0.0% (–86 to 270) in patients receiving 360 mg/m2 epratuzumab (n=23) and placebo (n=19), respectively. In EMBLEM, week 12 B-cell count changes were –19.3% (–99 to 85) and –14.6% (–58 to 1767) in patients receiving 600mg epratuzumab (n=28) and placebo (n=29), respectively. In SL0006, absolute median B-cell counts were 40–55 cells/μL at most timepoints. The median percentage change in B-cell numbers from BL was –37.7% at SL0006 visit 1, increasing to –50% two years into the study, and remaining between –55% and –65% at most timepoints thereafter. T-cell counts remained stable over 12 weeks in ALLEVIATE and EMBLEM, and up to 4 years in SL0006. Median IgA and IgG levels decreased minimally from BL and were stable throughout SL0006, with median percentage changes ranging from –8.8% to 18.5%, and –13.2% to 8.0%, respectively. Median IgM levels dropped to –29% of BL by year 1, but remained between –30% and –40% at most timepoints thereafter.
Conclusions: B-cell counts were moderately reduced after 12 weeks of epratuzumab treatment in ALLEVIATE and EMBLEM, and remained within the normal range in most patients. With longer-term treatment, B-cell levels stabilized 55-65% lower than baseline levels. Immunoglobulin levels remained within normal ranges.

Role of the study sponsor

The ALLEVIATE and SL0006 studies were funded by Immunomedics, Inc. The EMBLEM study was funded by UCB Pharma.

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Efficacy of Belimumab in a Subpopulation of Systemic Lupus Erythematosus Patients With High Disease Activity in Key Organ Systems: Pooled BLISS Data

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Statement of Purpose: To assess the efficacy of belimumab in patients with SLE involving key organ systems and high disease activity - defined as evidence of renal, neurological, hematological or cardiovascular, or respiratory involvement, anti-dsDNA+ and/or low complement at baseline.
Methods: Data from 2 randomized, double-blind, multicenter studies (HGS1006-C1056: BLISS-52 and HGS1006-C1057: BLISS-76) were combined for analysis (GSK study BEL114246). The primary endpoint was the SLE Responder Index at Week 52. Other endpoints included response defined as $\geq$4 points reduction in SS score at week 52, change in SF-36 physical component score (PCS) at week 24, time to first flare

Median (range) absolute B-cell counts (cells/μL) and median percent (range) change from baseline in B-cell counts during short and long-term SLE treatment with epratuzumab.

	ALLEVIATE 360 mg/m^2	ALLEVIATE 720 mg/m^2	ALLEVIATE All active	ALLEVIATE Placebo	EMBLEM 600 mg weekly	EMBLEM 100 mg EOW	EMBLEM 400 mg EOW	EMBLEM 1200 mg EOW	EMBLEM 1800 mg EOW	EMBLEM Placebo
Baseline	102.5 (10–1814)	167.5 (61–1529)	122.5 (10–1814)	111.0 (10–946)	125.0 (6–1002)	140.0 (10–818)	149.5 (19–931)	94.0 (9–727)	116.0 (11–1122)	142.5 (3–508)
n	26	8	34	23	34	39	34	37	37	36
Week 12	53.0 (10–659)	62.0 (27–362)	60.5 (10–659)	163.0 (10–1291)	109.0 (1–615)	100.5 (14–558)	91.0 (17–533)	94.5 (13–415)	80.0 (18–465)	111.0 (16–474)
% change (range)*	–35.5 (–92 to 45)	–67.9 (–85 to 103)	–40.7 (–92 to 145)	0 (–86 to 270)	–18.0 (–95 to 150)	–10.3 (–64 to 155)	–21.3 (–65 to 49)	–16.7 (–65 to 116)	–19.7 (–61 to 138)	–6.0 (–67 to 1355)
n	23	7	30	19	29	32	28	32	35	31
	SL0006 360 mg/m^2									
Screening V1	41.0 (20–1303)									
% (range)*	–37.7 (–89 to 357)									
n	25									
Week 48	56.5 (20–586)									
% (range)*	–45.7 (–88 to 313)									
n	28									
Week 96	63.5 (20–394)									
% (range)*	–51.1 (–81 to 319)									
n	22									
Week 144	51.0 (20–460)									
% (range)*	–48.0 (–93 to 325)									
n	21									
Week 192	–66.6 (–84 to 462)									
% (range)*	48.5 (20–449)									
n	18									

Median (range) percent change in B-cell counts from baseline

after 24 weeks and number of flares. A logistic regression model was applied.

Results: 1016 SLE patients (60%) met high disease activity criteria on entry to the BLISS trials. Belimumab 1mg/kg and 10mg/kg plus standard of care demonstrated higher SRI response rates compared with placebo at Week 52 in patients with key organ involvement and high disease activity (Table 1). Significantly more subjects had a ≥4 point reduction in SELENA SLEDAI score over baseline compared with placebo at Week 52 (47.1% and 50.7% for belimumab 1 and 10mg/kg respectively vs. 35.8% for placebo). Improvements in SF-36 PCS score were achieved at Week 24 for each belimumab dose, although they were not statistically different compared with placebo (4.37 and 4.27 point improvements for belimumab 1mg/kg and 10mg/kg respectively vs. 3.67 for placebo). Belimumab-treated subjects were 26%-34% less likely to have an SLE flare after 24 weeks (modified SLE flare index) compared with placebo (HR 0.66, p-value <0.001 for belimumab 1mg/kg and HR 0.74, p <0.01 for 10mg/kg respectively vs. placebo).

Table 1. Efficacy in Patients with SS≥6, Renal, Neurologic, Hematologic or CV/Resp Involvement at Baseline and anti-dsDNA+ and/or Low Complement

Response parameter	*Belimumab 1mg/kg*	*Belimumab 10mg/kg*	*Placebo*
	N = 342 (MITT = 559)	*N = 347 (MITT) = 563)*	*N = 327 (MITT = 562)*
SRI response: wk 52, %	45.9	49.6	33.6
p value	<0.001	<0.001	
Flares per subject year (LS mean)	3.98	3.96	4.81
p value	<0.001	<0.001	

Conclusion: Patients with SLE and high disease activity in key organ systems reported substantial evidence of efficacy and decreased flare rate with belimumab 1 mg/kg and 10 mg/kg.

Disclosures: all authors are employees of and own stock in GlaxoSmithKline.

Role of the Study Sponsors: Human Genome Sciences, Rockville, Maryland, USA, was involved in study conception, design, implementation, and supervision; data analysis and interpretation; and statistical analyses. GSK was involved in data analysis and interpretation; statistical analyses; and abstract drafting and revision.

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Post-Hoc British Isles Lupus Assessment Group Index Musculoskeletal Organ Domain Analysis of Systemic Lupus Erythematosus Patients in Phase 3 Belimumab Trials

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Background: The British Isles Lupus Assessment Group (BILAG) index is made up of 8 organ system domains. The focus of this analysis is the musculoskeletal system, one of the most commonly involved organ systems in SLE, as reported in 53%–95% of patients. The purpose of this analysis was to determine the belimumab treatment effect on individual BILAG musculoskeletal items in the phase 3 BLISS trials.

Patients and Methods: Data from BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) were pooled by treatment group (placebo, belimumab 10 mg/kg) to evaluate the effect of belimumab in combination with standard therapy vs standard therapy alone (placebo). Overall, musculoskeletal organ system results showed more improvement in patients treated with belimumab plus standard therapy vs standard therapy alone. To identify those items contributing to this effect, each of the 9 items within the musculoskeletal organ system examination and symptom recording tool were analyzed. Post-hoc analysis only included patients with an item scored as present at baseline, and each item required ≥20 patient observations/cohort to make any comparisons. The analysis evaluated each item scored "not present" at wk 52 in patients with the same, worsening, or new/recurrent disease at baseline for the given item (dropout = failure), revealing the number of patients with musculoskeletal involvement at baseline who had resolution of these manifestations by wk 52.

Results: Improvement rates in the overall musculoskeletal domain were 50.0% and 60.2% with placebo and belimumab 10 mg/kg, respectively. Statistically significant improvement in both arthralgia and arthritis was seen with belimumab 10 mg/kg. The table shows results from the 4 items that met the threshold criteria. Improvement rates for the arthritis organ domain item in the SELENA- SLEDAI disease activity scale were also significantly increased in the belimumab 1 mg/kg (58.3%; n=362) and the belimumab 10 mg/kg (56.6%; n=364) groups compared with placebo (49.3%; n=371).

Conclusions: These data indicate that belimumab 10 mg/kg is effective on BILAG musculoskeletal items and are consistent with a favorable response in the overall musculoskeletal organ system.

BILAG Musculoskeletal Improvement[a]	*Placebo*	*Belimumab 10 mg/kg*
Overall domain	171/342 (50.0%)	204/339 (60.2%)
p value		0.012
Arthralgia	131/390 (33.6%)	166/392 (42.3%)
p value		0.012
Arthritis[b]	112/340 (32.9%)	140/332 (42/2%)
p value		0.013
Myalgia	56/124 (45.2%)	61/130 (46.9%)
p value		0.778
Severe polyarhtritis[c]	15/46 (32.6%)	10/30 (33.3%)
p value		0.948

[a]Dropout/medication failure=no improvement; p values are nominal (likelihood ratio test); [b]resolution of arthritis=absence of arthritis and arthralgia; [c]resolution of severe polyarthritis=absence of severe polyarthritis/arthritis/arthralgia at wk 52.

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Role of Sponsors: HGS: study conception/design/implementation/supervision; data analysis/interpretation; statistical analyses; abstract drafting/revision. GSK: data interpretation, abstract drafting/revision.

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Adjuvant Therapies in Lupus Nephritis and its Impact in attempting Remission Induction at Twelve-Months in a Cohort of Patients from Two Reference University Hospitals

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Background: The 2012 American College of Rheumatology (ACR) guidelines for screening, diagnosis and treatment of lupus nephritis (LN) suggest that all patients should receive antimalarials, since their use is associated with fewer relapses and less cumulative damage. Furthermore, if there is evidence of proteinuria, data from literature recommends the use of a renin-angiotensin-aldosterone system inhibitors (inhibitors of angiotensin-converting enzyme –ACE- and /or aldosterone receptor antagonists -ARA 2 -), for decreasing intraglomerular pressure, preserves renal function, and slows the progression to end-stage renal disease (ESRD). These guidelines also aim to achieve a target blood pressure below 130/80, a condition that precludes the course of LN progression, and submits the conventional use of statins to obtain an LDL cholesterol below 100 mg%. The purpose of this survey was to determine the percentage of adherence to these guidelines and whether the use of antimalarials, ACE, ARA 2 alone or in combination, statins, and blood pressure goals fulfillment were correlated with 12-month remission in a cohort of patients with LN in two reference centers

Material and Methods: We conducted a nested case-control retrospective study of patients with biopsy-confirmed LN according to 2003 classification of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) between January, 2005 and September, 2012. Case control ratio: 1:1.5. Statistical Analysis: Descriptive statistics, bivariate analysis (chi-square test) and multivariate analysis (logistic regression)

Results: 167 patients were enrolled. 83.9% were female, with a mean age of 24.7 years (16-31). Calculated time between diagnosis of SLE and LN: Two months (0-35). 142 patients (85.02%) used antimalarials for one year follow-up: 118 subjects chloroquine, and 24 individuals hydroxychloroquine. 65.5% (n = 73) of patients used enalapril and 4.5% (n = 5) captopril, whereas 33.3% (n = 56) received losartan. 30.7% of subjects had dual axis blockade. Their indication were: antiproteinuric effect: ACE inhibitors (62%, n = 105) and ARA 2 (40%, n = 68); on the remaining individuals, these agents were used as antihypertensives before the development of NL. Only 29.3% of patients (n = 49) received statins. 85% of subjects achieved the target blood pressure. In bivariate analysis, hydroxychloroquine use (OR = 0.149: 0034-0647; p = 0.011), and the accomplishment of blood pressure goals (OR = 0.248: 0.1-0.615; p=0.003) were associated with remission at 12 months. Similar results were found in the multivariate analysis: OR = 0.181: 0.04-0.81; p=0.026 for hydroxychloroquine and OR = 0.271: 0107-0684 to achievement of blood pressure goals.

Conclusions: In this cohort of patients, both the use of hydroxychloroquine and fulfillment of blood pressure level below 130/80 were associated with achievement of remission of LN at 12 months. We highlight

the high percentage of patients who received antimalarials (85.02%), higher than several existing cohorts, where this frequency does not exceed 70%.

P176

Euro-Lupus IV cyclophosphamide is also efficacious for severe lupus nephritis cases

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Objective: To demonstrate that the Euro-Lupus regime [low-dose (LD) intravenous (IV) cyclophosphamide (CY) followed by azathioprine (AZA)] is not less efficacious than high-dose (HD)IVCY followed by AZA in lupus nephritis (LN) patients with poor prognostic factors at baseline.
Methods: In the Euro-Lupus Nephritis Trial (ELNT), 44 and 46 patients were assigned a LDIVCY or a HDIVCY regime, respectively, followed by AZA in both groups (mean followup:115 months). In the MAINTAIN Nephritis Trial (MNT), 105 patients received LDIVCY for induction and AZA (52) or MMF (53) for maintenance (mean followup:48 months). Poor prognostic factors were defined as a serum creatinine $\geq$1.3mg/dl and/or a 24-h proteinuria $\geq$3.5g at entry in the trial. Poor long-term renal outcome was defined as a serum creatinine of $\geq$1.4mg/dl at last follow-up. In a first analysis ("ELNT analysis"), renal outcome of HDIVCY/AZA vs LDIVCY/AZA ELNT patients with poor prognostic factors at baseline was compared. In a second analysis ("ELNT/MNT analysis"), also performed exclusively in patients with poor presentation, we pooled the data from ELNT LDIVCY/AZA and MNT LDIVCY/AZA patients, as they received the same treatment, and compared their renal outcome to that of ELNT HDIVCY/AZA patients.
Results: Out of the 90 ELNT patients, 38 (42%) belonged to the poor prognostic group at baseline. Out of the 142 patients from the pooled ELNT/MNT analysis (44 ELNT LDIVCY/AZA + 52 MNT LDIVCY/AZA + 46 ELNT HDIVCY/AZA), 55 (39%) presented with poor prognostic factors. Their renal outcome is compared below, according to their treatment allocation.

Only patients with poor prognostic factors at baseline	*ELNT analysis n=38*		*ELNT/MNT analysis n=55*	
	LDIVCY/AZA n=14	*HDIVCY/AZA n=24*	*LDIVCY/AZA n=31*	*HDIVCY/AZA n=24*
Poor long-term renal outcome	3 (25%)	7 (29%)	7 (23%)	7 (29%)
ESRD/Death	2/1	3/2	2/1	3/2

Conclusion: LN patients with renal impairment and/or nephrotic syndrome at baseline treated with LDIVCY/AZA have a similar long-term renal outcome compared to patients given HDIVCY/AZA. The assumption that the Euro-Lupus regime is adequate for benign LN cases only is therefore not supported by data.

P177

Repeat cycles of B cell depletion therapy in SLE: advantages of humanised anti-CD20 drugs

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Background: B cell depletion is widely used in SLE. Relapse is common, but time to relapse is highly variable, with a subset of patients with very long responses accompanied by delayed repopulation of post-germinal centre B lineage cells[1]. In RA, some initial non-responders to rituximab responded to a repeat cycle of treatment given at 6 months. Ocrelizumab is a humanised anti-CD20
Objective: Evaluate the outcome of repeat cycles of rituximab in SLE responders and non-responders
Methods: 51 patients received a first cycle (C1) of 2 x 1000mg rituximab with 2x 100mg methylprednisolone and prednisolone 60mg od days 1-7 and 30mg od days 8-14. Clinical response was assessed by BILAG criteria. B cell depletion and repopulation were monitored by 6-colour flow cytometry. Likely Human Anti-Chimaeric Antibody syndrome (HACA) was defined by $<50\%$ B cell depletion (frequently accompanied by infusion reaction lasting >24h after a second or later infusion of rituximab). A second cycle of rituximab (C2) was administered on clinical relapse. Ocrelizumab was used in patients with evidence of HACA.
Results: After C1 45/51 patients responded clinically and features of likely HACA were not observed in any patient. 28 patients have received C2: 4 at 6 months (C1 non-responders); and 24 on relapse (C1 responders). Of 4 C1 non-responders, 4/4 also had non response to C2 with features of HACA.

Of 24 C1 responders, 5/24 had non-response to C2, also with clinical features of HACA. Patients who lost response in C2 had significantly longer time to retreatment than those who continued to respond: median (IQR) 164(86-259) vs. 50(42-90) weeks.

1 C1 non-responder and 3 patients who lost response in C2 were treated with 2x1000mg ocrelizumab. All had complete depletion of B cells after ocrelizumab. All 3 patients with loss of response in C2 responded clinically. The patients with C1 non-response had normalisation of autoantibody titres but died due to complications of SLE less than 8 weeks after treatment.
Conclusions: Time to relapse after rituximab in SLE is highly variable. Although initial responses were good, some patients with longer-lasting responses did not respond to retreatment. This appears to be due to development of HACA due to very poor B cell depletion and prolonged infusion reaction. Retreatment of first-cycle non-responders did not appear to be effective in SLE, in contrast to RA. This also appears to be due to HACA. Humanised anti-CD20 can overcome deteriorating B cell response in repeat cycles of rituximab.

P178

Targeting of long-lived autoreactive plasma cells and their precursors is required to achieve persistent depletion of the autoreactive plasma cell memory in lupus prone NZB/W mice

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Introduction: In the past decade, plasma cells (PC) have emerged as an important therapeutic target for antibody-mediated diseases. Above all, long-lived plasma cells (LLPC) represent the most interesting candidate as they are refractory to conventional immunosuppressive or cytotoxic drugs, irradiation and B cell depletion therapy. The therapeutic depletion of PC including LLPC using the proteasome inhibitor bortezomib leads to significant benefits in NZB/W lupus prone mice. However, it is assumed that after discontinuation of bortezomib administration pathogenic PC can rapidly regenerate due to constant B cell hyperreactivity. Therefore, in this work we studied new treatment approaches aimed at depleting PC and, at the same time, preventing the generation of new autoreactive PC from B cell activation.

We combined bortezomib with several approaches of B cell targeting with the aim to identify effective ways to block the new generation of pathogenic PC.

Materials and Methods: NZB/W lupus prone mice were injected twice with 0.75 mg/kg body weight (BW) bortezomib. Contextually, one group of mice was treated with a weekly dose of 250 μg of a murine anti-CD20 antibody, one group with a dose of 35 mg/kg BW cyclophosphamide every fourth day, and one group with TACI-Ig at dose of 5 mg/Kg BW every 3.-4. day. The mice were sacrificed at 1, 3, 7 and 15 days after the last bortezomib injection and PC and B cell subsets were characterized by FACS and ELISPOT.

Results: The monotherapy with bortezomib leads only to transient depletion of plasma cells as production of newly formed LLPCs continued throughout life and contributed to the regeneration of the autoreactive pool. Bortezomib combined with anti-CD20 therapy was not efficient in suppressing the continuous supply of newly generated autoreactive LLPC although it could partially target the short-lived PC compartment. Conversely, the continuous application of the anti-proliferative drug cyclophosphamide or TACI-Ig (blocking the BAFF/APRIL mediated B cell differentiation) after PC depletion with bortezomib was able to keep the number of LLPC and autoreactive PC low.

Conclusions: In this study we shed new light on the dynamics between B cells and PC in autoimmunity and we could show that strategies for depleting LLPC have to have two components a) initial depletion of LLPC and b) continuous prevention of regeneration of autoreactive PC trough the targeting of B cell differentiation.

P179

Peripheral neuropathy due to systemic lupus erythematosus itself: incidence, disease risk factors and outcome.

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Background/Objective: Peripheral neuropathy (PN) solely attributable to systemic lupus erythematosus (SLE) itself is difficult to define since most of these patients are exposed to several other conditions that may cause this manifestation. The aim is to determine characteristics and outcome of PN attributed exclusively to SLE and its possible association with clinical/laboratorial features in a large cohort.

Patients and methods: SLE patients (ACR 1997) with PN were identified from our Lupus Outpatient Clinic computerized database of 1038 patients. Only patients with definitive PN proved by electroneuromyography were included. Exclusion criteria were conditions related to PN: diabetes mellitus, alcohol consumption, use of any drug related to neuropathy (thalidomide, statins, etc.), thyroid disease, infection, cancer, vitamin B12 deficiency, renal or hepatic failure, and other autoimmune disease (antiphospholipid syndrome, Sjogren's syndrome, etc.). Medical records were extensively reviewed and included clinical/laboratorial data, treatment, and evolution. Each SLE patient with PN [n=22] was compared with 2 SLE patients without PN (controls) [n=44] that were age- and sex-matched and had similar disease duration.

Results: PN exclusively attributed to SLE was identified in 22 patients (2.1%). The mean age (34.4±11.6 vs. 33.9±9.6 years, p=0.85) and disease duration (9.2±7.7 vs. 9.9±6.8 years,p=0.73) of PN were similar to controls. The interval between SLE onset and PN diagnosis was 4.9±5.7 years and the mean SLEDAI scores was higher in PN patients (5.4±7.6 vs. 1.8±2.9,p=0.001). The most common pattern on electroneuromyography was sensorimotor polyneuropathy of lower limbs (50%), followed by mononeuropathy (26.9%), and polyradiculoneuropathy (15.3%). PN was associated to hematological involvement (72.7% vs. 43.2%,p=0.036), leukopenia (50% vs. 20.5%,p=0.022), lymphopenia (68.2% vs. 29.5%,p=0.004), cutaneous vasculitis (54.5% vs. 22.7%,p=0.014), and anti-Sm (50% vs. 15.9%,p=0.007). Multivariate analysis revealed that PN was related to anti-Sm (OR=5.36; 95%CI 1.37-20.99) and cutaneous vasculitis (OR=4.97; 95%CI 1.23-20.08). All SLE patients received corticosteroids, most of them associated with immunosuppressive drug (59% cyclophosphamide; 31.8% azathioprine). After immunosuppressive therapy, 63.6% improved of neurological symptoms and 31.8% remained stable.

Conclusion: Our study suggested that PN attributed to SLE itself is rare in the absence of other conditions and seems to be strongly associated to anti-Sm antibodies and cutaneous vasculitis. A favorable outcome with immunosuppressive therapy is observed in most of SLE patients with this neurological manifestation.

Further studies are needed to a better understanding and clinical management of peripheral neuropathy in SLE patients.

P180

Mycophenolate Treatment for Severe Proliferative Lupus Nephritis Patients Non Responding to Cyclophosphamide: A Multicentre Review

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Introduction: The treatment strategy in severe proliferative lupus nephritis (LN) patients who are not responding to cyclophosphamide (CYC) induction remains controversial and challenging for clinicians. There is however little information in the available literature on the treatment outcome of mycophenolate in this cohort of difficult patients.

Patients and Methods: This is a retrospective multicentre review on all consecutive adult LN patients who were diagnosed and treated in 3 centres in Malaysia with biopsy proven proliferative LN (Class III, IV, III+V and IV+V) who failed to respond to CYC induction from year 2000 to 2011. Treatment failure with CYC was defined as proteinuria reduction < 50% from baseline or proteinuria > 3 g/d after completion of CYC, or worsening of renal function during CYC treatment. These patients were subsequently treated with oral mycophenolate (mycophenolate mofetil or mycophenolate sodium) for re-induction. Laboratory parameters, clinical response and treatment outcome were assessed at 6, 12 and 24-month of mycophenolate treatment. Clinical response was defined as complete response, partial response and no response.

Results: A total of 32 patients were included; 94% were female with mean age of 28.4 years old. Eighty one percent were Class IV, 13% of mixed class (Class III+V or Class IV+V) and 6% were Class III. Baseline serum creatinine, albumin and 24-hour urine protein before re-induction with mycophenolate were 98.3 umol/L, 25.5 g/L and 3.4 g/d respectively. 10 patients (34%) had renal impairment at baseline. Mean CYC dose at treatment failure was 7.8 g (3.0-20.9). All patients received mycophenolate mofetil (mean dose of 2g/d) except one on mycophenolate sodium (1.44g/d). The treatment response was illustrated in Table 1. Response to mycophenolate re-induction (complete and partial response) was 47% at 6-month, and had increased to 68% at 12-month. More patients with partial response initially attained complete response after 24 months. For those with renal impairment at baseline, 8 had improved renal function, 1 remained stable and 1 progressed to dialysis at 12-month of treatment. None of the responders had worsening renal function at 24-month, 1 non responder progressed to dialysis at 12-month.

Table 1

Treatment Response (%)/Duration	*6 months*	*12 months*	*24months*
Complete Response	19	29	36

(continued)

Table Continued

Treatment Response (%)/Duration	*6 months*	*12 months*	*24months*
Partial Response	28	39	24
No Response	53	32	32

*2 patients excluded at 24-month analysis (1 died, 1 relapse)

Conclusions: Our findings suggest that mycophenolate treatment is beneficial and effective in severe proliferative LN patients who have failed CYC induction. Greater clinical response is observed at 12-month and more patients might attain complete response with prolongation of treatment to 24 months. Mycophenolate should be considered as viable rescue therapy in those LN patients not responding to CYC.

P181

A Real-World Survey of Clinical Practice Among Rheumatologists and Nephrologists in the United States Reveals Differences in Care of Non-nephritis Systemic Lupus Erythematosus and Lupus Nephritis as Compared With American College of Rheumatology Treatment Guidelines

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Introduction: Current pharmacotherapy for systemic lupus erythematosus (SLE) and lupus nephritis (LN) includes combinations of nonsteroidal anti–inflammatory drugs (NSAIDs), antimalarials, glucocorticoids, and cytotoxic immune modulators (IMs). The objective of this analysis was to evaluate the use of therapies for SLE and LN in the United States and to compare these practices with current treatment recommendations for non–nephritis SLE (NNSLE) and LN issued by the American College of Rheumatology (ACR).
Patients and Methods: Data were extracted from the Adelphi Real World Lupus Disease–Specific Programme®, a cross–sectional survey of 50 rheumatologists and 25 nephrologists conducted (December 2009–May 2010) in the United States. Each physician completed a comprehensive form regarding his or her 5 most recent consulting lupus patients. Treatment history, current therapy, and other data were summarized and compared with the ACR treatment guidelines.
Results: Physicians reported data for 375 patients: 168 with NNSLE (164 treated by rheumatologists), and 207 with LN (121 treated by nephrologists). The 1999 ACR guidelines recommend the use of NSAIDs for milder NNSLE, antimalarials for skin and joint manifestations, corticosteroids for moderate to severe disease, and cytotoxic IMs for severe NNSLE. Survey results revealed that the proportion of all NNSLE patients (n=168) receiving NSAIDs, antimalarials, glucocorticoids, or IMs was 29%, 69%, 54%, and 39%, respectively. The predominant induction treatments prescribed by rheumatologists for NNSLE patients (n=164) were antimalarials alone (27%) or the following ± antimalarials: glucocorticoids (27%), IMs (15%), or IMs plus glucocorticoids (16%). In 2012, the ACR published their first set of guidelines for treating LN, recommending antimalarial treatment for all patients, and IM plus glucocorticoid induction therapy for LN classes III, IV, and V (categorized based on renal biopsy). Survey results did not include patients' renal pathology classifications; however, the data revealed that the proportion of all LN patients (n=204) receiving antimalarials, glucocorticoids, NSAIDs, and IMs was 42%, 76%, 17%, and 67%, respectively. However, only 20% of LN patients (n=121) treated by nephrologists began therapy with IMs plus glucocorticoids during the survey; more LN patients began IMs without glucocorticoids (28%), or glucocorticoids without IMs (27%). The proportion of LN patients receiving IMs plus glucocorticoids increased with second and third therapies to 42% and 33%, respectively. The ACR guidelines suggest that rituximab may be used in some LN patients after 6 months of treatment with IM plus glucocorticoids if nephritis worsens or does not improve. Within the overall LN patient group (n=204), 1.5% received biologic therapy at some point.
Conclusions: Real–world surveys of NNSLE and LN treatment by rheumatologists and nephrologists, respectively, revealed some differences between the current ACR treatment guidelines and real–world clinical practice in the United States. Differences from guidelines were minor for NNSLE and more pronounced for LN, possibly due to the publication of the LN guidelines (2012) after the survey period (2009–2010). However, it should be noted that the guidelines summarized current expert recommendations rather than proposing radical changes in therapy, and therefore the potential gaps in both NNSLE and LN treatment warrant further investigation.

P182

A Survey of Physician and Patient Satisfaction With Control of Systemic Lupus Erythematosus and Lupus Nephritis

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Introduction: Patient satisfaction with disease control is an important component of overall health and wellbeing. Current treatment options for systemic lupus erythematosus (SLE) ±lupus nephritis (LN) include antimalarials, glucocorticoids, and immune modulators, but unmet treatment needs still remain in this disease. The **objectives** of this analysis were to evaluate (1) patient and physician satisfaction with treatment–mediated disease control and (2) degree of physician–patient agreement with respect to treatment satisfaction.
Patients and Methods: Data were extracted from the Adelphi Real World Lupus Disease–Specific Programme®, a cross–sectional US survey of 50 rheumatologists, 25 nephrologists, and their consulting patients, conducted December 2009–May 2010. Each physician completed a comprehensive form regarding his or her 5 most recent lupus patients (N=375); data collected included disease severity, treatment history, and current therapy(ies). Physician– and patient–reported satisfaction with the level of disease control was assessed using a 3–point scale.
Results: Physician–reported data were obtained regarding 168 patients with non–nephritis SLE (NNSLE), 164 of whom were treated by rheumatologists, and 206 LN–patients, 120 of whom were treated by nephrologists; patient–reported data were obtained from 212 of these patients (NNSLE, 99; LN, 113). Physicians were satisfied with disease control in 79% (132/168) of NNSLE–patients; 76% (75/99) of NNSLE–patients were satisfied. However, agreement (71%) on the level of satisfaction with disease control among NNSLE–patients and their rheumatologists was "slight" (kappa=.1445). Notably, agreement on the level of satisfaction with disease control declined significantly with NNSLE severity (p=.0062); the greatest agreement was observed for mild NNSLE (59/75; 79%), with less agreement for moderate NNSLE (9/21; 43%) or severe NNSLE (2/3; 67%). As the number of drugs taken by NNSLE–patients increased, agreement on the level of satisfaction decreased (nonsignificant trend, p=.2035): 1 drug, 22/27 (81%); 2 drugs, 22/30 (73%); ≥3 drugs, 26/42 (62%).

Physicians were satisfied with disease control in 74% (152/206) of LN–patients; 65% (74/113) of LN–patients were satisfied. Agreement (71%) on the level of satisfaction among LN–patients (112) and their nephrologists was "fair" (kappa=.3695). Agreement tended to be higher (nonsignificant trend [p=.0740]) in patients with mild (42/56; 75%) or moderate LN (31/41; 76%), compared with severe LN (7/15; 47%). As the number of drugs taken by LN–patients increased, agreement on the level of satisfaction decreased (nonsignificant trend,

p=.0764): 1 drug, 17/20 (85%); 2 drugs, 30/39 (77%); ≥3 drugs, 31/51 (61%).
Conclusions: For NNSLE, 21% of rheumatologists and 24% of patients were not satisfied with the level of disease control achieved. For LN, 26% of nephrologists and 35% of patients were not satisfied with the level of disease control achieved. Patients with more severe disease and those taking a higher number of anti–lupus drugs were less likely to agree with their physicians' level of satisfaction with disease control. Thus, these data highlight the need for more effective treatment options for both NNSLE and LN, as evidenced by the disease–control disparities that remain among these patients and their physicians.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 2 Immunology & Pathogenesis"

Atlantico A+B+C

P183

Circulating T Helper Cells in Patients with Systemic Lupus Erythematosus Share Phenotypic and Functional Properties with Germinal Center T Follicular Helper Cells

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Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoreactive B cells and autoantibody production. Follicular helper T (Tfh) cells, a T cell subset located in the germinal center (GC) of secondary lymphoid organs, have emerged as key contributors in regulation of B cell tolerance and antibody production. Uncontrolled generation of Tfh cells in GCs or peripherally could lead to autoimmunity. Studies have shown that SLE-prone mice have an aberrantly expanded Tfh population. Blockage of the signals from Tfh cells resulted in significant reduction of Tfh cell numbers, decreased production of interleukin 21 (IL-21), delayed GC formation, and ameliorated SLE-like pathological features. To identify the pathophysiological role of Tfh cells in SLE patients, we compared the phenotypic and functional properties of circulating T helper cells in lupus patients to normal GC-Tfh cells, and correlated the percentage of Tfh-like cells with autoantibody production and SLE disease activity.
Patients and Methods: Peripheral blood was collected from 29 patients with a clinical diagnosis of SLE and fulfilled at least 4 of the American College of Rheumatology 1997 revised criteria for disease classification. Peripheral blood from 25 age and gender-matched healthy controls was also obtained. Clinical disease activity was quantified by SLE Disease Activity Index SELENA Modification (SLEDAI), and divided into inactive/mild (SLEDAI 0-5) and moderate/severe lupus patients (SLEDAI > 5). Other serum laboratory measurements such as anti-double standed DNA antibody (dsDNA Ab), anti-nuclear antibody (ANA), and complements C3 and C4 were collected. Tonsils were obtained surgically from non-SLE controls and used to extract GC-Tfh cells. Tfh-like cells were defined by their signature surface markers (CXCR5, ICOS, CD57, and PD-1) via flow cytometry. IL-21 expression levels from Tfh cells were measured by real-time PCR and intracellular staining. Plasmablasts were identified by surface $CD20^{lo}CD38^{hi}$ expression. Tfh cells, non-Tfh cells, and B cells were purified by MACS columns and co-cultured in vitro. IgG in the culture supernatant was detected by enzyme-linked immunosorbent assay.
Results: Circulating T helper cells in SLE patients expressed surface molecules (CXCR5, ICOS, CD57, and PD-1) and IL-21, which were also expressed by GC-Tfh cells in tonsils. The circulating T helper cells were capable of driving B cells to differentiate into IgG-secreting plasma cells in vitro, which were observed in GC-Tfh cells. The frequency of circulating T helper cells was significantly increased in the peripheral blood of lupus patients compared to that of healthy controls ($P < 0.01$). In addition, the elevated frequency of circulating T helper cells correlated positively with the percentage of circulating plasmablasts, levels of serum anti-dsDNA Ab and ANA.
Conclusions: The increased circulating T helper cells in patients with SLE share phenotypic and functional properties with GC-Tfh cells. Tfh cells may serve as perpetrators of the pathogenesis in SLE patients and are a possible target for treatment.

P184

Autoantibodies to Sm, Ro60 and double stranded DNA in prolidase deficiency

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Background: Prolidase deficiency is a rare inborn error of metabolism characterized by the secretion of proline containing dipeptides in the urine and a variety of clinical manifestations. Prolidase is an ubiquitous enzyme found in the cytoplasm. The enzyme specifically cleaves dipeptides containing C-terminal proline or hydroxyproline, in one of the last steps of collagen metabolism. Only about 50 patients have been reported with the deficiency, of which approximately 10% have systemic lupus erythematosus.
Methods: Four patients with prolidase deficiency, three individuals with heterozygous prolidase activity and eight unaffected individuals (all from a large extended Amish pedigree) were studied for lupus-associated autoimmunity. Prolidase genetics and enzyme activity were confirmed. Antinuclear antibody was measured using indirect immunofluorescence. Antibodies against extractable nuclear antigens were determined by double immunodiffusion, immunoprecipitation, and BioRad 2200 multiplex bead assay. Serum C1q levels were measured by ELISA.
Results: Positive ANA was found in two of the four homozygous prolidase deficient patients. One patient had anti-dsDNA antibodies, while another had precipitating anti-Ro60 antibodies. Three of the four patients had anti-Sm and anti-chromatin by the BioRad 2200 multiplex bead assay. One of the three heterozygous subjects had a positive ANA and immunoprecipitation of a 75,000 MW protein. Serum C1q levels were not changed in the prolidase deficient patients. The unaffected controls had normal prolidase activity and were negative for autoantibodies.
Conclusion: Prolidase deficiency leads to a loss of immune tolerance to lupus-associated autoantigens even without clinical systemic lupus erythematosus. Individuals heterozygous for prolidase mutations may be at risk for systemic lupus erythematosus.

P185

Alterations in circulating T follicular helper cells and T regulatory cells in autoimmune rheumatic diseases treated with B cell depletion therapy: rituximab.

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Background: Systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA) are autoimmune diseases which develop due to failure of immune self-tolerance. T follicular helper cells reside in lymphoid tissues within the germinal centres and are a minor subset of $CD4^+$T cells in peripheral blood. They have been linked with autoimmunity in animal models, where they are thought to reduce the threshold for B cell survival. In contrast, T regulatory cells are able to suppress autoimmune responses.
Hypothesis: In SLE and GPA there is a decrease in the T regulatory (TREG) cell population and an increase in the circulating T follicular helper (cTFH) cell population during active disease. B cell depletion therapy may correct disease-associated changes of cTFH and TREG frequencies in autoimmune disease patients who have a positive clinical response.
Methods: An observational longitudinal study. Demographics and baseline characteristics of 10 SLE pre-rituximab patients, 10 SLE controls, 10 GPA pre-rituximab patients, 10 GPA controls and 15 healthy controls recruited to date have been analysed. SLE and GPA patient pre-rituximab and post-rituximab 1 month, 3 month and 6 month clinical assessments and flurochrome-labelled antibody cell staining (FACS) flow cytometry of isolated peripheral blood mononuclear cells have been analysed for $CD4^+CD25^{high}CD127^{low}$ T regulatory cells, $CD3^+CD4^+CXCR5^{high}PD1^{high}$ circulating T follicular helper cells and B lymphocyte subsets. Statistical analysis by GraphPad Prism 4.
Results: Mean age of SLE patients=42 years old (18-64), GPA patients=51 years (38-67) and healthy controls=42 years (25-65). SLE mean total BILAG score pre-rituximab=29, 1 month post-rituximab=19 [p=0.003], 3 months post-rituximab=12 [p=0.003]. GPA pre-rituximab mean BVAS=18, 1 month post-rituximab=7 [p=0.002], 3 months post-rituximab=3.5 [p=0.01].

Mean cTFH%$CD4^+$ lymphocytes in healthy controls=0.21% (SD 0.12), SLE pre-rituximab=0.61% (SD 0.37) [p=0.003] and GPA pre--rituximab=0.54% (SD 0.28) [p=0.0037]. The frequency of cTFH cells is decreased at intervals post-rituximab with SLE 3 months post-rituximab mean=0.32% (SD 0.28) [p=0.02] and GPA 3 months post-rituximab mean=0.25% (SD 0.05) [p=0.04].

Mean TREG%$CD4^+$ lymphocytes in healthy controls=8.42% (SD 2.3), SLE pre-rituximab=7.79% (SD 3.37) [p=0.31] and GPA pre-rituximab =5.42% (SD 2.92) [p=0.023]. The frequency of TREG cells is increased at intervals post-rituximab with SLE 3 months post-rituximab=12.92% (SD 3.9) [p=0.046] and GPA 3 months post-rituximab=10.8% (SD 3.54) [p=0.05].
Conclusions: We have shown that frequencies of cTFH are higher and TREG are lower in autoimmune disease compared to healthy controls, however these frequencies are restored to normality following treatment with rituximab. A high ratio of cTFH:TREG cells may highlight clinical disease activity or relapse of autoimmune disease.

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Serum Osteoprotegerin and RANKL Levels in Patients with Systemic Lupus Erythematosus and Systemic Sclerosis

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Background: Besides the effect on osteoclast differantiation and functions, osteoprotegerin (OPG)/ the receptor activator of nuclear factor-ΚB ligand (RANKL)/ RANK system plays a crucial role in the biology of dendritic cells, promoting their survival and ability to stimulate T cells as well as vascular biology. Our aim was to investigate the role of serum OPG and RANKL levels in the pathogenesis of systemic lupus erythematosus (SLE) and systemic sclerosis (SSc).
Patients and Methods: Fourty patients with SLE (38 female, 2 male, mean age 37.2±10.6 yrs), 28 SSc (27 female, 1 male, mean age 38.2±11.6 yrs) and 20 healthy controls, matched for age and sex, were included in this study. Serum OPG and RANKL levels were measured by an ELISA. In patients with SLE, the presence of specific organ involvement, autoantibody positivity (anti-ds DNA, anti-Ro, anti-La, anti-Sm/RNP, anticardiolipin IgM and G), serum levels of compleman C3,C4 and acute phase reactans (ESR and CRP) were determined. Disease activity score according to SLEDAI was measured. In patients with SSc, the presence of limited and diffuse organ involvement, pulmonary hypertension, active digital ulcer, pulmonary, gastrointestinal system and cardiac involvement, autoantibody positivity (anti-Scl70 and anti-centromere) and laboratory parameters (compleman C3, C4, ESR and CRP) were determined.
Results: Serum OPG levels in both SLE (51.7±36.6 pg/ml, p=0.002) and SSc (84.8±83.9 pg/ml, $p < 0.001$) patients were significantly higher than those of healthy controls (30.6±14.4 pg/ml). Serum RANKL levels were not statistically different between each group (SLE and SSc) and healthy controls (respectively, 0.88±1.97 ng/ml, 0.5±0.71 ng/ml, 0.36±0.71 ng/ml, $p > 0.05$). In patients with SLE, serum OPG levels were significantly correlated with SLEDAI score (r=0.547, $p < 0.001$) and ESR (r=0.383, p=0.016). Serum OPG levels in SLE patients with proteinuria (84.0±77.7 pg/ml, p=0.017) and thrombocytopenia (85.9±62.5 pg/ml, p=0.005) were significantly higher than those without (respectively, 46.0±21.1 pg/ml and 44.5±24.3 pg/ml). In patients with SLE, there was no significant association between serum RANKL levels, clinical and laboratory parameters. In patients with SSc, serum OPG and RANKL levels also did not show any association with diffuse, limited and specific organ involvement.
Conclusion: Our findings suggest that serum OPG levels seem to be a useful marker in disease pathogenesis and clinical outcome in patients with SLE. Although serum OPG levels in patients with SSc were significantly higher than those of healthy controls, further studies including large number of patients and long-term follow-up are necessary to demonstrate clinical significance of serum OPG and RANKL levels in SSc.

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Elevated IgE anti-ds-DNA levels are associated with serological disease activity in patients with SLE: potential for a new treatment target

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Background: Autoreactive IgE leads to activation of basophils and lupus-like nephritis in lyn -/- mice. Prior studies in subjects with Systemic Lupus Erythematosus (SLE) showed increased levels of IgE directed against ds-DNA. In this study we explored the correlation between IgE anti-ds-DNA levels and lupus disease activity.
Material and Methods: We collected blood samples over a period of 8 months from patients followed under SLE natural history protocol. Demographic information, clinical manifestations, current medications and laboratory data were collected; disease activity was measured using SLE Disease Activity Index SELENA modification (SELENA/

SLEDAI) scores. Serum IgE anti-ds-DNA was measured by our internally standardized ELISA. Statistical analysis was done using SAS Enterprise Guide 4.2 software (SAS Institute Inc. Cary, NC).
Results: In this cross-sectional study IgE anti-ds-DNA was measured on sera from 92 patients and 66 healthy controls. The average age of the patients was 41.5 yrs, 81/92 patients were females, 30 African-American, 31 white, 18 Hispanics and 13 were Asian. Mean SLEDAI score was 2 (min-max:0-37). Average serum IgE anti-ds-DNA level was 546.58 A.U. ±1760.32 (mean±SD) in patients and 22.71 A.U. ±93.32 (mean±SD) in healthy controls. Total serum IgE levels and IgE anti-ds-DNA levels did not correlate (Spearman Correlation Coefficient: 0.32) in a subset of 67 patients with available total serum IgE. IgE anti-ds-DNA levels correlated modestly with SLEDAI scores (Spearman correlation coefficient: 0.46). Median IgE anti-ds-DNA levels were higher (56.52 A.U.) in patients with SLEDAI≥4 (N=33) compared to those with SLEDAI < 4 (0 A.U.)(N=59)(p value < .0001). In contrast to our previous findings, there was no difference in IgE anti-ds-DNA levels in patients with or without lupus nephritis (p-value 0.23). Levels of IgE-ds-DNA correlated modestly with IgG-ds-DNA (Spearman correlation coefficient:0.49). Complement proteins C3 and C4 trended inversely with IgE-ds-DNA levels(Spearman correlation coefficient:-0.44 and-0.42 respectively). Patients with hypocomplementemia (26/92) had a higher IgE anti-ds-DNA level (median 247.99 A.U.) compared to those with normal complement levels (median 1.19 A.U.) (p-value < 0.0001).
Conclusion: Our results indicate that serologic activity in SLE includes increased production of IgE anti-ds-DNA antibodies. Levels of these autoreactive antibodies correlate with disease activity index and hypocomplementemia; suggestive of their role in disease pathogenesis. Based on this data we are planning a pilot treatment study using an anti-IgE monoclonal antibody.

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B cell depletion in neuropsychiatric disease in MRL/lpr mice

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Background: Neuropsychiatric disease in systemic lupus erythematosus (NPSLE) is a common and dangerous disease manifestation. However, the mechanisms underlying NPSLE are not fully understood, and the optimal treatment is not known. One postulated mechanism involves lupus autoantibodies with affinity for brain tissue, which due to a compromised blood brain barrier that allows for the passage from the serum into the brain can deposit in the central nervous system to induce cell damage and neuropsychiatric abnormalities. Therefore, B-cell depletion would be expected to be an effective intervention for NPSLE.
Materials and methods: To address whether B-cell depletion is an effective therapeutic intervention in murine neuropsychiatric lupus, we studied B-cell depletion in a murine lupus model with prominent neuropsychiatric manifestations, the MRL-lpr/lpr strain (JHD-MRL/lpr). Comprehensive neurobehavioral tests including forced swim, anhedonia, open field, object recognition, object placement, and social preference were employed to evaluate the neuropsychiatric manifestations in B cell depleted JHD-MRL/lpr as compared to B cell sufficient MRL/lpr mice.
Results: As expected, B cell depleted JHD-MRL/lpr mice had negligible titers of autoantibodies in the serum and cerebrospinal fluid. However, we found that complete B cell depletion did not ameliorate major NPSLE features, including depression-like behavior and cognitive dysfunction. Nevertheless, improved motor activity was observed in JHD-MRL/lpr mice.
Conclusions: Thus, the absence of B cells and autoantibodies is not sufficient to ameliorate the expression of NPSLE in MRL/lpr mice. Whether therapeutic depletion using a pharmacologic approach or a conditional B cell knockout would display similar effects in this mouse model is not known at this time. Our results implicate non-autoantibody mechanisms as driving neuropsychiatric lupus in this model.

P189

Th1/Th2 cytokine profile in childhood-onset systemic lupus erythematosus

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Objective: To determine the serum levels of Th1 (IL-12, IFN-γ,TNF-α) and Th2 (IL-5, IL-6 and IL-10) cytokines in childhood-onset SLE, first-degree relatives and healthy controls. To elucidate their association with disease activity, laboratory and treatment features.
Methods: We included 60 consecutive childhood-onset SLE patients [median age 18 years (range 10-37)], 64 first-degree relatives [median 40 (range 28-52)] and 57 healthy [median age 19 years (range 6-30 years)] controls. Controls were age and sex-matched to SLE patients. SLE patients were assessed for clinical and laboratory SLE manifestations, disease activity (SLEDAI), damage (SDI) and current drug exposures. Mood and anxiety disorders were determined through Becks Depression (BDI) and Anxiety Inventory (BAI). Th1 (IL-12, IFN-γ,TNF-α) and Th2 (IL-5, IL-6 and IL-10) cytokines levels were measured by ELISA and compared by non-parametric tests.
Results: Serum TNF-α (p=0.004), IL-6 (p=0.007) and IL-10 (p=0.03) levels were increased in childhood-onset SLE patients when compared to first-degree relatives and healthy controls. TNF-α levels were significantly increased in patients with active disease (p=0.014) and correlated directly with SLEDAI scores (r=0.39; p=0.002). IL-12 (p=0.042) and TNF-α (p=0.009) levels were significantly increased in patients with nephritis and TNF-α in patients with depression (p=0.001). No association between cytokine levels and SDI scores or medication was observed.
Conclusion: Th1 cytokines may play a role in the pathogenesis of neuropsychiatric and renal manifestations in childhood-onset SLE. The correlation with SLEDAI suggests that TNF-α may be a useful biomarker for disease activity in childhood-onset SLE, however longitudinal studies are necessary to determine if increase of this cytokine may predict flares in childhood-onset SLE.
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P190

Quantitative evaluation of Toll Like Receptors 3,7,8, and 9 expression in kidney sections of lupus nephritis patients.

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A variety of humoral and cellular mechanisms, belonging both to adoptive and innate immunity, are involved in the pathogenesis of lupus nephritis (LN). Thanks to their ability to recognize microbe

specific and endogenous molecules released from injured cells, Toll-like receptors (TLRs) may contribute to renal inflammation. Mouse models and *in vitro* studies provided evidence for the role of TLRs in LN. TLR3, TLR7, TLR8, and TLR9 are expressed in the endosomal compartments of immune competent cells and act as nucleic acid receptors. TLR3, TLR7, TLR8 and TLR9 have been detected in kidney section from small populations of lupus patients.

Aim of this study was to quantify by immunohistochemistry the expression of TLR3, TLR7, TLR8 and TLR9 in kidney sections of SLE patients and healthy subjects and correlate TLRs expression with histological, clinical and serological features.

We evaluated kidney sections from 26 consecutive LN patients (6 class II, 9 class III, 9 class IV, 1 class V and 1 class VI, according to ISN/RPS 2004 criteria) and 4 kidney donors. Kidney sections was analyzed by standard immunohistochemistry using anti-human TLR3/7/8 and 9 MoAbs. The sections were digitalized with Aperio CS scanner and evaluated for the number of nuclei per mm2 positive for TLRs.

The table summarizes TLRs expression in patients and controls. Glomerular and tubulo-intersitial expression of TLR3 and TLR9 was significantly higher in proliferative LN (class III and IV) than in controls (p=0.05, p= 0.03 and p=0.003, p=0.007 respectively). Moreover, glomerular TLR3 expression was higher in class III than in classes II and IV (p=0.04 and p=0.03) and tubular TLR9 in class IV than in classes II and III (p=0.018 and p=0.021). In class IV, tubulointerstial TLR 7 was significantly more expressed than in controls (p=0.003). TLR7 and TLR8 expression was higher in glomeruli than in tubuli in all LN classes. Direct correlation between tubular TLR3 and disease duration and between tubular TLR9 and active sediment while inverse correlation between tubular TLR7 and age at the time of biopsy were observed.

The present study represents the wider observation of TLRs expression in kidney from lupus nephritis patients. For the first time we have quantified the number of cells expressing TLR3,7,8 and 9 detecting a higher expression of TLR3 and TLR9 in both glomerli and tubuli of proliferative LN.

Our data reinforces the hypotesis that activation of TLRs may contribute to the pathogenesis of LN acting as nucleic acid sensors able to activate the inflammatory cascade responsible for organ damage.

Glomerular (G) and tubulointertitial (TI) expression of TLRs (mean+standard deviation) in LN and controls

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Contribution of Megakaryocytes to SLE in Lupus Prone NZB/W mice

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Background: Autoantibodies - secreted by short- and long-lived plasma cells in bone marrow and spleen - contribute to the pathogenesis of the autoimmune disease Systemic Lupus Erythematosus (SLE), for they trigger the immune response, and immune complex deposits in the kidneys can lead to the development of a severe nephritis. In NZB/W mice - a mouse model for SLE - both parental strains New Zealand Black (NZB) and New Zealand White (NZW) contribute different *sle-loci* to the formation of SLE. The NZB strain passes the *sle2c locus* that contains the gene for the Thrombopoietin (TPO)-receptor (*c-mpl*). Considering the relevance of megakaryocytes for the plasma cell niche and the correlation between plasma cell and megakaryocyte numbers, we wanted to elucidate whether c-Mpl and/ or megakaryopoiesis is altered in autoimmune mice. Furthermore, we investigated the role of megakaryocytes in the multi-component-plasma-cell-niche in autoimmunity.
Methods: We examined the amount, the location and the cellular environment of megakaryocytes and plasma cells in spleen and bone marrow of wildtype, NZB, NZW and NZB/W mice via flow-cytometry and confocal microscopy. The occurrence of genetic variations for *c-mpl* and the intensity of megakaryopoiesis upon TPO stimulation were assessed by gene analysis and in vitro studies.
Results: We found in the spleens of NZB mice 10-times higher numbers of long-lived plasma cells and megakaryocytes compared to wildtype, in NZW mice equal numbers and in NZB/W mice numbers between those for NZB and NZW or wildtype. Moreover, in the spleen a fraction of plasma cells clustered around megakaryocytes. We also detected a missense mutation in the *c-mpl* gene of NZB mice leading to an amino acid replacement within the essential TPO-binding site. Upon TPO stimulation of splenocyte and bone marrow cultures NZB cultures responded significantly stronger resulting in the double amount of megakaryocytes compared to NZW cultures.
Conclusions: In summary, our data indicate that augmented megakaryopoiesis enables the accumulation of a greater number of autoreactive plasma cells in lupus prone NZB/W mice. Thus, we assume that enhanced megakaryopoiesis and higher megakaryocyte numbers are contributing to the development and/or pathogenesis of SLE.

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Seafood consumption and persistent organic pollutants as triggers of autoimmunity among Gullah African Americans

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Background: Local seafood is a dietary staple among the African American Gullah population of South Carolina. High levels of persistent organic pollutants (POPs) have been found in local bottlenose dolphins, sentinel species for human health and consumers of many of the same fish as the Gullah. Links have been established between these bioaccumulating, ubiquitous compounds and deleterious health effects in humans. The objective was to determine whether levels of POPs, specifically perfluorinated compounds (PFCs), correlate with fish intake and markers of immune dysfunction in genetically at-risk individuals.
Methods: At the onset of the Persistent Organic Pollutants in AutoImmunity (POPAI) study, one-on-one interviews were conducted with Gullah community members to validate a comprehensive environmental exposure questionnaire. The validated questionnaire, including a seafood intake survey, was then administered prospectively to patients with lupus, first-degree relatives of lupus patients, and unrelated nonlupus controls participating in the SLE in Gullah Health (SLEIGH) study. PFC levels (PFOS, PFOA and PFNA), antinuclear antibody titers and other autoantibodies were measured in the serum of participants drawn at the time of their study visit.
Results: Seafood intake questionnaires received from 103 Gullah participants enrolled in the SLEIGH study found 57% consumed locally caught seafood at least once a month and 40% consumed species known to contain high levels of POPs in the Charleston Harbor area. Preliminary results from 33 Gullah controls show that all have measurable serum levels of PFCs (specifically PFOS, PFOA and PFNA) from baseline and follow-up visits 7.3 $\pm$ 1.4 years apart, with annual servings of seafood directly correlating with serum

PFOS and PFNA (p=0.02 and 0.03).. ANA positive controls (48% at baseline) had higher mean levels compared to ANA negative controls for PFOS (75.1 vs 48.2 ng/ml, p=0.06), PFOA (7.0 vs 5.8, p=NS) and PFNA (3.2 vs 2.1, p=0.04).
Conclusion: These ongoing studies address concerns of the Sea Island Gullah community regarding the potential immune health effects of the bioaccumulating pollutants found in local dietary staples such as fish.

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Intrarenal Foxp3+ regulatory T cells expansion and decreased number of infiltrating CD4+ T cells in murine lupus by IL-2 therapy
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Background and objectives: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by an acquired IL-2 deficiency, which leads to a homeostatic imbalance between regulatory T cells (Treg) and effector T cells (Tcon). Humrich et al. (2010) demonstrated that the IL-2 deficiency in diseased (NZBxNZW) F1 mice can be rebalanced in lymphoid organs using a treatment with recombinant IL-2 (IL-2) by promoting the homeostatic proliferation of regulatory T cells. The aim of this study was to investigate the impact of IL-2 therapy on intrarenal Foxp3+ Treg and kidney infiltrating CD4+ T cells in (NZBxNZW) F1 mouse model of lupus nephritis.
Materials and Methods: (NZBxNZW) F1 mice with active nephritis were treated with recombinant IL-2 either over a short period or for a total of 30 days. Absolute numbers, phenotype and proliferation of kidney infiltrating CD4+ T cells were determined by flow cytometry.
Results: (NZBxNZW) F1 mice treated over a short term with IL-2 showed an enhanced proliferation of Foxp3+ Treg and increased numbers and frequency of CD4+Foxp3+ Treg compared to untreated treated control mice. On the other hand, long term IL-2 treatment did not result in a persistent expansion of the intrarenal Foxp3+ Treg population. Nevertheless, total numbers of kidney infiltrating CD4+ T cells were diminished and the CD4+ T con showed reduced signs of cellular activation.
Conclusions: Our data indicates that short term IL-2 treatment is able to expand the size of the intrarenal Treg pool. In contrast, long term IL-2 treatment decreases the numbers of kidney infiltrating CD4+ T cells. These results may in part explain the delay of disease progression induced by treatment with IL-2 and underline the important role of intrarenal Treg for the suppression of kidney disease in lupus mice. These results also provide additional rationales for an IL-2 based immunotherapy of human disease.

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Clinical manifestations and associated laboratory IL-17 in childhood systemic lupus erythematosus
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Background: Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem disease that affects several tissues, characterized by periods of exacerbation and remission and with intense participation of the immune system. The disease course is unpredictable and can be mild or even severe, due to the appearance many autoantibodies associated with a failure in the suppression of their training, ie, they were deposited in the tissues, may suffer a response that will determine the severity and development of disease. Evidence recent link to a higher level of IL17 in patients cSLE than in healthy controls, in addition, the frequency of IL17 cells is increased in peripheral blood of patients with cSLE, but clinical and laboratory features associated with this increase has not were identified.
Objectives: To determine the level of IL-17 in cSLE patients and evaluate the association between IL-17 and clinical manifestations, disease activity, laboratory findings and treatment.
Patients and methods: We included 67 consecutive cSLE patients (61 women; mean age of 18.19 years; SD±4.04), 55 first-degree relatives (50 women; mean age of 39.70 years; SD±5.58) and 47 healthy controls (42 women; age of 19.30 years; SD±4.97) matched for age and sex. cSLE patients were evaluated for activity [SLE Disease Activity Index (SLEDAI)], cumulative damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug at the day of blood withdrawal. Mood disorders were determined through Beck Depression and Anxiety Inventory (BAI and BDI). Serum IL-17 was measured by enzyme-linked immunoabsorbent assay (ELISA) using commercial kits.
Results: The mean serum IL-17 level was 36.8 ±16.96 pg/mL in cSLE patients and 29.66±12.82 pg/mL in healthy controls (p=0.009). We observed an association between serum IL-17 levels and migraine (p=0.03) and nephritis (p=0.01). Serum IL-17 levels were not associated with disease activity (p=0.32), cumulative damage (p=0.34), medication (p=0.63), anxiety (p=0.42) and depression (p=0.42).
Conclusion: The serum IL-17 levels were significantly higher in cSLE patients when compared to healthy controls and first-degree relatives. Nephritis and migraine were associated with serum IL-17. Longitudinal studies are necessary to determine if serum IL-17 can be used as a biomarker in cSLE.
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A Novel Biomarker: Nucleotide-binding Oligomerization Domain 27 in a Dominican Systemic Lupus Erythematosus Cohort.
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Introduction: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease in which a variety of autoantibodies may contribute to the diversified disease phenotype expression. The pattern recognition receptor known as Nucleotide-binding Oligomerization Domain 27 (NOD27) plays an important role in the host anti-viral responses. Our previous studies suggest that NOD27 might be a novel autoantigen in patients with Systemic Lupus Erythematosus. In lupus-prone mice, administration of antibodies accelerated lupus symptoms, suggesting a role in lupus pathogenesis. The purpose of this study is to determine if anti-NOD27 autoantibodies are detectable in the sera of SLE patients in a Dominican cohort of 52 SLE patients and if the serum levels have relation with active disease.
Methods: Patients with a recent SLE diagnosis who met at least four of the 1982 ACR criteria were enrolled in this study. 58 matched healthy volunteers with no known rheumatic disease were used as controls. We obtained Mex-SLEDAI as disease activity index in all SLE patients. Patients with a Mex-SLEDAI score of 4 or higher were considered to have active disease. Enzyme-linked immunosorbent assay (ELISA) was performed to determine the serum titers of anti-NOD27, dsDNA, SSA,

SSB, Sm, and nRNP autoantibodies and complement C3 and C4 levels in SLE patients and controls. Two tailed Mann Whitney test and Pearson correlation test were used for statistical analyses.
Results: Titers of anti-NOD27 autoantibodies are significantly higher in the sera of SLE patients than healthy controls in our cohort ($p < 0.0001$). Anti-NOD27 levels are also higher in the sera of SLE patients with Mex-SLEDAI ≥ 4, compared to those with Mex-SLEDAI < 4 ($p = 0.027$). Among all the autoantibodies analyzed including anti-dsDNA, SSA, SSB, Sm, and nRNP, anti-NOD27 titers have the best correlation with patients' MEX-SLEDAI ($p = 0.033$). Furthermore, anti-NOD27 titers also correlate with anti-Sm ($p < 0.0001$), nRNP ($p < 0.0001$), SSA ($p = 0.0002$), and reversely correlated with C4 levels ($p = 0.04$) in our cohort.
Conclusions: The serum titers of anti-NOD27 autoantibodies in SLE patients are present and significantly increased compared to controls, and correlate with higher Mex-SLEDAI activity index in our Dominican cohort, suggesting that anti-NOD27 could be used as a disease biomarker for SLE. Further studies with bigger sample sizes and different cohorts of patients will be needed to evaluate this in the future.

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Analysis of the Expression of Interferon Regulatory Factors on Myeloid Dendritic Cells from Systemic Lupus Erythematosus Patients

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Background: Dendritic cells (DC) are a key element between the innate and the adaptive immune response, they are considered professional antigen presenting cells, and the main source of type-I interferon (IFN-I). Elevated levels of IFN- I have been detected in many autoimmune diseases in humans. The genomic and proteomic studies have shown that elevated serum levels of IFN-I and the interferon related genes overexpression are the molecular signature of systemic lupus erythematosus (SLE). The interferon regulatory factors (IRF) are among these upregulated genes. These transcription factors are induced by many different receptors, mainly toll-like receptors and interferon receptors. Diverse genetic association studies have found relationship between many IRF-5 polymorphisms and increased susceptibility to SLE in different ethnic groups. However these studies have been done with total mononuclear cells, which may not reflect specific DC alterations. The aim of this study was to evaluate the expression of IRF-3, 5 and 7 on myeloid DC (mDC) from SLE patients.
Methods: We included 34 patients with SLE diagnosis (17 with SLEDAI=0, 17 with SLEDAI > 6) as well as 34 healthy controls. Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque centrifugation. Monocytes were purified by positive selection with anti-CD14 mAb coated microbeads. mDC were generated by culturing monocytes for 6 days in presence of GM-CSF, IL-4 and for 2 additional days in presence of LPS to induce maturation. In vitro generated mDC were analyzed for HLA-DR, CD11c, CD40, CD80, IRF3 and IRF5 expression by flow cytometry. We also analyzed the expression of IRF3, IRF5 and IRF7 by Western Blot and real time PCR (RT-PCR). Data were analyzed by the Mann–Whitney U test.
Results: We found no differences between the expression of surface molecules (HLA-DR, CD11c, CD80 and CD40) on mature mDC from SLE compared with controls. Neither we found differences on IRF3, IRF5 and IRF7 expression analyzed by flow cytometry (IRF3: 24.85% vs 28% and MIF 31 vs 23.5; IRF5: 30.8% vs 32.5% and MIF 35.5 vs 28), Western Blot (IRF3: 0.77 vs 0.62, IRF5: 1.39 vs 1.42 and IRF7: 0.72 vs 0.96) and RT-PCR (IRF3: 1765.9 vs 1141.3 copies/microliter; IRF5: 2975 vs 1970 copies/microliter and IRF7: 1163 vs 1772 copies/microliter). No differences were found between active and inactive SLE patients.
Conclusions: mDC from SLE patients do not display abnormalities in the expression of IRF3, 5 and 7.

P197

The Rai adaptor inhibits Th17 cell development in lupus autoimmunity

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Rai, a Shc adapter family member, acts as a negative regulator of antigen receptor signaling in T and B cells. Rai-/- mice develop lupus-like autoimmunity associated to the spontaneous activation of self-reactive lymphocytes. Here we have addressed the potential role of Rai in the development of the proinflammatory Th1 and Th17 subsets, which are centrally implicated in the pathogenesis of a number of autoimmune diseases, including lupus. We show that Rai-/- mice display a spontaneous Th1/Th17 bias. In vitro polarization experiments on naive and effector/memory CD4+ T cells demonstrate that Rai deficiency favours the development and expansion of Th17, but not Th1, cells, indicating that Rai modulates TCR signaling to antagonize the pathways driving naïve CD4+ T cell differentiation to the Th17 lineage while indirectly limiting Th1 cell development in vivo. Th1 and Th17 cell infiltrates were found in the kidneys of Rai-/- mice, providing evidence that Rai deficiency contributes to the development of lupus nephritis not only by enhancing lymphocyte activation but also by promoting the development and expansion of proinflammatory effector T cells. Interestingly, T cells from SLE patients were found to have a defect in Rai expression, suggesting a role for Rai in disease pathogenesis.

P198

In vitro 4-hydroxy-2-nonenal effect on catalase activity shows that the degree of oxidative damage may differentially affect catalase activity in systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a chronic and complex disease. Autoantibodies to self-antigens are a characteristic feature of the disorder. Our group and others have observed free radical mediated oxidative damage in SLE. Our previous data showed that two red cell membrane proteins from SLE patients underwent 4-hydroxy-2-nonenal (HNE- a by-product of oxidative damage) modification, resulting in HNE-protein adducts. Membrane-bound catalase was found to be one of the targets of HNE-modification. In this study we tested the hypothesis that HNE modification would inhibit catalase activity.
Methods: Equal amounts of purified catalase were incubated with 0, 0.05, 0.1, 0.25, 0.5, 2, 5 or 10 mM HNE in 5 mM Tris-HCl (pH 8.3) at 37°C for 7 hours. Following the incubation step, the unbound HNE was removed by centrifugation at 4°C using 10,000 molecular weight cut off spin-tubes. HNE binding to catalase was determined by immunoblotting and enzyme linked immunosorbant assay using an anti-HNE antibody. Enzyme activity was determined using an assay kit that utilized the peroxidatic function of catalase.

Results: Western blotting results showed that there was a progressive increase in HNE-crosslinking when catalase was incubated with increasing amounts of HNE. Anti-HNE bound the strongest to catalase modified with 10, 5 and 2 mM HNE. Anti-HNE antibody did not bind to unmodified catalase. Similar results were observed in ELISA (values are means ± standard deviation for 8 determinations in all cases). Anti-HNE antibody bound to catalase modified with 0.05 mM HNE (OD = 0.14 ± 0.05), 0.1 mM HNE (OD = 0.276 ± 0.03), 0.25 mM HNE (OD = 0.5 ± 0.168), 0.5 mM HNE (OD = 0.7 ± 0.10), 2 mM HNE (OD = 1.5 ± 0.15), 5 mM HNE (OD = 2.2 ± 0.196) and 10 mM HNE (OD = 2.64 ± 0.42). Unmodified catalase had an activity of 2.29 nmol/min/mL formaldehyde. The activity increased initially to 2.58 nmol/min/mL formaldehyde, when catalase was modified with 0.05 mM HNE. The activity further increased to 2.76 and 3.35 nmol/min/mL formaldehyde when catalase was modified with 0.1 and 0.25 mM HNE respectively. However, activity decreased with further increase of HNE. Catalase activity dropped to 2.62, 1.49 and 0.45 nmol/min/mL formaldehyde following modification with 0.5, 5 and 10 mM HNE respectively.
Conclusion: Our results show that catalase activity is dependent on the level of HNE used to modify the enzyme. There is a gain of function at lower levels (0.05 to 0.25 mM) of HNE, while levels of 0.5 mM or higher inhibited the enzyme activity. Thus, it may be important to study catalase activity based on the degree of oxidative damage in SLE patients. In addition, HNE-products are potential neoantigens and could be involved in the pathogenesis of SLE.

P199

Elucidating the role for TWEAK in the pathogenesis of cutaneous lupus

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by involvement of multiple organ systems. Involvement of the skin, or cutaneous lupus (CLE), is a common sign of active lupus, and is one of the earliest clinical manifestations of this disease. TNF-like weak inducer of apoptosis (TWEAK) is a soluble cytokine member of the TNF superfamily that binds its sole receptor, Fn14. The TWEAK/Fn14 pathway is involved in angiogenesis, cell survival and cell death, and is upregulated following injury and inflammation. Increasing evidence indicates a role for TWEAK/Fn14 interactions in the pathogenesis of organ damage in SLE. However, whether TWEAK is involved in inflammatory skin disease, or CLE, has not been determined.
Materials and methods: To evaluate a possible role for TWEAK in the pathogenesis of CLE, we generated a lupus prone mouse strain, MRL-lpr/lpr (MRL/lpr), deficient in Fn14, and evaluated the development of skin disease in this strain as compared to age and gender matched MRL/lpr mice.
Results: We found that MRL/lpr Fn14 knockout (Fn14 KO) mice had significantly attenuated cutaneous disease as compared to MRL/lpr Fn14 wild type (WT) mice, as assessed by the incidence of skin disease and the severity of cutaneous involvement. Histopathological and immunohistochemical studies of skin from MRL/lpr Fn14 KO mice demonstrated notable improvement in several of the features of CLE present in MRL/lpr Fn14 WT mice, including epidermal acanthosis, follicular plugging, and dermal infiltration by T cells and macrophages. In in-vitro studies preformed to clarify the contribution of TWEAK to CLE, we found that murine keratinocytes express surface Fn14. TWEAK stimulation promoted keratinocyte apoptosis and induced the secretion of several proinflammatory mediators, including RANTES. Furthermore, keratinocytes exposed to ultraviolet light (UVB), a known trigger of CLE, underwent apoptosis which was exacerbated by the addition of TWEAK. In addition, a combination of UVB irradiation and TWEAK stimulation significantly increased RANTES production in keratinocytes as compared to TWEAK alone.
Conclusion: Our data suggests a previously unrecognized role for TWEAK/Fn14 interactions in the pathogenesis of cutaneous disease, and suggest a possible new target for intervention in CLE.

P200

B cell home to inflamed kidneys of NZB/W mice through a distinct CXCR5-mediated mechanism whereas plasma cells are attracted by other chemokines

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NZB/W mice spontaneously develop a lupus-like disease leading to lethal immune complex-mediated nephritis. Disease manifestation is accompanied by inflammatory infiltration of the kidneys by lymphocytes. Here, we show that the immigration of B cells is mediated via CXCR5 whereas plasma cell infiltration is differently.

Histology was used to analyze the distribution of lymphocyte subsets and chemokines within inflamed NZB/W kidneys, and flow cytometry was used for the qunatification of, the phenotyping and chemokine receptor expression of particular lymphocyte subsets.

Our data show that kidney-infiltrating B cells accumulate within small, follicle-like structures of the kidney, whereas plasma cells and plasmablasts are scattered in conglomerates of several cells throughout the whole organ. B cells expressing the chemokine receptor CXCR5 can be found in areas of high CXCL13 concentration. In contrast plasma cells and plasmablasts express low levels of CXCR5 but high levels of CXCR3 and CXCR4, the ligands for CXCL10 and CXCL12 respecitvally known to be overexpressed in inflammatory tissue and bone marrow which might explain the different distribution pattern.

Interestingly, the kidney-infiltrating B cell population contains 50% IgD/IgM+ naïve cells and also includes smaller proportions of cells exhibiting a phenotype of CD93+/CD23+/- T1/T2/3 immature B cells.

These data suggest that B cells accumulate in the kidneys through homing mechanisms involving CXCR5/CXCL13 attracting primarily naïve B cells whereas plasmablast and plasma cell infiltration seems to be mediated by different mechanisms yet unclear mechanism.

P201

Regulatory T cell - deficient scurfy mice develop systemic lupus-like disease.

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Objective: Systemic lupus erythematodes (SLE) is a severe systemic autoimmune disease leading to inflammation in different organs. It is well known that B cell autoimmunity and autoantibodies are crucial for pathophysiology in skin, joints, lung and kidney, which are the main organs affected. Several studies described deficiencies of regulatory T cells (Treg) in SLE, but direct evidence for an important role of Treg malfunction in SLE pathophysiology is still missing. We therefore analyzed, if Treg-deficient scurfy mice share typical features of SLE.
Methods: Scurfy mice have dysfunctional Treg due to a genetic defect in the transcription factor foxP3 which is crucial for Treg development

and function. 9 scurfy and 9 matched controls (C57Bl76) were analyzed at 4-5 weeks of age. Using indirect immunofluorescence we screened for autoantibodies and also performed hematological workup. Specimen of skin and inner organs were stained with H/E and screened for inflammation by a blinded pathologist; kidneys were also stained with PAS and by direct immunofluorescence. We analyzed joint pathology after staining with H/E (overview), tolloidin blue (cartilage) and TRAP (osteoclasts); immunhistochemistry allowed for further analysis of the cellular composition of the inflammatory infiltrate, which was finally quantified by image analysis systems (Osteomeasure and HistoQuest, respectively).

Results: We confirmed previous reports that scurfy mice spontaneously develop severe systemic autoimmune disease which includes pneumonitis and hematological abnormalities similar to those seen in SLE. We here show that scurfy, but not WT control mice, exhibit various additional features typical for SLE: They develop severe interface dermatitis, show elevated serum levels of ANA and anti-dsDNA-abs and develop mesangio-proliferative glomerulonephritis comparable to lupus nephritis WHO2 (8 out of 9 scurfy [88.9%] vs. 0/6 [0%] of controls, respectively, p=0.0014). In contrast to controls, all scurfy mice showed increased cartilage degradation (destained/normal cartilage area 0.050±0.009 vs. 0.018±0.003, p=0.004) and developed inflammatory arthritic infiltrates (mean area 0.38±0.25mm^2). There were no osteoclasts within the joint space and, consecutively, no erosions. Besides fibroblasts, the inflammatory infiltrate consisted mainly of CD3$^+$ T lymphocytes (13%), with 7% B cells and <3% neutrophils and macrophages.

Conclusion: Our observations support the hypothesis that lupus-like disease develops in the absence of functional Treg.

P202

Serum circulating angiogenesis inhibitor angiostatin levels in patients with systemic lupus erythematosus

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SLE is a chronic multysystem autoimmune disease with an unknown aetiology, characterized by the production of non-organ specific autoantibodies. The primary pathological findings are those of inflammation, vasculitis and vasculopathy. Vascular homeostasis, in SLE, requires both proangiogenic and antiangiogenic factors.

Angiostatin is a physiologic angiostatic factor derived from the proteolytic cleavage of plasminogen. Angiostatin is also known as a potent antiangiogenic mediator that can be found in increased levels in the patients during various states of inflammation. It has been reported that angiostatin directly inhibite neutrophil migration and neutrophil mediated angiogenesis and also might inhibit inflammation. The purpose of this study was to determine serum levels of angiostatin and the relationship with disease activity index in patients with SLE in comparison with healthy subjects.

In this study, 62 patients with SLE (48 female, 14 male, mean age 23,1 ± 6,3 years, mean disease duration 13,3 ± 4,8 months) and 32 healthy controls (21 female, 11 male, mean age 25,8 ± 3,1 years) were included. Serum angiostatin levels were measured by ELISA. The mean serum angiostatin levels were 155,9 ± 18,3 ng/ml in patients with SLE and 48,2 ± 11,5 ng/ml in the healthy controls. The mean levels of serum angiostatin were 235,1 ± 26,3 ng/ml in active SLE patients and 75,9 ± 9,9 ng/ml in inactive SLE patients.

According to these results; serum angiostatin levels were significantly higher in patients with SLE compared with healthy controls ($p<0.001$). In addition, Serum angiostatin levels were significantly higher in active patients with SLE compared to in inactive patients with SLE ($p<0.001$). In the inactive patients with SLE, serum angiostatin concentrations were found to be higher compared to healthy controls s ($p<0.01$). We found a positive correlation between serum angiostatin level and SLE activity according to SLAM score ($r=0.485$, $p<0.001$)

In conclusion, Serum levels of angiostatin may play an important role in SLE pathogenesis.

P203

Soluble BAFF and its correlation with SLE autoantibodies and disease activity

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Introduction: The B cell activating factor (BAFF) is a cytokine belonging to the TNF family that stimulates proliferation, differentiation and survival of B lymphocytes and is increased in some autoimmune diseases, including systemic lupus erythematosus (SLE). Our objective was to establish the correlation between different autoantibodies, disease activity and soluble BAFF levels in SLE patients.

Patients and Methods: A cross-sectional study was carried out including a group of Colombian SLE patients and a group of healthy controls.The levels of soluble BAFF were determined by sandwich ELISA (Quantikine® Human BAFF/BLyS immunoassay; R&D Systems, USA), and the correlation between BAFF levels and the clinical variables and autoantibodies titers was evaluated by Spearman rank correlation coefficient.

Results: Ninety-two patients (80 females and 12 males, aged 16-76 years) and 68 controls (58 females and 10 males, aged 16-76 years) were included.Median of SLE disease activity index (SLEDAI) score was 6.5 (IQR: 2.25-13) and median of SLICC/ACR damage index was 2 (IQR: 0-2). Higher levels of BAFF were observed in patients (median: 1412 pg/ml, IQR: 962-2084) compared with the controls (median: 611 pg/ml, IQR: 436-1037) $p < 0.0001$. Correlations with different autoantibodies were established but none was significant (Sm, RNP, Ro, La, IgG and IgM anticardiolipin antibodies; $r = 0.15, 0.06, 0.17, 0.18, -0.08$ and 0.01 respectively), except the anti-double-stranded DNA antibody titers ($r = 0.42$ IC 95% 0.10 to 0.66, $p = 0.009$). The correlation between disease activity measured by SLEDAI and soluble BAFF levels also was not significant ($r = -0.04$ IC 95% -0.25 to 0.16, $p = 0.67$). Forty-three (46.7%) patients had renal involvement, but there was no correlation between BAFF levels and creatinine clearance or levels of proteinuria. With respect to the treatment, higher levels of BAFF were found in the patients that had been treated with Rituximab (median: 3324 pg/ml, IQR: 1828-5479) in comparison to those not treated (median: 1378 pg/ml, IQR: 929-2063) $p = 0.01$. No differences in the levels of BAFF were observed between the patients according to the use of other immunomodulatory drugs.

Conclusions: Our patients presented significantly higher levels of BAFF compared to the healthy controls, which is similar to that has been described in other populations. Such levels are correlated with the anti-double-stranded DNA antibody titers but no with other autoantibodies, confirming its importance in disease pathophysiology. This correlation could potentially help identify a subgroup of patients with SLE and high levels of anti-double-stranded DNA antibodies that would benefit from anti-BAFF therapy

P204

BLyS gene expression in Lupus Nephritis

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Introduction: B lymphocyte stimulator (BLyS), a novel TNF family ligand, has proved to be a key factor in the selection and survival of B population. B cells are involved in lupus nephritis (LN) as a source of auto antibodies and BLyS may have a pivotal role in the expansion of this B-cell population. There is a little information about BLyS gene expression in LN. This biomarker might be involved in LN pathogenesis.

The purpose of this project is to evaluate BLyS gene expression correlated with histology class in Lupus Nephritis Patients (LNP).

Patients and Methods: Kidney biopsies from 25 patients with LN (20 F/5 M, age 32,68 ± 11,65; range: 21-72) were evaluated. Biopsies were classified according to ISN/RPS scoring system. There were 11 samples with mesangial lesions, Class I and Class II, included in Group 1, 14 samples with diffuse proliferative lesions, Class IV, included in Group 2. Kidney biopsies from renal transplant patients with Acute Tubular Necrosis were included as controls in Group 3.

Levels of gene expression of BLyS were evaluated using Quantitative Real Time PCR (QPCR). All amplifications were carried out in duplicate and threshold cycle (Ct) scores were averaged for calculations of relative expression values. The Ct scores were normalized against Ct scores by subtracting the corresponding β2Microglobuline (β2M) control, or ΔCt=Ct,gene- Ct,B2M. To test for differential gene expression between groups a variance analysis (ANOVA) and t-test were performed.

Results: BLyS gene expression (ΔCt) is shown in Table 1.

Table 1.

Groups	*n*	*Mean (ΔCt)*	*S.D*	*Min*	*Max*
Group1	11	9,22	2,93	5,35	15,32
Group2	14	8,66	2,56	5,78	14,33
Group3	30	9,98	2,13	7,23	17,09

ΔCt is inversely proportional to the gene expression level. After t-test, we observed a significant difference for BLyS gene expression between Group II vs. Group III (p= 0.0022), but there is no difference in gene expression level between Group I vs. Group II and Group I vs. Group III. Results from ANOVA analysis showed that the levels of mRNA of BLyS in Group 2 were higher than those from Group 1 and Group 3 (p= 0,0195).

Conclusions: In the present study, increased levels of BLyS were observed in LNP with glomerular lesions Class IV compared to Class I and II. This might be associated with B cell activation leading to glomerular lesion. The role of this local production in the course of LN deserves further evaluation.

P205

Decreased proportions of non-classical monocytes in patients with Systemic Lupus Erythematosus (SLE). Effects of non-classical monocytes and apoptotic cells on classical monocyte function.

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Background: Alterations in mononuclear phagocytes are involved in the development and progression of SLE. These alterations include inabilities to remove apoptotic cells (ACs) and immune complex. In addition, these cells might modulate inflammation and the activity of the disease at both the innate and the adaptive responses.

This study aims to analyze subpopulations of circulating monocytes in patients with SLE, with other autoimmunities (OAD) and healthy controls. To characterize the effects of the coculture of classical monocytes and CD16-positive in presence and absence of ACs on mononuclear phagocyte differentiation and T cell responses in healthy controls.

Materials and methods: Samples were from patients with SLE, healthy controls and OAD. Peripheral blood cells were stained with anti-CD14, anti-CD16, anti-HLA-DR and analyzed by flow cytometry. Monocytes were electromagnetically sorted and the classical ones and co-cultured in the presence or absence of CD16-positive monocytes (6:4) and ACs from Jurkat limphocytes during 120 h; then, the expression of CD80, CD36 and HLA-DR was evaluated by flow cytometry or co-cultured for 96 h with purified autologous lymphocytes CD3+, stained with CFSE and stimulated with PHA to assess proliferation and the proportion of IFN-γ+ cells.

Results: Patients with active SLE display decreased percentage and number of non-classical monocytes; in addition, most of their monocytes subsets had decreased expression of HLA-DR. In presence CD16-positive phagocytes and CAs, classical monocytes did not up regulate CD80 and HLA-DR, CD4+ and CD8+ had decreased proliferation. In absence of CAs there was a low percentage of CD4+IFN-γ+ and CD8+IFN-γ+ proliferating cells.

Conclusion: Our findings support the idea that CD16-positive monocytes affect the differentiation of classic monocytes and most of their effects are reinforced in the presence of apoptotic cells; CD16-positive monocytes in presence of ACs decreased the expression of CD80, HLA-DR on classical monocytes, the proliferation and the proportion of LT producing IFN-γ. These evidences suggest us that CD16-positve cells might have a regulatory effect that could correlate with their low number in patients with LES.

P206

Th1/Th2 cytokine profile in patients with systemic lupus erythematosus

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Objective: To determine the sera levels of Th1 (IL-12, IFN-γ,TNF-α) and Th2 (IL-4, IL-5, IL-6 and IL-10) cytokines in SLE patients and healthy controls. To elucidate their association with disease activity, laboratory and treatment features.

Methods: We included 109 consecutive SLE patients [median age 39 years (range 19-70)], and 98 healthy [median age 37 years (range 17-68 years)] controls. Controls were age and sex-matched to SLE patients. SLE patients were assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], cumulative damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Mood and anxiety disorders were determined through Becks Depression (BDI) and Anxiety Inventory (BAI). Th1 and Th2 cytokines levels were measured by ELISA and compared by non-parametric tests.

Results: Sera Th1 cytokines levels [IL-12 (p=0.028), IFN-γ (p=0.002), TNF-α (p < 0.01)] and sera Th2 cytokines levels [IL-4 (p=0.045), IL-5 (p=0.003), IL-6 (p < 0.01) and IL-10 (p=0.007)] were increased in SLE patients when compared to healthy controls. Patients with leukocyturia had significantly higher levels of IFN-γ (p=0.049), IL-4 (p=0.026) and IL-5 (p=0.015). Patients with proteinuria had increased IL-4 levels (p=0.026) and patients with dysmorphic hematuria had higher levels of IL-6 (p=0.045). No association between cytokine levels and disease activity, SDI scores or medication was observed.

Conclusion: Th1 and Th2 cytokines were significantly higher in SLE patients compare to healthy controls. Th2 cytokines may play a role in the pathogenesis of renal manifestations in SLE patients. However, to extend the findings of the present study, it would be necessary to design longitudinal studies to establish a cause-effect relationship.

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P207

Adaptor protein Grb2 and PLC gamma-1 contribute to a preactivated state in peripheral blood T lymphocytes from patients with systemic lupus erythematosus, by localizing at the immunological synapse.

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Objective: To evaluate the presence of preassembled supramolecular activation clusters (SMACs) at the immunological synapse which may contribute to a preactivated state in lupus T cells.
Patients and Methods: 1. Systemic lupus erythematosus (SLE) patients were diagnosed according to the American College of Rheumatology criteria. Healthy donors were from the blood bank of *Hospital Universitario de Caracas*. All individuals signed an informed consent previously approved by the bioethics committee (n=5). 2. Highly enriched T cells, obtained from peripheral blood samples and subjected to RosetteSep^{TM} isolation, were adhered to pLL coated slides and activated for 5 and 15 minutes at 37°C with 4.5 μm superparamagnetic polystyrene beads coated with antibodies against CD3ε and CD28. The cells were fixed, permeabilized and stained with antibodies recognizing Grb2 and PLCγ1, and cholera toxin B subunit. The cell-bead complexes were evaluated by confocal microscopy and the densitometries were obtained using ImageJ, v1.6, NIH, USA.
Results: We previously showed an increased metabolization of transmembrane adaptor protein LAT in TCR/CD3 stimulated lupus T cells, associated with delocalization of LAT from lipid rafts and the immunological synapse after TCR/CD3-CD28 stimulation of lupus T cells. Unstimulated T cells from SLE patients seem to be in a preactivated state showing augmented phosphorylation of signaling proteins, among other evidences, compared to non-SLE patients and healthy controls. Our preliminary results suggest an increased localization of Grb2 at the immunological synapse in unstimulated T cells from lupus patients. PLCγ1 also showed increased localization at the immunological synapse in these cells. The colocalization of Grb2 and PLCγ1 with GM1, as a lipid raft marker, was similar between SLE patients and healthy controls. In addition, we observed a similar colocalization of Grb2 and PLCγ1 in T cells of both study groups.
Conclusion: Our findings support a preactivation signaling state in SLE T cells by showing increased localization of Grb2 and PLCγ1 at the immunological synapse in unstimulated peripheral blood T cells. These two molecules are key for LAT signalosome formation and downstream activation of MAPKs, potentially contributing to loss of tolerance in SLE T cells.

P208

Global DNA methylation pattern in Brazilian patients with systemic lupus erythematous

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Introduction: Epigenetic alterations imprinted by methylation can exert effects on normal and abnormal immune response, influencing disease susceptibility and severity. Nucleic acids methylation may have major effects on gene expression and development of autoimmunity. Based on these concepts, we investigated the pattern of global DNA methylation in Systemic Lupus Erythematosus (SLE) patients with active and non-active disease.
Material and Methods: Genomic DNA was isolated from 49 SLE patients with non active (SLEDAI < 6), 46 SLE patients with active (SLEDAI > 6) disease and 50 healthy individuals macthed for gender and age. Global DNA methylation was evaluated by digestion of genomic DNA with HpaII and MspI. Two μg of genomic DNA were incubated with 2 μl of each enzyme in separate reactions. at 37oC for 16 hours and after this period 1 μl of each enzyme was added and the tubes were kept at 37oC for one more hour. Samples were then resolved onto 0.8% agarose gel. The intensity of the band corresponding to intact genomic DNA in different samples was determined using ImageJ software. Percentage of methylation was calculated using the formula: relative global methylation content=(HpaII-MspI)x100/genomic DNA. For statistical analysis, non-parametric One-way Anova test followed by post-hoc test Dunńs was used using GraphPad Prisma version 5 for Windows. The significance level was established at * $p < 0,05$.
Results: A statistical difference of DNA global methylation was observed when SLE patients with active and inactive disease were compared to healthy individuals, however, no difference between active and inactive SLE patients was found regarding DNA methylation.
Conclusions: Using this approach, we observed that the relative amount of DNA methylation is reduced in healthy individuals when compared with SLE patients regardless of disease activity. Differentially methylated genes could alter gene expression and contribute to the pathogenesis of SLE.

P209

Serum Interleukin-9 Levels Are Increased In Brazilian Systemic Lupus Erythematosus Patients

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Introduction: Interleukin-9 (IL-9) is a cytokine related to inflammation and allergy with different cellular sources including T helper cells (Th) and mast cells. IL-9 can function as a positive or negative regulator of immune responses but its role in systemic lupus erythematosus (SLE) is not established.
Objective: The aim of this study was to determine serum levels of IL-9 in SLE patients and investigate a possible correlation with disease activity.
Methods: Serum levels of IL-9 were measured in 117 patients with SLE (114 women with mean age of 37.5 ± 10.4 years) and in 24 healthy controls using enzyme-linked immunosorbent assay (ELISA). Clinical and laboratory variables were assessed through clinical questionnaire and chart review. Correlations of IL-9 serum levels with disease activity measures, clinical and laboratory data and demographic factors were assessed for all patients. Mann Whitney and Spearman test were used for statistical analysis and $p < 0.05$ was considered significant. All participants signed a consent form approved by Ethics Committee at Universidade Federal de Pernambuco.
Results: IL-9 serum levels were significantly increased in SLE patients when compared with controls (mean 12.03 pg/ml versus 1.22 pg/ml, p=0.0007). Disease duration presented a positive correlation with IL-9 serum levels (p=0.03). Nevertheless, there was no association of serum IL-9 levels with disease activity or cumulative damage evaluated by SLEDAI and SLICC scores respectively. No significant association was found regarding IL-9 levels with proteinuria, anti-dsDNA serum levels or serum complement.
Conclusion: IL-9 serum levels were elevated in patients with established SLE and presented a positive correlation with disease duration. Further studies are necessary to clarify the role of this cytokine in this autoimmune diseases.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 3 Autoantibodies & Biormarkers"

Atlantico A+B+C

P210

Neurotrophic factors as novel biological markers for systemic lupus erythematosus activity

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Introduction: Recent studies showed that neurotrophic factors play an important role in the immune system. There is considerable evidence that neurotrophic factors induce the expression of many proinflamamatory mediators, such as IL-1, TNF-α and IL-6 and activate monocytes, T and B cells. Changes in neurotrophic factors levels were found in the synovium and in the serum of patients with rheumatoid arthritis, in the serum of patients with juvenile idiopathic arthritis, but few studies have evaluated these factors in individuals with systemic lupus erythematosus (SLE). The purpose of this study was to compare the plasma levels of brain-derived neurotrophic factor (BDNF), neurotrophic factor -3 (NT-3), neurotrophic factor -4 (NT-4), nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) in patients with SLE with the control group and their role in the disease activity.
Patientes and Methods: We measured plasma levels of BDNF, NT-3, NT-4, NGF and GDNF in 34 patients who fulfilled the American College of Rheumatology criteria for the classification of SLE and 34 healthy controls age and sex matched. SLE activity and damaged were assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2000) and the Systemic Lupus International Collaborating Clinics (SLICC) respectively.
Results: The mean SLEDAI and SLICC scores were 4.7 and 0.2 respectively. Twenty-eight patients were on regular use of prednisone. GDNF levels were lower in patients taking prednisone [36.6 (21.8-66) x 82.3 (60.2-216.7) pg/ml, p=0.009]. Median serum levels of neurotrophic factors were lower in SLE patients than in the control group, with significant differences in serum levels of GDNF (P=0.031), NGF (P < 0.001), NT-4 (P=0.002) and BDNF (P < 0.001). We found a negative correlation between the levels of GDNF with the SLEDAI score (p=0.042). NGF serum levels were positive correlated with complement C3 (p=0.006) and complement C4 (p=0.025). Patients with positive anti-dsDNA antibodies had lower serum levels of GDNF (p=0.018) and NGF (p=0.005). BDNF serum levels were lower in patients with hematological amendments (p=0.041).
Conclusion: Serum levels of neurotrophic factors were lower in SLE patients compared to control group. We have shown that SLE activity was associated with reduced serum levels of GDNF, NGF and BDNF. Our results suggest that neurotrophic factors may be promising markers of SLE activity.

P211

Has the role of ANA in differential diagnosis of Connective Tissue Diseases been changed after Technological Developments?

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Background: The mostly recommended method used in the detection of auto-antibodies for ANA is immune fluorescent antibody technique (IFA). In parallel with technological developments, new patterns as actin, ku, granular chromosomes (DFS-70) are also reported. However, clinical significance of these findings is currently not very well understood. In this study, we aimed to investigate the concordance of ANA results with clinical diagnosis of connective tissue diseases, and meanings of new patterns for autoimmune diseases.

Method: The results of Immunology laboratory between January - June 2012 was used for this study. Totally 2195 ANA-IFA results of 2114 patients who were followed in our rheumatology clinic were reevaluated. ANA analysis, the IFA method using Hep-2, and liver cells (Euroimmun, Germany) was performed and the results were reported by an experienced specialist in microbiology. Clinical data were obtained from hospital records. For each connective tissue disease and the IFA pattern, ANA titers were identified. The clinical significance of the IFA patterns in connective tissue diseases and other diseases were investigated.
Results: Among the study group 850 (40.2%) patients had a connective tissue disease. 227 patients had non-inflammatory musculoskeletal disorders. In 29 (11.4%) SLE patients, ANA was negative at the time of study. Seventeen of them had ANA positivity in previous tests. The other 9 ANA negative SLE patients were under treatment when tested and 3 (1.2%) patients were ANA (-) since the beginning of the disease. The frequency of newly reported patterns (cytoplasmic, ku, nuclear membrane, actin and dense fine granular (DFS70)) were as 11.8%, 0.6%, 1.8%, 0.4% and 9.7%, respectively. Regarding DFS70 pattern positive 104 patients; 52.8% did not have a rheumatic disease, but in 19.2% had RA (p < 0.001). In nuclear membrane positive 17 patients, 8 didn't have a rheumatic disease, but 5 had RA. There was no difference between the groups for cytoplasmic, ku and actin patterns.
Conclusion: ANA tests requested in rheumatology clinic can be false positive up to %35. However, only 12.3% of them had titers ≥1/320. The sensitivity of the ANA in patients with SLE as assessed by IFA was more than 98%. Nuclear membrane and DFS70 patterns are not specific to any connective tissue disease and they can be detected positive in rheumatoid arthritis and in the absence of any rheumatic disease.

P212

Hepcidin, interleukin-6 and anemia of chronic inflammation in systemic lupus erythematosus (SLE)

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Objectives: Hepcidin is an acute phase reactant that has been linked to anemia of chronic inflammation. The present study was carried out to evaluate the serum hepcidin and interleukin (IL)-6 levels in patients with SLE and their relationship with hemoglobin, disease activity and organ damage.

Method: Consecutive patients who fulfilled >=4 ACR criteria for SLE were recruited. Those with obvious/known cause(s) of anemia were excluded. Blood was taken for assay of hepcidin, IL-6 and high-sensitivity C-reactive protein (hsCRP). SLE disease activity was assessed by the SELENA-SLEDAI and physician's global assessment (PGA) scores. Organ damage of SLE was assessed by the ACR/SLICC damage index (SDI). Correlation among hepcidin, IL-6, hsCRP, disease activity and damage score of SLE was performed by linear regression.
Results: 289 SLE patients were invited but 72 were excluded because of obvious causes of anemia (renal insufficiency N=46; active hemolysis N=4; iron deficiency N=4; thalassemia N=18). Finally, 217 patients were studied (94% women; age at SLE onset 32.1+/-13 years; disease

duration 7.3+/-6.1 years). The mean SLEDAI score was 4.3+/-4.7 (median 3.5) and PGA score was 0.70+/-0.7 (median 0.5). 85 (39%) patients had clinically active SLE and 80 (37%) other patients had active SLE serology without clinical signs/symptoms. Anemia (hemoglobin < 11.6g/dL in women and < 13.4g/dL in men) of inflammation was present in 74 (34%) patients. Among patients with anemia, clinical SLE activity was present in 40 (54%) patients and serological activity was present in 33 (45%) patients. The mean serum hepcidin, IL-6 and hsCRP levels were 20.7+/-28.1 (median 11.5) ng/ml, 1.60+/-3.91 (median 0.30) pg/ml and 4.49+/-11.0 (median 0.94) mg/L, respectively. Hepcidin level correlated significantly with the total SLEDAI score (r=0.14, p=0.046), clinical SLEDAI score (total SLEDAI scores minus those contributed by lupus serology) (r=0.16; p=0.02), PGA score (r=0.23; p=0.001), as well as IL-6 (r=0.26; p < 0.001) and hsCRP level (r=0.47, p < 0.001). Moreover, hepcidin level correlated negatively and significantly with the hemoglobin level (r=-0.21, p=0.002). The levels of hepcidin, IL-6 and hsCRP were significantly higher in patients with anemia than those without (28.4+/-33.6 vs 16.7+/-24 ng/ml, p=0.009; 2.76+/-5.5 vs 1.00+/-2.6ng/ml, p=0.01; and 8.53+/-17 vs 2.39+/-5.0 mg/L, p=0.003, respectively). However, hepcidin level did not correlate significantly with anti-dsDNA titer, complement levels or SLE damage SDI scores.

Conclusions: In patients with SLE, the serum hepcidin, IL-6 and hsCRP levels are elevated in relation with clinic disease activity. This acute phase response to systemic inflammation is associated with the development of anemia of chronic inflammation.

P213

Assessment of Counterimmunoelectrophoresis and Enzyme-Immunoassay for the Detection of Antibodies to Extractable Nuclear Antigens.

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Introduction: The diagnosis of connective tissue disease (CTD), such as Lupus Erythematosus Systemic (SLE), is based on the clinical history, physical examination, and detection of antinuclear antibodies (ANA). A particular class of ANAs specific for Extractable Nuclear Antigens (ENA) can have diagnostic and prognostic relevance and an important role in the management of these patients. The anti-ENA includes anti-SS-A/Ro, anti-SS-B/La, anti-Sm, and anti-Rnp antibodies, and they are generally requested after an initial ANA screening. Its determination has historically been performed by gel immunoprecipitation techniques such as the counterimmunoelectrophoresis (CIEP). Over the last two decades, solid phase enzyme-linked immunosorbent assays (ELISA) have been developed.

Due to the diverse nature of the antigenic source employed and the intrinsic features of the methodologies, the results obtained can be discordant. The **objectives** of this study were to calculate concordance, sensitivity, and specificity of in-house CIEP by using the ELISA as the reference standard for detection of anti-ENA antibodies, and to calculate the percentage of anti-ENA antibodies from ANA negative sera.

• **Material and methods:** Anti-ENA testing was performed in sera from 150 individuals that were received consecutively for ENA testing. ANAs were assayed by indirect immunofluorescence (IFI) with Hep-2 substrate, total anti-ENA by in house CIEP with fetal bovine thymus, and anti-Ro, La, Sm and Sm/Rnp antibodies by ELISA kit with purified antigens. Additionally, another ELISA specific to recombinant anti-Rnp70Kd was performed.

Kappa (κ) concordance index, sensitivity and specificity were calculated for CIEP in relation to ELISA (MedCalc software).

• **Results:** 24% of the sera were positive on CIEP while 37% on ELISA. Sensitivity and specificity of the CIEP were of 64% and 100%, respectively, and κ index of 0,69. Anti-Ro were positive in 22% of samples, anti-Sm/Rnp 20%, anti-Rnp70Kd 16%, anti-La 9.3%, and anti-Sm 6.7%.

CIEP were positive in 2.7 % of samples with ANA negative; 2 of them showed cytoplasmatic speckled stain, and 2 anti-ribosomal-P pattern. Furthermore, 3.3% of anti-ENA antibodies positive on ELISA were ANA negative (1 sample showed cytoplasmatic speckled stain, and 2 samples ribosomal pattern). 80% were specific for Ro and 20% for Sm/Rnp.

From the sera with anti-Sm/Rnp autoantibodies: 9.3% were positive only for anti-Rnp70Kd, 4.7% positive for anti-Sm and Anti-Rnp70kd, 4% negative for anti-Sm and anti-Rnp70kd, and 1.33% positive only for anti-Sm.

• **Conclusions:** CIEP by total anti-ENA antibodies cannot be used as a screening technique.

Anti-ENA tests could be useful for patients with high clinical suspicion of CTD, negative ANA and cytoplasmatic pattern.

Mostly samples with anti-Sm/Rnp autoantibodies whithout reactivity to Sm recognize Rnp70Kd, but a small percentage could be recognizing the protein A or C from the U1-snRNP complex. Futhermore, an additional ELISA would be performed to discriminate sera with Sm/Rnp and Sm antibodies.

P214

Anti-collagen type I and type IV autoantibodies: lack of association with heart valve disease in systemic lupus erythematosus and antiphospholipid syndrome.

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Aim: Autoantibodies to type I and IV collagen have been described in rheumatic fever and infective endocarditis. Our aim was to elucidate if a humoral autoantibody response against collagen I and IV exists in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) patients with heart valve disease.

Patients and methods: Over a period of 5 years, 172 patients with SLE, primary APS (PAPS) and secondary APS (sAPS) were assessed for valvulopathy by transthoracic echocardiograms, and plasma levels of collagen I and IV autoantibody were assayed and compared with 50 healthy controls. Autoantibody positivity was set at two standard deviations above the mean antibody level of normal controls.

Results: Positive anti-collagen I autoantibody rate was similar between patients and controls (P=0.08) and no differences in type I collagen antibody level were seen between patients with in respect to those without valve disease (P=0.45). Positive anti-collagen IV autoantibody rate was significantly (P=0.001) higher in SLE patients in respect to the rest of patients with PAPS, sAPS and controls. Regardless, anti-collagen IV antibodies did not differ significantly between SLE patients with and without valvulopathy (P=0.2).

Conclusion: Our data indicate that autoimmunity against collagen I is not present in SLE and APS, whereas anticollagen IV autoantibodies are increased in SLE patients but without relation to heart valve disease.

Table 1. Patient's characteristics.

(continued)

Table Continued

	Patients (n=172)		*Controls (n=50)*		
	SLE (n= 79)	*PAPS (n=83)*	*sAPS (n=10)*		*P*
Women (%)	65 (82,3)	48 (57,8)	8 (80)	23 (46)	0,02
Age (mean, SD)	48 (15)	51 (16)	47 (8)	42 (13)	0,01
Valvulopathy (%)	40 (50,6)	28 (33,7)	5 (50)		0,08
Mitral	14 (35)	14 (50)	3 (60)		
M-Ao	10 (25)	7 (25)	2 (40)		
Thickness (%)	20 (50)	16 (57)	4 (80)		
Vegetations	2 (5)	3 (11)	0		
Surgery (%)	5 (12,5)	5 (17,8)	0		
Positive anticollagen I (%)	12(15,2)	17 (20,5)	2 (20)	4 (8)	0,08
Positive anticollagen IV (%)	14 (17,7)	2 (2,4)	0	1 (2)	0,001

P215

Long-term nephritis prognosis evaluation in lupus patients with concomitant anti-ribosomal P antibodies and anti-dsDNA

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The coexistence of anti-ribosomal P proteins and anti-dsDNA antibodies was reported to have a greater nephritogenic role but whether these antibodies are associated with renal disease severity is still unknown. The aim of this study was to evaluate if the concomitant presence of both antibodies discloses distinct histopathological pattern and worse lupus nephritis long-term survival than the presence of anti-dsDNA alone.

Methods: Thirty-nine consecutive SLE patients (ACR criteria) with serum samples positive for anti-P/anti-dsDNA or isolated anti-dsDNA at the time of biopsy (2004 International Society of Nephrology and the Renal Pathology Society) were prospectively assessed. Renal survival parameters evaluated were: plasma creatinine, 24-hours proteinuria, renal function (normal creatinine was arbitrarily established as < 1.5 mg/dL), end-stage renal disease (dialysis), and death associated to renal involvement. Anti-P and anti-dsDNA were detected by ELISA and results were confirmed by immunoblot and indirect immunofluorescence, respectively.

Results: Concomitant anti-P/anti-dsDNA antibodies were detected in 10 patients (25.6%) and 29 had isolated anti-dsDNA antibodies (74.6%). Demographic features were similar in these groups ($p > 0.05$). At entry, frequency of class IV histopathological pattern (60% vs. 69%, p=0.7), mean creatinine levels (2.8 ± 1.8 vs. 2.4 ± 1.6 mg/dl, p=0.54), proteinuria (7.7 ± 6.1 vs. 5.1 ± 3.5 g/24h, p=0.14), SLEDAI scores (8.1 ± 4.2 vs. 9.5 ± 4.2, p=0.62), and normal renal function (40% vs. 41%, p=1.0) were comparable in both groups. Likewise, both studied groups had similar long post-biopsy follow-up (8.7 ± 1.6 vs. 8.0 ± 4.0 years, p=0.5). At the final evaluation, the frequency of normal renal function (30% vs. 62%, p=0.14), dialysis (50% vs. 38%, p=0.71), and death associated to renal involvement (0% vs. 10.3%, p=0.55) were also alike in patients with anti-P/anti-dsDNA and isolated anti-dsDNA. Moreover, no significant difference was detected in the overall renal survival among groups (10 ± 5.7 vs. 9.8 ± 6.6 years, p=0.6).

Conclusion: The long-term lupus nephritis prognosis of anti-P/anti-dsDNA mutual occurrence is not distinct from patients with isolated anti-dsDNA, since the presence of the latter determines a predominance of proliferative lesion with a reduced renal survival for both groups.

P216

Cytokine profile in patients with systemic lupus erythematosus

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Objective: The aim of this study was to investigate if the ongoing production and serum levels of cytokines reflect disease activity and the presence of organ manifestations in patients with systemic lupus erythematosus (SLE).

Methods: The study involved 26 patients with definite SLE: 5 male, 21 female; mean age Me 27 [23-40]y; with disease duration from 9 to 300 months (Me 72[36-108] months) and 30 healthy individuals. Blood samples were collected for assessment of cytokines levels. Disease activity was assessed using SLEDAI2K. Serum 27 cytokine levels were measured using X-MAP on the BioPlex 200 (Anti-Human / Cytokine 27-Plex Conjugated Beads, USA). Patients were divided into 2 groups: those with lupus nephritis (LN) (n=13) and without renal involvement (n=13).

Results: In patients with LN were significantly higher levels of IL4, IL6, IL7, IL13, G-CSF compared with patients without renal involvement (p=0,039; 0,03; 0,037; 0,03; 0,028 respectively). ROC analysis found high sensitivity and specificity of these parameters in LN (Tab. 1). The area under ROC curve of IL6 was 0,75, specificity was 77%, sensitivity was 70%. The levels of IL17, GM-CSF, MIP1b were statistically significant increasing in patients with SLE compared with healthy controls (p=0.016, 0.02, 0.015, respectively).

Conclusion: Patients with LN have the statistically significant increased production of IL4, IL6, IL7, IL13, G-CSF. Our results confirm earlier reports that IL-6 to be a good biomarker of lupus nephritis.

Tab. 1. Summary of ROC analysis of cytokines in patients with lupus nephritis ($p < 0,05$)

Parameter	*Sensitivity %*	*Specificity %*	*Split point*	*Area under ROC curve*	*p index*
IL4	70	77	2,44	0,74	0,039
IL6	70	77	4,1	0,75	0,03
IL7	70	61	7,34	0,74	0,037
IL13	62	85	7,4	0,75	0,03
G-CSF	70	69	18,55	0,75	0,028

P217

Serum Anti-C1q antibodies in patients with lupus nephritis

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Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). Detection of anti-C1q antibodies has been proposed as an immunologic marker for SLE activity with proliferative LN.

Objectives: To assess the relationship between anti-C1q and renal involvement in patients with SLE course of less than 3 years. To explore whether anti-C1q in patients without renal involvement at the time of diagnosis is associated with a higher probability of developing renal disease within the 5-year follow-up period.
Methods: We included patients with SLE (ACR 1997) who had a serum sample in the serum bank of our hospital obtained less than 3 years after being diagnosed. In addition they would have at least four serum samples available within the next five years. Disease activity, which belonged to each sample of serum, were obtained by the review of medical records.

Samples were collected in the time period from Jan-1995 until Oct-2012. Anti-C1q (cut-off value 15 U/mL. ELISA), anti-DNAds (ELISA) and CH50% (Kent-Fife's) were measured. Kidney activity was assessed by the renal BILAG score and confirmed by histology. Mann-Whitney test was used to compare numerical variables and Fischer's exact test for ratios.
Results: Serum samples from 24 female patients, median age 27 years (17-55) at the time of diagnosis were tested.

The median time from SLE diagnosis to the first anti-C1q testing was 18 weeks (0-169).

The antibody was found to be present in 8/24 (33.33%) patients at the time of diagnosis.

There were 5/8 patients (62.5%) anti-C1q positive and renal involvement confirmed by histology (3 type IV, 1 type V+III, 1 type II). The median value of anti-C1q was 28 U/mL (16-128). The presence of anti-C1q was associated with renal disease (p=0.0069).

Three out of 8 patients (37.5%) were antibody positive without renal involvement who became negative for this antibody over the five-year period.

There were 2/5 patients with nephropathy and persistent renal disease, who required a repeated biopsy and continued having high levels titers of this antibodies. Besides, 3/5 patients who responded to treatment became antibody-negative.

Fifteen out of 16 patients had negative antibody titers and had no severe renal disease during follow-up. Only 1/16 had nephropathy and negative anti-C1q; he was on immunosuppressants at the time of testing.
Conclusions: A significant association was found between the presence of anti-C1q and severe renal involvement in patients with SLE at the time of diagnosis. During the course of nephropathy, the antibody behaviour might be a marker of response to treatment, and increased levels might be associated with severe renal injury. In this small number of patients, the absence of this antibody appeared to be associated with a low probability of developing severe renal involvement. A greater number of patients is required to further assess this potential association.

Authors have declared no conflicts of interest.

P218

Staining Patterns For Antinuclear Antibody and Extractable Nuclear Antigen Subgroups in Systemic Lupus Erythematosus Patients

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Objectives: Antinuclear antibodies (ANA) are considered a hallmark of autoimmune rheumatic diseases and the standard method for ANA detection is the indirect immunofluorescence (IIF) assay on HEp-2 cells (ANAHEp-2). We evaluated staining patterns for ANA on ANA-HEp-2 cells and extractable nuclear antigen (ENA) subgroups in patients with systemic lupus erythematosus (SLE) patients. In addition, we investigated whether there were any relationships between varios antibodies and clinical features of SLE.
Methods: Twohundred-and-sixteen SLE (208 F, 8 M) patients were included into the study. Clinical and demographic features; disease activity and damage indices according to SLEDAI was assessed. ANA-HEp-2 test was considered positive when a clear ANA pattern was observed at 1/80 dilution in two distinct commercial HEp-2 slides by two blinded independent observers. All ANA-HEp-2 positive sera were screened for antibodies against ENA (Sm, U1-RNP, SS-A/Ro, SS-B/La, histone, nucleosome, centromere) by double immunodiffusion against calf spleen extract as antigen source.
Results: ANA was positive in 207 of 216 SLE patients (96.3%) and anti-DNA was positive in 77 patients (36.7%) (Table 1). We observed that a homogenous staining pattern was associated with renal involement (OR:2.38), nucleoplasmic staining pattern was more frequent in patients with raynaud phenomenon (OR:3.53) and that a cytoplasmic pattern was more frequent in patients with neurological involvement (OR:7.01). We also found that anti-DNA positivity is associated with raynaud phenomenon (OR:1.80, 95%CI:1.006-3.25, p=0.032), renal involvement (OR:9.44, 95%CI:4,9-18.1, p=0.001), and hematological involvement (OR:2.31, 95%CI:1.1-4.5, p=0.009). Anti-SmRNP positivity was associated with raynaud phenomenon (OR:4.02, 95%CI:1.10-14.1, p=0.015), renal involvement (OR:2.75, 95%CI:1.09-6.90, p=0.029), and anti-Sm was more frequently positive in patients with raynoud phenomenon (OR:3.13, 95%CI:1.6-3.21, p=0.017). The prevalence of renal involvement was higher in anti-nucleosome positive patients (OR:4.55, 95%CI:1.41-13.8, p=0.006). When we compared anti-DNA positive and negative SLE patients, we found that the mean age (36.2±10.3 vs. 40.1±10.1, p=0.008), sedimentation rate (71.3±37.1 vs. 53.4±32.8, p=0.001), and SLEDAI score (3.1±3.9 vs. 1.4±1.6, p=0.001) at diagnosis were significantly higher in anti-DNA positive patients than in negative patients. In addition, anti-nucleosome positive SLE subgroups had higher mean SLEDAI scores than the negative subgroup (3.4±4.2 vs. 1.94±2.7, p=0.048).
Conclusions: IIF ANA test had very good sensitivity for the diagnosis of SLE in our patient population. Anti-DNA and nucleosome antibodies were associated with high levels of SLE activity and renal involvement.

P219

Anti M3 Muscarinic Actylcholine Receptor Antibodies in Systemic Lupus Erythematosus and Sjogren Syndrome: Association with other Autoantibodies and Clinical Manifestations

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Introduction: antibodies against M3 muscarinic actylcholine receptors (mAChRs) have been described in patients with Sjögren syndrome (SS). Little is known about these antibodies in systemic lupus erythematosus (SLE) patients.

The aim of this study was to describe the levels of anti M3 mAChR in patients with SLE and SS, associations with other auto-antibodies and clinical manifestations.
Patients and Methods: patients with SLE and primary SS were included. Serum autoantibodies against M3 mAChR synthetic peptide were measured by ELISA (normal value: Mean: 0.26; SD: 0.01). Anti-Ro, anti-La, anti-Sm and anti nRNP were tested by double-diffusion. Anti dsDNA was tested by Critidia lucillae IFI assay. Clinical variables were analyzed in SLE patients only, activity score was measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and damage by Systemic Lupus International Collaborating Clinics

(SLICC) damage score. Student's t test and Mann-Whitney test were used to analyze continuous variables.

Results: Thirty two patients with SLE and 21 patients with SS were studied. Forty seven (88.7%) were female. Mean age at diagnosis was 37.6 ± 12.9. Levels of anti M3 mAChR in SLE patients were mean 0.73 ± SD 0.75 and in SS mean 1.18 ± 0.52 ($p < 0.02$). Table 1 shows the anti M3 mAChR antibodies titer and its association to other autoantibodies in the total population studied (SLE and SS).

	Anti M3 AChR			
Type of autoantibodies	*mean*	*SD*	*p*	*Number of patients studied*
Anti-Ro negative	0.55	0.65		21
Anti-Ro positive	1.14	0.64	0.002	32
Anti- Sm negative	0.92	0.70		52
Anti- Sm positive	0.14	0.00	0.27	1
Anti-La negative	0.88	0.77		42
Anti-la positive	1.00	0.31	0.16	11
Anti-nRNP negative	0.97	0.70		48
Anti-nRNP positive	0.33	0.39	0.05	5
Anti dsDNA negative	0.90	0.67		49
Anti dsDNA positive	0.96	1.12	0.86	4

No associations were detected between anti M3 mAChR autoantibodies and SLEDAI ≥ 6 (p=0.18) or SLICC ≥ 1 (p=0.87).

Patients with SLE and hematological manifestations had levels of anti M3 mAChR median 0.79 (range 0.11- 3.7) and those without hematological manifestations had levels of anti M3 mAChR median 0.16 (range 0.13-0.74) (p 0.05). No significant differences were found in other clinical manifestations.

Conclusions: Anti M3 mAChR autoantibody levels was significantly higher in SS compared to SLE. In the total population (SS and SLE) patients with anti-Ro positive and nRNP negative had higher levels of anti M3 mAChR autoantibody. In SLE patients with hematological manifestations had significantly higher antibody levels compared to SLE without hematological manifestations.

P220

Platelet Indices and Disease Activity in Systemic Lupus Erythematosus

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Objectives: Platelet indices, especially mean platelet volume, are recently on spotlight in various chronic inflammatory diseases and atherosclerosis. In this study, we aimed to assess the relation between these indices and disease activity and inflammatory markers in systemic lupus erythematosus (SLE) patients.

Methods: We studied 187 patients with SLE (181F, 6M, mean age:38.3). Their platelet indices (mean platelet volume, MPV, platicrit, PCT, platelet distribution width, PDW) at the time of diagnosis and after remission were recorded. The clinical features were obtained from medical files. Disease activity (ESR, CRP, SLEDAI) and whole blood count were determined at the time of diagnosis and also after treatment.

Results: The mean disease duration of patients was 4.6 years ranging from 1 to 15 years. Of all SLE patients, 32.6% had renal involvement while central nervous system involvement was present in 15.5%. The presentation was with thrombocytopenia in 13.8% of patients. Anti-DNA positivity was present in 31.6% of patients and antiphospholipid antibodies were positive in 8% of them. The treatment modalities were hydroxychloroquine (98.4%), glucocorticoids (90.8%), azathiopurine (28.3%), and cyclophosphamide (27.3%).

We compared SLE patients with and without renal and central nervous system involvement. MPC, PCT and PDW values were not significantly different in patients with and without renal or central nervous system involvement (all p values > 0.05). PCT level in patients with central nervous system involvement was significantly higher than in patients with no involvement (0.22±0.07 vs. 0.18±0.08, p=0.005) at the time of diagnosis. There were no significant differences in the levels of MPV and platelet distribution width at the time of diagnosis (all p values > 0.05).

Platelet indices in active (SLEDAI > 5) and inactive (SLEDAI ≤ 5) SLE patients were not significantly different (all p values > 0.05). In addition, no correlation was observed between SLEDAI score and platelet indices. MPV correlated positively only with PCT (r=0.26, $p < 0.001$); and negatively with platelet count (r=-0.21, p=0.006). At the time of diagnosis, MPV had a positive correlation with platelet distribution width (r=0.56, $p < 0.001$) and a negative correlation with platelet count (r=-0.29, $p < 0.001$). The mean baseline levels of ESR, CRP and SLEDAI decreased significantly (p values < 0.001) after treatment. Mean number of platelets did not change significantly after treatment ($p > 0.05$); however, PDW and MPV levels were significantly reduced (p values < 0.001).

We evaluated the mean variation of ESR, CRP and platelet indices in SLE before and after therapy. Changes in MPV significantly correlated with PDW and PCT (p values < 0.001); but, not with alterations of ESR and CRP (p values > 0.05). The change in SLEDAI did not correlate with MPV and other platelet indices.

Conclusions: In our study, we observed a change in MPV and other platelet indices with the reduced disease activity without a relation with disease activity parameters of SLE such as ESR and SLEDAI.

P221

Soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) in patients with active and inactive systemic lupus erythematosus

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Introduction: Placental growth factor (PlGF) is a member of vascular endothelial growth factor (VEGF) family and induces the production of nitric oxide and prostacyclin by endothelial cells vasodilators, reducing the vascular tone and blood pressure, stabilizes endothelium when it is damaged and increases vascular permeability. Soluble Fms-like tyrosine kinase-1 (sFlt-1) is a soluble receptor of VEGF family, working as antagonist of the angiogenic factors (VEGF, PlGF) in situations where its production is increased, such as preeclampsia. The pattern of serum sFlt-1 and PlGF in pregnant and non-pregnant patients with systemic lupus erythematosus (SLE) according to disease activity is unknown.

Objective: To examine if serum concentrations of sFlt-1 and PlGF are influenced by SLE activity.

Patients and Methods: Peripheral blood was collected in 25 non-pregnant SLE women according to ACR criteria (1997), including 21 patients with nephritis (classes III to V). SLE activity was measured by SLEDAI-2K criteria. We defined inactive disease when SLEDAI was < 2 and active disease when SLEDAI was > 6. sFlt-1 and PlGF were measured by ELISA. The study was approved by local IRB.

Results: Twelve patients were considered with inactive SLE and 13 patients had active disease. The mean age was 34 in both groups and there was no statistical difference in disease's length (inactive: 7.83 x active: 9.30; p=0.52) or SLICC index (inactive: 0.75 x active: 1.31; p=0.42). The mean values for sFlt-1 and PlGF in the inactive SLE group were 92.0pg/mL and 93.7pg/mL, respectively, while the active SLE group had mean result for sFlt-1=111.3pg/mL and for PlGF= 85.3pg/mL, with no statistical difference when both groups were compared (sFlt-1 p=0.63;PlGF p=0.89).

Conclusions: Few studies have evaluated sFlt-1 and PlGF in SLE patients. Our study found similar serum values of sFlt-1 and PlGF in patients with active and inactive SLE, including 84% of patients with nephritis. More studies are needed to find if it is possible to use angiogenic (VEGF, PlGF) and antiangiogenic (sFlt-1, soluble endoglin) cytokines in SLE patients during pregnancy to help differentiate lupus nephritis and preeclampsia.

P222

The estimation of the level of Serum Brain-Derived Neurotrophic Factor and characteristics of some cognitive functions in patients with systemic lupus erythematosus. Preliminary report

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Cerebral brain-derived neurotrophic factor (BDNF) is an important modifier of synaptogenesis, neuroplasticity, cognitive functioning, and memory. Changes in BDNF expression in serotoninergic and dopaminergic neurons have been found in pathological behavior as well as the serum low BDNF concentrations. That mechanism is well known in primary dementias for example in Alzheimer and Parkinson diseases. Neurocognitive disturbances were recognized in patients systemic lupus erythematosus (SLE) on the level of neuropsychological examinations but the is no data about serum BDNF concentrations. The assessment of the serum BDNF concentration and neurocognitive functions in patients with SLE were examined in that study. The BDNF concentration was compared in healthy subjects matched by age, sex, level of education and socioeconomic factors. The study was carried out the 40 SLE patients aged 32 ± 3,4 years and 63 healthy subject aged 28 ± 1,3 years (30 women and 30 men). The concentrations of BDNF in the serum of subjects were measured by sandwich-ELISA method using commercial test. The neurocognitive functions were assessed by use of tests of memory, attention, efficacy of learning and level of intelligence. The SLE subjects have the statistically significant lower mean level of serum BDNF than healthy ones ($p < 0{,}001$). There are no statistically differences between sex and sociodemographic factors. The strong linear significant positive correlation between serum level of BDNF and neurocognitive functions – memory and attention in SLE patients were found. This preliminary study suggests that SLE can decrease the level of BDNF and may be a risk of neuropsychological deficits.

P223

Associations between antinuclear antibody staining patterns and clinical features of systemic lupus erythematosus

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Introduction: An abnormal antinuclear antibody (ANA) titer evaluated by immunofluorescence (IF) microscopy is a cornerstone in the 1982 American College of Rheumatology (ACR–82) classification criteria of systemic lupus erythematosus (SLE) as well as in the newly postulated Systemic Lupus International Collaborating Clinics (SLICC) criteria. Several studies have addressed the clinical value of ANA fine-specificities in SLE but, to our knowledge, has none evaluated how distinct ANA staining patterns are related to clinical features of SLE. Thus, we aimed at comparing indirect IF microscopy patterns with SLE phenotypes in a local Swedish SLE-register comprising virtually all adult patients in the county of Östergötland with 340.000 citizens.
Methods: The study population consisted of 222 SLE patients (24 men, 198 women; mean age 50.6 years; range 18–88) taking part in the prospective control programme KLURING (a Swedish acronym for 'Clinical Lupus Register in North-eastern Gothia') at the Rheumatology clinic, Linköping university Hospital. 93% were Caucasians. 178 patients (80%) met the ACR–82, whereas 44 (20%) had a clinical diagnosis of SLE based on a history of abnormal ANA titer (titer ≥1:200 corresponding to a cut-off level at >95th percentile based on 150 healthy female blood donors), and at least 2 typical organ manifestations at the time of diagnosis (referred to as the 'Fries criteria'). ANA was analyzed by indirect IF microscopy using multispot slides with fixed HEp-2 cells. Anti-dsDNA antibodies were analyzed by *Crithidia luciliae* (cut-off titer 1:10 based on >99th percentile among 100 female blood donors). Autoantibodies to extractable nuclear antigens (SSA, SSB, Sm, snRNP, Scl-70 and Jo-1) were analyzed by double radial immunodiffusion and/or line-blot. Differences in the proportions of patients with homogenous, speckled, homogenous/speckled and nucleolar ± combination with other patterns were analyzed using chi-square test (or Fisher's exact test when appropriate).
Results: 119/222 (54%) SLE patients displayed homogenous staining, 22% speckled, 11% homogenous/speckled, 9% nucleolar ± other patterns, 1% centromere, 2% miscellaneous and 1% were ever ANA-negative. Staining patterns of patients meeting only Fries criteria did not differ from those of patients fulfilling ACR–82. Findings from tests of proportions revealed that homogenous staining pattern was associated with immunologic disorder ($p < 0.001$). Speckled pattern was inversely associated with arthritis ($p=0.02$), immunologic disorder ($p < 0.001$) and SLICC/ACR damage index of at least 1 ($p=0.007$). Positive anti-SSA antibody test was associated with photosensitivity ($p=0.023$) and inversely associated with arthritis ($p=0.016$).
Conclusions: This Swedish cohort of 222 well-characterized patients confirmed that homogenous nuclear staining is the most common IF-ANA pattern in Caucasian SLE patients. The inverse relation between speckled pattern and arthritis was strengthened by the corresponding relation between anti-SSA and arthritis. The previously described association between anti-SSA and photosensitivity was confirmed. The inverse relationship between speckled staining and SLICC/ACR damage index could indicate a milder disease with a better prognosis for individuals with this ANA pattern.

P224

Anti-chromatin antibodies in Colombian patients with Systemic Lupus Erythematosus: A useful marker for activity.

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Background: The anti-chromatin antibody frequently is elevated in patients with active Systemic Lupus Erythematosus (SLE) and its titer correlates with activity.

The objective is to determine the diagnostic value of anti-chromatin antibodies in clinically active SLE.
Patients and Methods: A cross-sectional study. 74 patients (110 samples) diagnosed with SLE. Disease activity was evaluated by Safety of Estrogens in SLE National Assessment— SLE Activity Index

(SELENA-SLEDAI) and the British Isles Lupus Activity Group 2004 (BILAG 2004) index. Serological titers of anti-dsDNA high avidity, anti-chromatin and anti-C1q antibodies were measured by ELISA kits INOVA Diagnostics, Inc.

Values in this study were expressed as mean ± standard deviation (SD). The chi-squared test for the categorical variables. The Wilcoxon Rank-Sum test was used and Correlation among biomarkers and disease activity scores by the nonparametric Spearman's rank correlation test (correlation coefficient ρ [rho]). Values of $p < 0.05$. STATA SE-11,1 (STATA Corp®).

Results: 110 samples. The mean SLEDAI was 3,36±3,19 (0-14). 49,9% (n=54) patients had a SLEDAI ≥ 4 and 23% (n=25) ≥ 6. Activity by BILAG A/B: Renal 9% (n=10), mucocutaneous 8,18 (n=9), musculoskeletal 6,5% (n=7), neuropsychiatric 1,8% (n=2), hematological 1,8% (n=2), cardiorespiratory and constitucional 0,9% (n=1).

Biomarkers: Anti-chromatin antibodies 64,08±74,3 (1-251), anti-dsDNA 54,99±77,63 (12-543), anti-C1q antibodies 14,66±23,09 (2-153), C3 97,81±30,5 (26-152) and C4 16,53±8,99 (2-42).

The prevalence of positive anti-chromatin, anti-dsDNA and anti-C1q antibodies in the recruited patients was 51%, 45%, and 16,5%. Anti-chromatin antibodies and anti dsDNA antibodies were found to be positive in 70% and 72% active-SLE patients by SLEDAI ≥ 4 ($p < 0,0001$). Anti-chromatin antibodies were found to be 27,8% positive in SLE patients lacking anti-dsDNA antibody.

The Wilcoxon Rank-Sum Test showed an excellent correlation between anti-chromatin antibodies and SLEDAI ≥ 4 ($p < 0,0001$). Spearman's rank correlation test among disease activity and anti-dsDNA (ρ=0,38), anti-chromatin (ρ=0,41), anti-C1q (ρ=0,53) with $p < 0.001$.

The anti-chromatin titers correlated significantly with anti-dsDNA antibody (ρ=0,45;$p < 0,001$), anti-C1q (ρ=0,62;$p < 0,001$), C3 (ρ= -0,3;$p < 0,001$) and C4 (ρ= -0,46;$p < 0,001$) but not with renal SLEDAI score.

Conclusion: Our study suggests that anti-chromatin antibodies may be useful marker in the assessment of SLE disease activity. Anti-chromatin antibodies may be a useful marker for early activity assessment in anti-dsDNA negative SLE patients.

P225

Behavior of reticulocyte-bound C4d in Colombian patients with Systemic Lupus Erythematosus.

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Background: Early detection of lupus activity is essential to prevent the onset of irreversible damage and improve disease morbidity and mortality, however early diagnosis of this is not easy because of the heterogeneity of manifestations and the absence of clinical and laboratory parameters accurate and specific. Because complement activation is important in the pathophysiology of systemic lupus erythematosus (SLE) the measurement of complement activation products bound to cells (CAP) is an interesting alternative. The youngest and shortest-lived erythrocytes (lifespan 24–48 hours), emerge from the bone marrow, they are immediately exposed to and acquire C4d at levels proportionate to the extent of complement activation at that time, thereby reflecting disease activity in SLE

Objective: to describe the behavior of serum levels of C4d bound to reticulocytes (R-C4d) in SLE patients with different degrees of lupus activity.

Patients and Methods: Cross-sectional study. R-C4d was measured in 51 patients with SLE and disease activity was estimated by SLE Disease Activity Index (SELENA-SLEDAI). R-C4d Processing: R-C4d was measured through flow cytometry from a 3 ml sample of blood collected in EDTA tube that was processed the same day it was collected. A mouse monoclonal antibody specific for human C4d was used. Levels of C4d on the surface of reticulocytes were expressed as specific median fluorescence intensity (SMFI). Currently, a cutoff is unknown. Statistical analysis: the patients were divided into 3 groups according to the SELENA-SLEDAI score: 0 to 2, 3 to 4, greater than or equal to 4 and descriptive statistical analysis was performed by calculating statistics of central tendency and dispersion.

Results: The results of R-C4d ranged between 0 and 47%. 16 patients (31.37%) had a SELENA-SLEDAI 0-2, 19 patients (37.25%) a SELENA-SLEDAI > 2 to < 4 and 16 patients > 4 (31.37%). For each group levels of R-C4d were 5.75 ± 7.60 SMFI (0-20), 11.05 ± 9.52 SMFI (0-28) and 17.12 ± 14.52 SMFI (0-47).

Conclusions: Preliminary results suggest that R-C4d levels vary in patients with SLE in proportion to their activity. However a large number of patients are needed to establish a cutoff and to evaluate the performance of R-C4d as a biomarker of lupus activity at that time.

P226

Title: Adiponectin in Systemic Lupus Erythematosus

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Introduction: Recently, several studies have been conducted to determine the role of adipokines in autoimmune diseases, particularly in rheumatic diseases such as systemic lupus erythematosus (SLE). Among the adipokines, adiponectin seems to have an anti-inflammatory activity and some authors have shown elevated levels in patients with SLE.

Objective: To evaluate serum adiponectin levels in patients with SLE and healthy controls, and to correlate the adiponectin levels with the activity and clinical manifestations in SLE.

Methods: Fifty two women with SLE, who met the American College of Rheumatology criteria, and 33 healthy women were studied. The patients with SLE were divided into two groups, the first who were with active SLE and the second who were with inactive SLE. Serum adiponectin levels (μg/ml) were measured by enzyme-linked immunosorbent assay.

Results: There were no significant difference in adiponectin levels between SLE and control (87.5 +- 69.7 μg/ml vs 118.1 +- 70.6 μg/ml P=0,053) and also no significant difference in adiponectin levels between patients with inactive and active SLE (85.5 +- 65.9 μg/ml vs 88.8 +-74.4 μg/ml P=0,866). There was no significant correlation of adiponectin with VHS and SLEDAI. Adiponectin levels did not associate with the presence of autoantibodies and clinical manifestations of SLE.

Conclusion: Adiponectin levels in SLE patients did not differ from controls and did not correlate with disease activity or clinical manifestation.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 4 Experimental Models"

Atlantico A+B+C

P227

Low-dose IL-2 therapy selectively expands regulatory T cells and ameliorates established disease in (NZBxNZW) F1 lupus mice

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Background: Our previous studies in the (NZBxNZW) F1 model provide strong rationales for an IL-2 based immunotherapy of lupus in order to restore regulatory T cell (Treg) mediated tolerance that is impaired due to an acquired IL-2 deficiency (Humrich et al. 2010). However, because of its pleiotropy, other cells than Treg can be activated by IL-2 in a dose dependent manner, which may induce unwanted side effects or even trigger autoimmunity. Thus, we aimed to determine an optimal regimen for an IL-2 based immunotherapy that is capable to induce a sufficient expansion of CD4+Foxp3+Treg in vivo while only marginally affecting other cells, and that most efficiently influences active disease in the (NZBxNZW) F1 model for lupus.
Methods: Recombinant mouse IL-2 at various single doses was injected subcutaneously either into young or diseased (NZBxNZW) F1 mice every day for the duration of five days as induction therapy. After the induction phase, IL-2 injections were continued every 4 days until the end of the experiment. Control animals received an equal amount of PBS (carrier). Cells from lymphoid organs and peripheral blood were analyzed by flow cytometry at different time points throughout the study. In addition survival and clinical parameters (weight, proteinuria, leukozyturia, autoantibodies) were analysed during IL-2 therapy of diseased mice for regimens with the single dosages of 5ng/g and 25 ng/g body weight.
Results: We found that the low-dose IL-2 regimen with a single dose of 5ng/g body weight sufficiently promoted the expansion of CD4+Foxp3+Treg, while not or only marginally affecting CD4+ conventional T cells (Tcon) and other potentially harmful cells. Although higher doses of IL-2 resulted in a more pronounced proliferation and expansion of Treg, this was accompanied by a considerable increase in CD4+ memory/effector Tcon and NK/NKT cells. Clinically, regimens with both 5ng/g and 25 ng/g were almost equally sufficient to influence nephritis and to decrease mortality in mice with established disease.
Conclusions: These studies show that a low-dose IL-2 regimen selectively targets Treg and is clinically effective and also safe in murine lupus providing essential rationales for the clinical introduction of an IL-2 based immunotherapy in SLE.

P228

Comparison of strategies for plasma cell depletion in NZB/W mice

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Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the generation of pathogenic antibodies directed against a variety of autoantigens. We have previously shown that long-lived autoreactive plasma cells can contribute to chronicity and refractoriness of SLE. Our study is aimed to develop new methods for depletion of long-lived plasma cells in NZB/W mice, a model of SLE.
Methods: We studied different treatment protocols on plasma cell survival and prevention of autoractive plasma cell regeneration in spleen and bone marrow of NZB/W mice. 10-12 week-old NZB/W mice were exposed to three different irradiation doses (10, 14, and 15 Gy in two splitted doses with a 3-h interval).

The following protocols were also investigated: 1) two bortezomib (Bz) injections (0,75 mg/kg, i.v.) combined with anti-mouse CD20 (10 mg/kg, i.v.), 2) three bortezomib injections combined with anti-mouse CD20, 3) three bortezomib injections combined with anti-LFA-1 and anti-VLA-4 antibodies (affecting directly the plasma cell niche) (200µg, i.p.) in a 2-d interval, plus anti-mouse CD20 and anti-B220 (250µg, i.v.). The plasma cells were analyzed in spleen and bone marrow by FACS and ELISPOT. BrdU chase was used to distinguish short-lived plasmablasts/plasma cells from long-lived plasma cells.
Results: The frequency of remaining plasma cells in bone marrow after 10, 14 and 15 Gy irradiation were 90, 47 and 0,7% respectively, and in spleen the frequencies were almost 99, 25 and 0,3%.

Short-term treatments with agents that affect plasma cells (bortezomib, anti-LFA1 plus anti-VLA4) effectively deplete plasma cells including long-lived plasma cells in spleen and bone marrow of NZB/W mice. Because of the B cell hyperactivity in NZB/W mice, we observe a rapid regeneration of autoreactive plasma cells in spleen and bone marrow. Therefore, plasma cell depletion protocols were combined with B cell depletion. Especially, the combination of plasma cell targeting with bortezomib, anti-LFA1 and anti-VLA4 with B cell targeting (anti-CD20 plus anti-B220) interrupted the repopulation of autoreactive plasma cells in spleen and bone marrow.
Conclusion: Very high doses of irradiation result in effective depletion of long-lived plasma cells but lower doses not.

Depletion of long-lived plasma cells can be achieved by the proteasome inhibitor bortezomib and by targeting both adhesion molecules LFA1 and VLA4. The combination with B cell depletion is needed to prevent regeneration of autoreactive plasma cells.

P229

Arthritis in a model for systemic lupus: Involvement of joints, inner organs and course of autoantibodies in pristane-induced lupus.

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Objective: Arthritis is frequently seen in human lupus, but rarely in lupus models. Pristane-induced lupus (PIL) can be induced in various mouse strains such as BALB/c and C57Bl/6. We herein characterize clinical and histological features of arthritis in the context of systemic lupus and provide a prudent comparison with models of rheumatoid arthritis (RA).
Methods: 57 BALB/c mice received pristane i.p. and were analyzed for serum autoantibodies (anti-chromatin-, -histone, -Sm), as well as for clinical features of arthritis, while PBS-injected mice served as controls. All mice were analyzed for histopathology of joints, lungs and kidneys after an experiment period of 8 months. Joint pathology was quantified by an image analysis system and by tissue cytometry. 10 C57Bl/6 mice and historical groups of two different RA models (hTNF-tg and CIA mice, respectively) were analyzed accordingly.
Results: In BALB/c, clinical arthritis started at 3 months, occurred finally in 79% of PIL (but not in controls, $p < 0.001$) and correlated with areas of inflammation, erosion, cartilage damage, osteoclast numbers and total severity score (for all: $r > 0.7$, $p < 0.001$). After 8 months, 58% of PIL (but no controls, $p < 0.001$) had mild-erosive arthritis: In contrast to murine RA, the most frequent inflammatory cell type of the pannus was granulocytes (17.7%). PIL had lower numbers of osteoclasts, erosions rarely affected both layers of the cortical bone and there was no progression to complete joint destruction (even after 1

year of observation). Serum auto-abs preceded arthritis and became significantly elevated in all PIL; affected joints showed increased deposits of IgG (and IgM) within the inflammatory tissue, indicative for an antibody-mediated process. PIL mice with arthritis also had pulmonary (100%) and renal (46%) lupus. In contrast to BALB/c, Bl/6 mice did not develop any signs of arthritis.
Conclusion: PIL in BALB/c mice is characterized by severe organ involvement, typical auto-abs and by a mild-erosive arthritis with similarities, but also with distinct differences to RA. PIL may help to study arthritis along with other key features of SLE after therapeutic interventions or in knockout models based on a BALB/c, but not on a Bl/6 background.

P230

Delayed Glomerulonephritis Onset and Increased Survival following SERPINB3 Administration in Lupus-Prone Mice (NZB/NZW F1)
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Background: Lupus nephritis (LN) is a major determinant of poor prognosis in systemic lupus erythematosus (SLE). Although the underlying mechanisms are still uncertain, dysregulated apoptosis is likely to enrich the available autoantigenic pool, promoting autoantibody binding to exposed glomerular nucleosomes. Inflammatory/antinflammatory cytokines may eventually drive glomerular inflammation.

Serpins (Serin protease inhibitors) can influence cellular viability. SERPINB3 may hinder apoptosis and is dampened by type I interferon (IFN I), which is highly increased in SLE. Interestingly, SERPINB3 is absent on SLE B lymphocytes [Vidalino L, et al. Exp Biol Med 2012;237:793-802], posing the question whether impaired SERPINB3 expression may boost SLE autoantigen burden or B cell autoreactivity.

We aimed to assess whether SERPINB3 administration may modify disease course in lupus-prone mice.
Materials and Methods: 24 NZB/NZW F1 mice were subdivided into two groups, 12 mice each. Group 1 mice were intraperitoneally injected with SERPINB3 and group 2 mice with PBS (SERPINB3 7.5μg/0.1mL; PBS 0.1mL) twice a week, since week 17 until natural death. We evaluated autoantibodies (anti-dsDNA and anti-C1q), proteinuria, proteinuria-free survival and overall survival. Proteinuria was analyzed once per week while antibodies were tested every 4 weeks (since week 17) and at death, by standardized home-made ELISA. Expression of inflammation (IFNγ) and fibrosis markers (collagen IV, TGFβ, αSmooth Muscle Actin) was evaluated on homogenized kidney tissue by real-time PCR.

Non-parametric tests were performed for statistical analysis. Proteinuria-free and overall survival were evaluated by Kaplan-Meier method.
Results: Numbers are expressed as median [interquartile range]. Autoantibodies appeared later and at significantly lower levels in group 1 vs. group 2 (anti-dsDNA: week 21, 0.0738 [0.045-0.104] vs. 0.1878 [0.136-0.242] $p < 0.0001$; week 25, 0.1030 [0.077-0.104] vs. 0.3368 [0.093-0.414] p=0.035; week 29, 0.3385 [0.304-0.480] vs. 0.570 [0.412-0.665] p=0.034. Anti-C1q: week 21, 0.1260 [0.117-0.212] vs. 0.2536 [0.179-0.488] p=0.004; week 25, 0.2256 [0.218-0.271] vs. 0.3373 [0.321-0.491] $p < 0.0001$; week 29, 0.3698 [0.309-0.457] vs. 0.8285 [0.436-0.903] p=0.018). Proteinuria (mg/dL) was delayed and significantly lower in group 1 vs. group 2 (week 21: 0 vs. 15 [0.00-15.00], p=0.002; week 23: 0 vs. 15 [15.00-97.50], $p < 0.0001$; week 29: 65 [30.00-150.00] vs. 300 [100.00-2000.00], p=0.034).

Both survival and proteinuria-free survival (i.e. proteinuria < 300mg/dL) were significantly prolonged in group 1 vs. group 2 (p=0.019 and p=0.017).

Fibrotic markers were decreased and inversely age-related in group 1, while they increased with age in group 2.
Conclusions: Early administration of SERPINB3 significantly improves disease course and delays glomerulonephritis onset in lupus-prone mice.

P231

Resveratrol Possesses Protective Effects in a Pristane-induced Lupus Mouse Model
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Background: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterized by the production of autoantibodies. To date, no therapy has been found to satisfactorily treat SLE. SIRT1 deficiency results in the development of an autoimmune syndrome in mice, including a high titer of anti-nuclear antibody in serum, immunoglobulin deposition in the kidney, and immune complex glomerulonephritis. Resveratrol is an activator of SIRT1 and possesses anti-inflammation and immune-regulatory properties.
Objective: To evaluate the preventive effects of resveratrol on a pristane-induced lupus animal model and assess its putative immune modulation effects.
Methods: BALB/c mice received a single intraperitoneal injection of 0.5 ml of pristane on day 1 and then various doses of resveratrol were given to the mice daily starting on day 2 and continuing for seven months. The autoantibodies in serum and supernatants were measured. Single cells isolated from spleen, isolated CD4+ T cells, and CD19+ B cells were cultured with or without resveratrol in vitro and assessed by flow cytometry.
Results: Resveratrol attenuated proteinuria, immunoglobuin depositon in kidney, and glomerulonephritis in pristane-induced lupus mice. Resveratrol also suppressed CD69 and CD71 expression in CD4+ T cells as well as T cell proliferation, induced T cell apoptosis, inhibited the Th1 cell percentage, and decreased the ratio of Th1/Th2 cells in vitro. Antibody production and proliferation of B cells in vitro were also inhibited.
Conclusion: Resveratrol possesses protective effects in pristane-induced lupus mice and may represent a novel approach for the management of SLE.

P232

Characterization of CD4+ T cell response and effects of regulatory T cells in pristane induced lupus (PIL)
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Background: CD4+ Tcells play a pivotal role in SLE and the Th1 subset is attributed with pathogenic importance. Regulatory Tcells (Treg) are essential for maintaining peripheral tolerance, but their number and function in SLE is decreased. We characterize CD4+Tcell and Treg homeostasis as well as the effects of intravenous administration of exogenous Treg on disease severity in a model of induced systemic lupus.
Methods: Mice were injected i.p. with 0.5ml of pristane or PBS as control and killed after 8 months. Upon pristane injection, mice develop ectopic lymphoid tissue within the peritoneum (“granulomas”). Lymphocytes were isolated from granulomas, lymphnodes (LN) and spleens and were analyzed separately by FACS. Upon in vitro restimulation, Tcells were analyzed for their Th1, Th2 and

Th17 phenotype. Naive CD4+ thymocytes were sorted and cultured: Treg suspensions with >80% CD4+FoxP3+ cells were injected intravenously when PIL was induced (5x106 Treg); in a pilot experiment Treg (1x106) were injected monthly.

Histological specimens were obtained from joints and inner organs; disease severity of arthritis and pneumonitis was assessed using an image analysis system (Osteomeasure®).

Results: We found similar frequencies of CD4, CD8 and CD19 in spleens and LN of PIL and controls as well as similar ratios of activated Teff/Treg (ranging from 0.4 to 0.6). Intraperitoneal granuloma typical for PIL appeared to be the hotspot of inflammation: Although the frequency of CD4+ cells was similar to the other sites, there was a significantly elevated Teff/Treg ratio of 1.3 ($p < 0.0001$). Upon re-stimulation, CD4+ cells showed a pronounced Th1 response (27% IFNγ producers) compared to LN and spleens from both PIL and HC (with Th1 percentages ranging from 9-16%), but also frequencies of Th2 and Th17 cells were elevated in PIL. The single injection of exogenous Treg reduced the Teff/Treg ratio in PIL granuloma to 0.7.

Clinically, PIL most frequently presented involvement of lungs (100% pneumonitis) and joints (58% erosive arthritis). Analyzed after 8 months, the single injection of exogenous Treg did not prevent organ manifestations, but decreased their severity compared to PIL as indicated by a reduction of mean perivascular infiltrate (0.038±0.03 vs. 0.017±0.009 mm2, $p < 0.05$) and of numbers of affected vessels in lungs (mean 7.27±5.67 vs. 2.05±1.46, $p < 0.05$), as well as by a decreased erosive area in paws (mean 0.11±0.08 vs. 0.025±0.002 mm2, $p < 0.05$). The monthly injection of Treg appeared to completely prevent arthritis and to reduce pneumonitis (inflammatory area 0.002±0.002 mm2 and affected vessels 0.32±0.45, respectively), but did not reach statistical significance due to the small number tested.

Conclusion: PIL is a lupus model with typical organ involvement and an increased Teff/Treg ratio at the major site of inflammation. Exogenous Treg reduce the Teff/Treg ratio as well as the severity of pneumonitis and arthritis. Further experiments will investigate if monthly injected Treg are capable to treat or prevent organ manifestations in PIL.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 5 Epidemiology & Quality of Life"

Atlantico A+B+C

P233

The reliability, validity and responsiveness of the Thai version of systemic lupus erythematosus quality of life (SLEQOL-TH) instrument

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Objectives: The English version of the Systemic Lupus Erythematosus Quality of Life Questionnaire (SLEQOL) is a validated disease-specific quality of life instrument. The aim of this study was to evaluate the psychometric properties of the Thai version of the SLEQOL (SLEQOL-TH).

Patients and Methods: Two independent translators translated the SLEQOL into Thai. The back translation of this version was performed by another two independent translators. The final version, SLEQOL-TH, was completed after resolving the discrepancies revealed by the back translation. One hundred and nine patients with SLE were enrolled to test the reliability, construct validity, floor and ceiling effects, and sensitivity to the changes of the SLEQOL-TH at six months. The differential item functioning (DIF) between the Thai and English versions was analyzed using the partial gamma.

Results: The internal consistency of the SLEQOL-TH was satisfactory with the overall Cronbach alpha of 0.86. The test-retest reliability of the SLEQOL-TH was acceptable with the intra-class correlation coefficient of 0.86. Low correlations between the SLEQOL-TH and SLEDAI were observed. The total score of the SLEQOL-TH was moderately responsive to changes in quality of life, with a standardized response mean of 0.50. Comparing the SLEQOL-TH from Thai SLE patients with the original SLEQOL version obtained from Singapore SLE patients, 11 out of 40 items showed a moderate to large DIF.

Conclusions: The SLEQOL-TH has acceptable psychometric properties and shows construct validity. In comparison with the English version of SLEQOL, there are some items which showed DIF. The applicability of the SLEQOL-TH in real life clinical practice and clinical trials needs to be determined.

P234

Chinese SLE Treatment and Research group (CSTAR) registry: Influence of familial history on phenotypes in Chinese patients with systemic lupus erythematosus

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Background: It is well accepted that the genetic susceptibility to systemic lupus erythematosus (SLE) could lead to a relatively high incidence of familial cases. But the severity and outcome of familial lupus was reported not significant different from sporadic cases. There is by now no large perspective study on familial lupus in China. Chinese SLE Treatment and Research group (CSTAR) developed the first on-line registry of Chinese patients with SLE, which provides an opportunity to focus on this issue.

Objectives: The clinical phenotypes of familial cases were characterized in a large cohort of SLE patients recruited in CSTAR registry.

Methods: A prospective cross-sectional study of 2002 patients with SLE was based on CSTAR registry. Familial lupus (FL) patients were defined as patients who had at least another familial member diagnosed SLE. Sporadic lupus (SL) patients were defined as patients who had no familial history of lupus or other rheumatic diseases. Other patients with familial history of other rheumatic diseases (such as rheumatoid arthritis, primary Sjogren's syndrome and et al) were defined as the familial-sporadic-intermediate (IL) group. We explored potential differences such as demographic data, clinical characteristics, laboratory findings and SLE disease activity among these three groups.

Results: 34 patients (1.7%) were found to have familial history of lupus and 1907 patients could be confirmed as SL. 50 patients (2.5%) with familial history of other rheumatic diseases. There was no significant difference in age, gender, disease duration, or presence of abnormal pregnancy among these three groups. Clinical characteristics were compared, which revealed that prevalence of discoid erythematosus was significant high in FL and IL than in SL (14.7% vs 10% vs 5.4%, P=0.026). There was no significant difference in clinical manifestation, laboratory findings or disease activity at registry.

Conclusion: CSTAR registry firstly provided epidemiological data and phenotypes of Chinese patients with SLE, which revealed that familial history did not significantly impact on phenotypes. But a long-term cohort study on outcome should be conducted to confirm the conclusion.

Table 1. Comparison of SLE phenotypes with or without familial history

Manifestation	*FL (n=34)*	*SL (n=1918)*	*IL (n=50)*	*p Value**

(continued)

Table 1. Continued

Manifestation	*FL (n=34)*	*SL (n=1918)*	*IL (n=50)*	*p Value**
Malar rash	20(58.8%)	927(48.3%)	17(34.0%)	0.061
Discoid rash	**5(14.7%)**	**103(5.4%)**	**5(10%)**	**0.026**
Photosensitivity	11(32.4%)	476(24.8%)	18(36.0%)	0.125
Oral ulcers	7(20.6%)	417(21.7%)	17(34.0%)	0.116
Nonerosive arthritis	16(47.1%)	1050(54.7%)	35(70%)	0.065
Pleuritis or pericarditis	3(8.8%)	314(16.4%)	13(26%)	0.093
Renal disorder	16(47.1%)	907(47.3%)	28(56.0%)	0.476
Neurological disorder	0(0%)	97(3.1%)	0(0%)	0.110
Hematological disorder	20(58.6%)	1075(56.0%)	28(56.0%)	0.949

P235

Cardiovascular morbidity in a long-term follow-up cohort of Systemic Lupus Erythematosus patients in Southern Sweden

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The main objective was to study the incidence of myocardial infarction in a cohort of patients with Systemic Lupus Erythematosus (SLE) assembled prospectively over 25 years within a geographically defined area in Southern Sweden.

All SLE patients living within a defined geographical area in Southern Sweden between 1981-2006 were included in the study. The patients were observed prospectively within a structured follow-up program. Myocardial infarctions (AMI) were registered according to the definitions in the SLICC/ACR organ damage index during follow-up. The frequency of AMI was compared with the general population in the same area. Population data on AMI in the study period 1981-2006 were obtained through central databases (Socialstyrelsen). Data were stratified for age and sex.

The health care district of Lund-Orup had a mean population during 1981-2006 of 176.460 persons (> 15 yrs of age). One-hundred seventy-five new cases were diagnosed with SLE from 1981-2006. There were 148 women and 27 male patients that received the diagnosis of SLE, with a mean age of diagnosis at 44.3 years. Average follow-up time was 12,4 years from the time of diagnosis. There were 23 cardiovascular related deaths during the study period. Females between the ages 45-54 had an increased risk for acute AMI compared to healthy paired controls (SIR 12,4 (95%CI 1.4-45). In the other 10-year age groups, both for males and females, no significant differences were found.

Acute myocardial infarction is more prevalent in females between the ages 45-54 with SLE compared with the population in a geographically defined area in southern Sweden.

P236

Demographic and socioeconomic profiles of 525 Brazilian patients with systemic lupus erythematosus

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Introduction: Systemic Lupus Erythematosus (SLE) is a prototype of autoimmune disease with polymorphic clinical manifestations. Studies have showing some differences of the clinical profile and outcomes depending of demographic, educational and socioeconomic status. Brazil is a country with continental dimension and presents a great socioeconomic variability between states.
Objective: to evaluate demographic and socioeconomic profile of 525 Brazilian patients attended in two states (Alagoas and São Paulo).
Methods: Inclusion criteria were: SLE according ACR classification criteria; ≥ 12 months of diagnosis; age > 18 years and signature of informed consent form approved by Institutional Ethic Committee. Beside of personal interview, the medical charts were reviewed to fulfill the study protocol. Disease activity was evaluated using MEX-SLEDAI score and the organ damage by SLICC/ACR score. Patients were classified according to the Brazilian Institute of Geography and Statistics (IBGE) criteria into five socioeconomic status (A - highest to E- poorest). The race was auto-nominated as white, mulatto, black and yellow (IBGE criteria). Education was evaluated according to the years of formal education (schooling years). Data are presented as descriptive statistics (mean and standard deviation or median with maximum and minimum value).
Results: The mean age at diagnosis: 28±10.3 years, the age at the study: 38±11.4 years and the mean disease duration: 9.7±6.6 years. Ninety-seven percent were women. The mean MEX-SLEDAI score was 1.8±2.8, varying from zero to 18. The classification according the race was: white (49%), mulatto (38%), black (11%) and yellow (2%). Forty-five percent were married. The mean schooling time was 10.2±3.4 and 47% completed the secondary school. Sixty-seven percent of patients were not working and among those 65% were men and 63.6% were women. Thirty percent of patients received benefit of health. 80% of patients from Alagoas state and 84% from São Paulo state were classified as class D and E (the poorest). Higher percentage of patients in São Paulo (81%) than in Alagoas state (67%) answered that is unable to pay for their own treatment; and higher percentage of patients in São Paulo (91%) than in Alagoas state (54.2%) was receiving medication for SLE treatment from the government (free). 84% of patients were treating at public services and 16% at private services. 49% of patients spend 1 to 2 hours and 25% of patients spend more than 2 hours to go from the home to the medical service. Eighty-one per cent of patients answered that attendant physician give a good explanations about the disease and considered their treatment as adequate.
Conclusion: most patients belong to the lower socioeconomic classes and depend on the government for access to medical treatment in both states. São Paulo state offer more free treatment than Alagoas. Despite the unfavourable socioeconomic status and the difficulty to access the health service, the majority of patients considered the treatment as adequate at both state.

P237

Late-onset Systemic Lupus Erythematosus: prevalence, survival, causes of death in a monocentric cohort of 330 Italian patients

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Background: Late-onset Systemic Lupus Erythematosus (LOSLE), defined as disease onset over 50 years, is not frequent, and it is considered rare over 65 years. It is associated with insidious onset, more benign course, but higher mortality.
Objectives: To evaluate the prevalence of LOSLE in a monocentric cohort of Caucasian Italian patients, survival, causes of death.
Methods: Information were retrieved from the database of patients with SLE attending our institution from 1970 to 2008, diagnosed according to the 1982 ACR criteria; clinical and serological manifestations, at the time of diagnosis and in the successive follow-up, were checked for. Death events, causes of death and survival rates were calculated.
Results: Data from 330 patients (W 298 and M 32) were analyzed. The mean age at diagnosis was 40.9 years; 96 patients out of 330 (29%) had LOSLE at the time of diagnosis, and 27 of them were over 65 (8%).

During the follow-up 34 patients died: 18 had their disease onset over 50 years (14 W, 4 M) and 7 of them were diagnosed over 65 years (5 W, 2 M). Kaplan – Meier survival curves, stratified by age at diagnosis (more or less 50 years), showed a significant divergence ($p < 0.0001$), demonstrating a worse survival for LOSLE patients.

The mean age of death, in patients diagnosed after 65 years (5W,2M), was 86,6 years for women and 77,9 for men, and the causes of death were heart failure, Alzheimer, cancer, myocardial infarction, infections.

Among patients, diagnosed between 50 and 65 years (9 W, 2 M), the mean age of death was 73.5 and 70.5 years for women and men respectively, and the causes of death were infections, cancer, hepatic failure, neuropsychiatric complications, cardiac failure, haemolytic acute anaemia.

Patients, diagnosed before 50 years (15 W and 1 M), died for infections, neuropsychiatric complications, cancer, uraemia, heart failure; the mean age of death was 52.7 for women and 49 for the man.

Conclusions: SLE onset over 65 years does not seem associated with a significant decreased life expectancy, appeared less severe and the causes of death were mainly associated with aging process.

In patients who developed the disease between 50 and 65 years, SLE related complications, treatment side effects and aging-related comorbilities seem to play a major role in determining the conditions leading to death; in younger patients (< 50 yrs) mortality did prove principally due to disease activity and therapeutic complications.

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Dyspigmentation and Scarring in Cutaneous Lupus: The Impact on Quality of Life

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Background: Patients with more severe cutaneous lupus (CLE) activity have a poorer quality of life (QoL). Racial and ethnic disparities have been reported in disease activity and outcomes in SLE but similar information is not available in CLE. The main objective of the current study was to evaluate the impact of lupus-related skin damage on skin-specific QoL, as well as differences stratified by ethnic backgrounds.

Patients and Methods: Data was collected between January 2007 and November 2011. Data included sex, race, diagnosis, Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI) scores, and Skindex-29 scores. These parameters were analyzed at the initial and last visits. CLASI damage scores (dyspigmentation and scarring) and CLASI activity scores were collected, grouped by ethnicity, and correlated with Skindex-29. 223 patients were analyzed at baseline, with 141 of these patients completing more than one study visit.

Results: The majority were Caucasians (63.7%), followed by African Americans (29.1%) and Asian Americans (4.0%). African American patients accounted for a disproportionate percentage of both localized (50% of cases) and generalized (48.9% of cases) DLE. Median CLASI damage scores significantly differed between our African American, Caucasian, and Asian American patients, at both first (8.5, 4.0, 7.0) (Kruskal-Wallis $p < 0.0001$) and last visit (10.0, 6.0, 8.5) (Kruskal-Wallis $p < 0.01$) (Dunn's Multiple Comparison $p < 0.0001$, $p < 0.01$). CLASI damage scores in African Americans correlated with CLASI activity scores (Spearman's $r=0.4480$, $p=0.0003$). Individually, dyspigmentation and scarring also did not have a significant effect on QoL.

Conclusion: Lupus related disease damage does not affect QoL, as measured by the Skindex-29. Ethnic differences in CLE patients were found: African American patients with CLE, do exhibit a high rate of DLE, experience damage early in their disease course, frequently in conjunction with disease activity.

P239

Malignancies in systemic lupus erythematosus: early appearance in the course of the disease

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Background: There is strong evidence in the literature that patients with systemic lupus erythematosus (SLE) have an increased risk of later developing cancer, especially lymphoproliferative disorders such as non-Hodgkin lymphoma, which could be explained by changes in the immune system and/or chronic immunosuppressive use. The aim of the present study was to evaluate the frequency and type of cancer in our large SLE population.

Patients and Methods: A total of 1,364 SLE patients (ACR criteria) in regular follow-up in our tertiary single center, from 2001 to 2011, were evaluated. The presence of cancer (histology) and its temporal relationship with SLE, as well as demographics and disease features, and their relationship with immunosuppressive therapy were analyzed.

Results: Malignancies were identified in 30 SLE patients (2.2%) of the total (27 women and 3 men). At the time of neoplasia diagnosis, the mean age of women and men was 55.2 ± 13.3 and 68.0 ± 8.9 years, respectively ($P=0.12$), with mean disease duration at neoplasia-onset of 17.5 ± 15.0 years. Half of cancer cases were identified after 10 years of SLE and 36.7% during the first 10 years of its course. Neoplasia diagnosis was prior to SLE onset in only two cases (6.7%) and concomitant to SLE diagnosis in other 2 (6.7%). The distribution of primary malignancy was: breast (26.7%), thyroid (16.7%), lung (10.0%), uterus (10.0%), skin (6.7%), pituitary (6.7%), parathyroid (6.7%), stomach (3.3%), colon (3.3%), central nervous system (3.3%), salivary gland (3.3%), and ovary (3.3%). Interestingly, no lymphoproliferative disorders were identified in this cohort. The frequency of SLE characteristics and immunosuppressive use was comparable in SLE patients with and without cancer ($P > 0.05$).

Conclusion: In this large SLE cohort, a high frequency of solid tumors unrelated to the immunosuppressive use was identified even in early stages of the disease.

P240

Socio-demographic factors, psychological symptoms and disease features influence on health related quality of life in chilean women with systemic lupus erythematosus

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Introduction: Socio-demographic and psychosocial factors play an important role in the course of Systemic Lupus Erythematosus (SLE), as well as disease features. These aspects influence the Health Related Quality of Life (HRQoL).

Objective: To evaluate HRQoL in a sample of women with SLE, determining associations with socio-demographic factors, psychological symptoms and disease features.

Methods: Cross sectional study in 82 Chilean females with SLE, recruited between July 2008 and December 2010 at the Health facilities of the "Red de Salud de la Pontificia Universidad Católica de Chile". Factors considered were age, years of education, actively working/studying, marital status, SLEDAI2K, SLICC, and disease duration. Patients completed the self-reported Hospital Anxiety and Depression Scale (HADS), subscales for anxiety and depression, and fulfilled the SF12 HRQoL questionnaire (best score 100), comprised of 8 domains (PF: physical function, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF social function, RE: role emotional, MH: mental health) and 2 summary scores (PCS: physical

component summary, MCS: mental component summary). Statistics: U Mann-Whitney, Pearson and Spearman correlations between sociodemographic factors, psychological symptoms, SLE features and SF12 scores were used ($P < 0.05$). QoL data from The National Survey ENCAVI 2006 of 2,536 women of similar age from the Chilean general population were obtained, with permission.

Results: Patients median age: 36 years (range 17-64), education: 14 years (8-21), actively working or studying: 63%, SLEDAI2K: 6 (0-25), SLICC: 0 (0-4), disease duration: 2 years (0.1-20). SLE patients considered their HRQoL as impaired at least standard deviation lower than general population; ranging from 29.65 to 44.74 (GH), and from 47.75 to 57.81 (VT), in SLE and the GP respectively ($P < 0.01$). Depression and anxiety higher scores correlated significantly with worse HRQoL in all domains and summary scores, excepting for anxiety which did not correlate with PCS. Higher SLEDAI2K scores correlated with worse RP, BP and PCS. Longer disease duration correlated with lower VT. Patients having a higher number of education years had better SF. Those patients actively working/studying had lower BP. No influence of age, marital status or SLICC on HRQoL was observed.

Conclusions: Patients with SLE have worse HRQoL than the general population. Disease activity impact may not be as relevant as psychological factors on HRQoL. Depression and anxiety affect all domains of HRQoL Interestingly, patients working or studying are those with less bodily pain. Pain, depression and anxiety are important aspects that should be addressed in order to improve HRQoL in SLE.

Disclosure: None

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Background: Despite the recognition that SLE is a severe disease with a major impact on the lives of patients, few studies have evaluated the psychological functioning of patients with SLE.

Patients and methods: Perception of the disease of 72 patients (11 male) with SLE according to ACR criteria and without other autoimmune diseases was evaluated in seven focus groups by a medical psychiatrist applying a semi-structured interview. Statistical analysis: Grounded theory was applied which was conducted by open, axial and selective encoding. **Results:** Mean age 30, 3 ± 11.8 (12-65). 84.7% women, median of disease duration 6 years (2-13), 77.7% living in a couple; 51% have college/university education. Most of patients are unemployed (68%).

Results:

Axial categories	*What patients think*
1. **The notification of the diagnosis** Why me? How patients get information about Lupus.	At diagnosis the doctor was not clear with the explanation of what lupus is, its causes and how to treat it, some of them turned to the Internet where they got more confusing answers
2. **Causes of the disease.** Auto guilt, mood and emotional problems as major factors in the disease.	Heredity, eating habits, environmental pollution, witchcraft and divine punishment. "A woman made me a curse"
3. **Family, social and work consequences**. • The disease is not noticeable on the outside. The patient "simulates" the symptoms. • Work problems • The importance of family and social support for patients. Vital resignations due to the disease.	Patients, at some time of the course of their disease have been branded as liars or simulators by other people. "my ex-wife left me because she did not believe I was sick"
4. **The difficulties in establishing the diagnosis**	Many patients felt puzzled to see that for several months or even years their symptoms had no logical explanation for them and even for doctors.
5. **Non-pharmacological or alternative treatments, poor adherence to drug treatment and rejection**	Almost all patients have tried some type of alternative therapy for the treatment of Lupus: acupuncture, apitherapy.
6. **Weaknesses identified by patients in health care.**	Opportunity for medical appointment with a rheumatologist.
7. **Disease Awareness:** Need for self-care, Lupus a deadly disease.	All patients manifest a hopeless about the future

Conclusion: SLE as a disease closely related to death requires interdisciplinary management and psychological support to patients and their families from the time of diagnosis and during the course of the disease. It is necessary to explain patients and their closest relatives all about lupus in order to generate an adequate doctor-patient relationship. While there is little evidence if perception of the disease may change with treatment, specifically cognitive behavioral therapy, is important to incorporate these assessment tools of perception of the disease in all patients with lupus to explore whether the representations of the disease may predict response to interventions.

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Analysis of focus groups in Colombian patients with Systemic Lupus Erythematosus: A qualitative view to illness representations.

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P242

Cognitive Impairment in Patients with Systemic Lupus Erythematosus: Association with Quality of Life, Functional Capacity and Disease Damage.

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Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease and patients can present with neurologic and psychiatric symptoms that lead to significant morbidity. The availability of questionnaires has allowed clinicians to screen for cognitive

impairment. Our objective was to evaluate the association of cognitive impairment with quality of life, functional capacity, and disease characteristics in patients with SLE.
Material and Methods: We studied 81 consecutive patients with SLE, who are participating in an ongoing clinical investigation to evaluate neuropsychiatric manifestations. Eligible patients fulfilled the 1997 criteria of the American College of Rheumatology for SLE and were over 18 years of age. Patients were recruited from the outpatient rheumatology clinic at Hospital Nacional Edgardo Rebagliati in Lima, Peru. Patient assessment included a standardized interview, physical examination, and review of medical records. Cognitive impairment was ascertained by the Mini Mental State Examination (MMSE) test, quality of life by the 36-item Short Form Health Survey (SF-36), functional capacity by the Modified Health Assessment Questionnaire (MHAQ), disease activity by the SLE disease activity index (SLEDAI) and damage by the Systemic Lupus International Collaborating Clinics (SLICC) damage index. The data are presented as mean±SD. Cognitive impairment was defined as less than 25 points in the MMSE score. Differences between patients with and without cognitive impairment were evaluated using the Wilcoxon Rank Sum test. All analyses used a two-sided significance level of 5% and were conducted using STATA 12.0.
Results: Patients were 45.31±8.15 years-old, had a mean disease duration of 10.33±10.13 years and 92.59% were female. There were seven (8.6%) patients with cognitive impairment. Patients with cognitive impairment had lower SF-36 total scores (31.8±13.2 vs. 53.9±21.5, p = 0.008), lower physical health (34.3±13.8 vs. 54.3±21.6, p = 0.016), lower mental health (34.0±13.4 vs. 53.6±21.3, p = 0.021), higher scores of functional disability (1.0±0.6 vs. 0.39±0.6, p = 0.008), and higher disease damage (3.7±1.8 vs. 1.4±1.7, p = 0.008). (Table)
Conclusions: Our results suggest that patients with SLE and cognitive impairment had lower scores for quality of life, higher levels of functional disability and higher scores of disease damage than patients without cognitive impairment.

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Hospitalizations and mortality in Systemic Lupus Erythematosus

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Objective: To analyze discharges of Systemic Lupus Erythematosus (SLE).patients
Materials and Methods: Hospital discharges of 15-year-old patients or older with SLE (principal diagnosis ICD 10: M321, 328 and 329) during 2006, 2007, 2008 and 2009 in Argentina were analyzed, through data provided by the Department of Health Statistics and Information, Ministry of Health of Argentina.

There was no access to medical records or other patient information. The diagnosis of SLE is based on judgment of the physician who completes the report as recommended by the Health Statistics System and not according to the classification criteria of the American College of Rheumatology (ACR) for SLE.

Data are for hospitals from the Public Health System and therefore private for-profit, private not-for-profit, and some university-associated hospitals were excluded. Discharges were analyzed by sex, age, length of stay (LOS) and in-hospital mortality. Finally we compared in-hospital mortality in the provinces that had Human Development Index (HDI) above or below the national average (0.83) according to data from the United Nations Program for Development (UNPD 2009). The HDI is a composite index that includes measures of health, education and wealth.

Results: There were 3300 discharges for SLE in the period 2006-2009: 2794 were women (84.7%) and 506 were men (15.3%). The mean age was 32.3 years (32.1 in men and 32.3 in women, P 0.7). Patients were hospitalized 9.9 days on average (LOS 10.9 in men and 9.66 in women, P 0.1) and the in-hospital mortality rate was 3.4% (2.8 in men and 3.5 in women, P 0.4).

The mean age of patients who died during hospitalization was 38.5 years vs. 32.09 in routine discharges (p < 0.0001). The mean LOS was 17.5 days in patients who died vs. 9.59 in routine discharges (p 0.001).

When analyzing discharges in the provinces according to their level of development it was observed that the more developed ones (HDI > 0.83) showed a trend to a higher proportion of men (17.3 vs. 14.5 in the others provinces, P 0.05), lower mean age (31.5 vs. 32.6, P 0.06), shorter mean LOS (8.85 vs. 10.28, P 0.07) and lower in-hospital mortality (2.6 vs. 3.7, P 0.1) although none of these differences were statistically significant. In the provinces with HDI > 0.83 the mean age of patients who died was 38.56 vs. 38.45 in the other provinces. (P 0.9).
Conclusions: No differences were observed in the mean age, mean LOS and in-hospital mortality between men and women. Older patients and with longer stays had worse prognosis. There was no difference in the in-hospital mortality rate between the more and less developed provinces, which could at least be detected through the HDI.

P244

Quality of Life Estimation and Utility Values in Patients with Systemic Lupus Erythematosus in a Fourth Level Complexity Universitary Hospital

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Background: Health-related quality of life (HRQoL) is a concept that affects several dimensions: physical, mental, cultural, sexual, psychological and social, as well as specifric disease-related factors, and treatments, independent of clinical improvement.Systemic lupus erythematosus (SLE) is a chronic disease that interferes with all these aspects, being mood disorders, depression, and anxiety common in these subjects and influenced by: pathophysiological mechanisms, the use of immunosuppressive agents, adaptation to chronic disease and psychosocial factors. The possibility of irreversible organ damage secondary to SLE activity or treatment, inevitably, influences the quality of life of these individuals, being a primary outcome in the prognosis of the disease. The aim of this study was to determine HRQoL and utility values in a cohort of patients with SLE and evaluate its correlation with activity and chronicity in a fourth level complexity universitary hospital.
Material and Methods: Design: Observational, descriptive, cross-sectional study. Patients or Participants: 152 subjects with SLE according to American College of Rheumatology (ACR) 1997 criteria. Interventions and Measurements: Assessment of HRQoL using the SF-36 instrument, utility values, psychological and social parameters related to the impact of the disease with the HAD scale, the Duke UNK questionnaire and its association with SLE disease activity with SLEDAI index and organ damage by SLICC/ACR index. Statistical Analysis: Mann-Whitney test to compare the median value for each of the domains; Spearmańs Rho correlation coefficient to estimate associations between each of the domains of the SF-36 scales with HAD, Duke-UNK, SLEDAI, and SLICC/ACR.
Results: 90.1% of subjects were women. Median age: 36 years (27-44). The average values of the HRQoL domains ranged from 52.9 to 67.3 to

physical performance domain and social function domain, respectively. These domains reported the highest values, showing a high positive correlation with higher scores on measures of physical and mental domains, respectively ($r = 0.805$ and $r = 0.771$, $p < 0.0001$). Scores for each of the domains and summary measures were higher in males, and this difference was statistically significant for the following domains: general health, mental health, social functioning and vitality ($p = 0.017$, 0.002, 0.008, and 0.003, respectively). The associations between the SF-36 domains with HAD scales, Duke-UNK, SLEDAI, and SLICC/ACR, showed weak correlations ($r < 0.45$) that were not statistically significant, except for social support variable (Duke-UNK), with which it was determined some type of association. Regarding HAD anxiety scale and the mental health domain, the relationship was negative and high ($r = -0.76$, $p = 0.0001$).
Conclusion: The majority of patients with SLE had a HRQoL located above the 50th percentile. The dimensions involved were related to physical, mental, and social domains.

P245

Clinical and immunological features of 888 systemic lupus patients from a monocentric cohort in Brazil
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Background: Epidemiological studies with systemic lupus erythematosus (SLE) patients have been reported worldwide but a large evaluation was not performed in our country. Therefore, the aim of the present study was to assess clinical and immunological features in our cohort of SLE patients and to identify differences according to gender.
Patients and Methods: The present study involved 888 consecutive adult SLE patients (ACR criteria) regularly followed at our center from 2008 to 2012. Data were obtained from the ongoing electronic database protocol carried out for all SLE patients at 1 - 6 month intervals, including those relevant for this study. Cumulative clinical and laboratorial features of SLE patients according to gender were recorded for analysis.
Results: The mean age at SLE onset was 29.9±9.5 years-old and the mean disease duration 14.5±8.4 years. A predominance of female gender (91.9 %) and Caucasian (69.9%) were observed. Cumulative mucocutaneous manifestations (90.7%) were most commonly identified [malar rash (83.2%), photosensitivity (76.9%)] followed by articular (87.4%), hematological (44.0%), and renal (36.9%) involvements. Antinuclear antibody was detected in all patients, anti-dsDNA in 35.1%, anti-Sm in 21.8%, and anti-ribosomal P protein antibodies in 19.8%. According to gender, only malar rash was statistically more prevalent in female patients (84.5% vs. 69.5%, P=0.001). In contrast, male lupus patients had a higher frequency of anti-dsDNA (45.8% vs. 34.2%, p=0.047) and a trend of more nephritis (47.2% vs. 36.0%, p=0.059).
Conclusion: A high prevalence of mucocutaneous manifestations was identified in this Brazilian SLE cohort compared to other countries. Malar rash was most commonly observed in female patients whereas renal disease and anti-dsDNA in male gender.

P246

The Relationship Between Anxiety, Depression, Somatisation And Clinic Findings And Quality Of Life In Patients' With Systemic Lupus Erythematosus
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Objective: Life quality of patients with systemic lupus erythematosus (SLE) is prominently deteriorated. Recently, new scoring methods of measurement have developed to evaluate systemic lupus erythematosus-quality of life (SLE-QOL) beside activity and severity indexes. We herein attempt to validate the Turkish version of SLE-QOL scoring, and to elucidate its association with clinical findings and diseases activity indexes.
Material and Methods: Sixty-four females fulfilling the American Collage of Rheumatology criteria on SLE were enrolled into study (median age: 38.2±11.7). Clinical, demographic and laboratory findings of all patients have been detected from patient files and recorded to a special form. While subjects were questioning for the SLE-QOL, simultaneously, diseases activity scores of all patients measured with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). SLE-QOL included 34 questions related with physical health, emotional health, body image, pain level, future planning, fatigue, intimate relationships, and burden to others. Patients were asked to respond these questions in terms of their state of nature within the last week. Also all subjects were questioned for anxiety (HADS-A), depression (HADS-D), and somatisation symptoms scores (SSC).
Results: Of the total SLE patients, twenty-three patients had renal, 10 patients had neurologic, and thirty had hematologic involvement. The age was positively correlated with and HADS-A score (r=0.38, p=0.011) and SSC score (r=0.3, p=0.05). Moreover, diseases duration was positively associated with pain score (r=0.37, p=0.015), HADS-A score (r=0.32, p=0.05), and intimate relationship (r=0.39, p=0.01). However, SLEDAI score was negatively correlated with intimate relationship (r=-0.34, p=0.025).

HADS-D score of the SLE patients those concurrently having Raynaud's phenomenon (RP) was significantly elevated comparing to others (7.03±4.3 vs. 3.7±3.8, p=0.016). The SLE patients with renal involvement had significantly increased scores of future planning (42.6±23.4 vs. 27±22.9, p=0.033) and HADS-D score HADS-D (7.4±4.9 vs. 4.2±3.1, p=0.016). SLE patients with Anti–dsDNA autoantibody positivity had significantly higher SLEDAI scores, and significantly lower physical health (48.8±41.3 vs. 77.4±51.7, p=0.049), intimate relationship (43.5±+49.6 vs. 85.7±67.7, p=0.023), burden to others (34.5±33 vs. 60.9±38.8, p=0.028), HADS-A score (6.14±3.9 vs. 10.04±4.1, p=0.003) and SSC score (1.14±1.5 vs. 3.04±1.9, p=0.001). Beside that SSC score of the SLE patients with anti-nucleosome positivity was significantly lower (0.7±1 vs. 2.4±2, p=0.003).
Discussion: Presence of renal involvement in SLE patients negatively affects the life quality of patients, particularly depression, and future planning. Anti–dsDNA autoantibody positivity is associated with diminished SLE-QOL score. However, low anxiety and somatisation score in SLE patients with anti–dsDNA autoantibody positivity was explicitly striking.

P247

Implementation of a model of renal health network for early detection and care of primary lupus nephropathy and glomerulonephritis in the colombian caribbean region
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Introduction: The latin american register of Nephrology reports the prevalence of Lupus Nephritis (LN) and Primary Glomerulonephritis (PGN) as a cause of chronic kidney disease (CKD) is 19.3%

There are many publications around the world on LN and PGN, in the Colombian Caribbean region, there are no data that analyzes their behavior and often these patients end up in CKD, increasing this problem of public health, that negatively impacts to this region in extreme poverty

The General system of Social Security of health presents faults such as the access barriers and lack of a model of integral care, that allows capturing patients at high risk of kidney disease in early stages and provides an effective management. It is then necessary to characterize LN and PGN

This is an applied research of development and technological innovation for design and implementation of a Territorial Network of early detection of patients with NL with a renewed focus on secondary and tertiary prevention

Objective: To Implement a model of renal health network for early detection and care of the LN and PGN in the Colombian Caribbean region

Materials and Methods

The data base of NEFRORED was implemented with the variables of the clinical records of the patients from the Colombian Caribbean. The nephropathies studied were divided into: 1) PGN and 2) LN classification International Society of Nephrology/Renal Pathology Society (ISN/RPS).

TICS were used for the collection of information as facilitator and strengthen element of the work, and effective collection of the required information from any geographical point, from each specialist Office

A web portal has been designed, under the domain www.nefrored.org. hosted in the Datacenter of the Simon Bolivar University of Barranquilla, which fulfills with the basic regulations of safety and availability for data and information networks

Results: Among the most relevant features we mention, at software level, the development of the portal that was made under PHP following appropriate methodology of development for the project and oriented toward the collection and analysis of information; the database is supported in a fully normalized relational structure and uses mySql as motor.

Currently, the network includes 17 notifiers units distributed in 7 departments. From January 2008 to October 2012, 805 biopsies of adults were studied; they showed that 68.03% were secondary to LN and the 31.97% to PGN. 83% of patients belonged to the mestizo race and 81% to the female sex. In the activity, according to renal biopsy, 65% of the patients had an index between 1 and 8, and 33% between 9 and 17.

Conclusions: A Renal health program implemented in the Colombian Caribbean for detection of patients with PGN and LN is a light for the timely identification of these patients. A model of intervention through the implementation of a regional network of patients with LN and PGN allows us to establish prevalence, geographic distribution, clinical epidemiological characterization and integral management with defined protocols for each case that allow to prevent CKD and establish protocols of adhesion that have permitted a better following of these patients.

P248

Review of the use of Health Related Quality of Life (HRQoL) Measures in Clinical Trials in Adults with Systemic Lupus Erthematosus (SLE)

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Background: The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recommended that patient-reported outcome (PRO) measures should be included during the assessment of a medical product in clinical studies. The aim of this study is to explore the use of validated multi-dimensional HRQoL measures used in randomized clinical trials undertaken in adults with SLE.

Methods: The following databases were searched using the key words "lupus" AND "trial": Ovid Medline, Embase and Cochrane Central Register of Controlled Trials. The search was limited to English, from January 2006 until October 2012 and to randomized clinical trials of medical products in SLE patients with active disease. Phase I and Phase II trials and trials focussing on cutaneous lupus and alternative medical products were excluded. When multiple papers for the same trial were reported, the paper that included the description and results of the primary and secondary outcomes was taken into consideration. Forty studies were identified. In accordance with CONSORT guidelines, we determined whether mutlti-dimensional HRQoL was assessed as an outcome measure in these studies and if the findings of the HRQoL were reported.

Results: More than half (n=25) of the clinical trials were undertaken in patients solely with active lupus nephritis. Only one of these employed a HRQoL PRO, as a primary outcome measure. Eleven of the remaining trials employed a HRQoL PRO, in five as a primary outcome measure and the rest as a secondary outcome measure. All 12 studies used the generic SF-36 and one study also used the SLE Symptom Checklist (SSC). All these studies reported the results of the HRQoL findings. No other disease-specific HRQoL measures were used in the 40 studies identified.

Conclusions: Among the HRQoL measures that have been validated in adults with SLE, the generic SF-36 is the most commonly used measure to assess HRQoL in clinical trials. The SSC is the only disease-specific measure employed in these trials and only in one study. HRQoL as an outcome measure was more widely assessed in clinical trials of interventions targeted at active multi-system disease rather than solely active lupus nephritis. Although recommendations from the FDA and EMA have encouraged incorporation of multi-dimensional HRQoL PROs as part of the outcome measures in clinical trials, only just under a third of the randomised clinical trials in adult SLE patients in the last six years employed these tools.

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Air pollution decrease sperm quality in systemic lupus erythematosus patients

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Studies (n=40)	*Systems Active*	*Multi-dimensional HRQoL employed*	*Primary/secondary*	*HRQoL results reported*
1	Renal	SF-36 and SSC	Primary	Yes
11	Multi-system: including renal (n=10) excluding renal (n=1)	SF-36	Primary (n=5) Secondary (n=6)	Yes
28	Renal (n=24) Articular & cutaneous (n=1) Multi-system (n=3)	None	Not applicable	Not applicable

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Background: Exposure to air pollution has been reported to affect male reproductive outcomes, particularly sperm quality, however this issue was not studied in systemic lupus erythematosus (SLE) population. Therefore, the objective of the present study was to investigate the correlation between exposure to concentrations of air pollutants in the Sao Paulo metropolitan region and the semen quality in SLE patients.
Methods: From 2000 to 2006, in a longitudinal panel study, we obtained 56 semen samples from 28 post-pubertal SLE patients, between 17 and 42 years, attending at the Pediatric Rheumatology Unit and Rheumatology Division, of our University Hospital. All patients fulfilled the ACR SLE classification criteria. Daily concentrations of inhaled particulate matter (PM10), sulfur dioxide (SO2), nitrogen dioxide (NO2), ozone (O3) and carbon monoxide (CO), and meteorological variables were evaluated on 90 days before semen collection dates. The generalized estimation equation (GEE) model was used to assess the impact of these measurements on the sperm concentration, total spermatozoa per ejaculate (count) and progressive motility, considering the effects for repetitive measurements. Changes were analyzed, mainly, during the key periods of spermatozoa development, which correspond to epididymal storage, development of motility and spermatogenesis (0-9, 10-14 and 70-90 days before collection, respectively). The regressions were adjusted for prednisone and/or immunosuppressant use, smoking, alcohol consumption, time of sexual abstinence, altered gonadal function, presence of lower testicular volume, presence of varicocele, use of others medications, current age, educational level, temperature and relative humidity.
Results: Sperm concentration and count were negatively associated with exposure to ozone 80-90 days before the date of sample collect. The cumulative effect of a nine days exposure (from lag 80 to lag 88) to an increase of 10μg/m^{3}in ozone was associated with a decrease in sperm concentration of 9.7 million per mL (95% CI, 2.67-16.73). The cumulative effect in the two days (lag 80 and lag 81) after the exposure to ozone was associated with a decrease in total spermatozoa per ejaculate of 14.7 million per ejaculate (95% CI, 2.16-27.24). We did not observe pollutants' effect on progressive motility in the two weeks after exposure, but we found negative effect in six and seven weeks after that (from lag 31 to lag 38), when the eight-day cumulative effect of exposure to ozone was associated with a decrease of 2.86% (95% CI, 1.14-4.66) in progressive motility.
Conclusion: Ozone presents consistent adverse effects on semen quality of SLE patients. Consequently, besides all well known hazardous factors that contribute to worsening sperm quality, minimizing exposure to air pollution should be taken into account when therapeutic or preventive actions are adopted.

P250

Overlap syndromes of idiopathic inflammatory myopathies with systemic lupus erythematosus, systemic sclerosis or rheumatoid arthritis

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Background: Since OS is rarely described in literature, we analyzed patients with dermatomyositis (DM)/polymyositis (PM) with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) or rheumatoid arthritis (RA).

Patients and Methods. This is a single center retrospective cohort study from 1992 to 2012 that included 31 DM/PM (Bohan & Peter's criteria, 1975) associated to well-defined SLE (ACR criteria, 1997), SSc (ACR criteria, 1990), or RA (ACR/EULAR criteria, 2010). We excluded mixed connective tissue diseases.
Results: The 31 patients (9DM and 22PM) had 44.6±15.4 years-old, 83.9% female, 58.1% Caucasian. Overlap was observed with SLE, SSc and RA in 29.0%, 48.4% and 22.6%, respectively. Gender, ethnicity, and type of inflammatory myopathies were comparable among these overlap groups ($P > 0.05$). Clinical and laboratory manifestations of DM/PM onset in SSc occurred prior, simultaneously or after this disease in 6.7%, 66.7% and 26.6%, respectively, whereas in RA was observed in 0%, 71.4%, and 28.6%. In the overlap with SLE, DM/PM features was mostly identified prior lupus clinical manifestations in 44.4% (34.7 months), 11.1% simultaneously, and 44.4% after (34.7 months) (P=0.03). Interestingly, a male patient with SLE (mucutaneous, joint and renal involvements, positive ANA) after 11 months manifested DM symptoms (Gottron's signal, muscle weakness, elevated sera level of the muscle enzymes, muscle biopsy with fiber necrosis and lymphomononuclear cell infiltrations) and, subsequently, in 2 months, RA was also diagnosed [hands x-ray showed erosive lesions in addition to positive anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF)]. Concerning to autoantibodies, all patients demonstrated positive ANA. SLE group had anti-Ro (77.8%), anti-P ribosomal (55.6%), anti-Sm (55.6%), anti-dsDNA (33.3%), anticardiolipin (11.1%). The SSc group had anti-Scl70 (20%), anti-PM/Scl (6.7%), and anti-Ku (6.7%) whereas in the RA group, anti-CCP (85.7%) and RF (28.6%). Comparing the three overlap groups, the skin ulcers and Raynaud's phenomenon were higher observed in SSc group (P=0.05). However, these data may be due to overlap or inherent characteristics of SSc. Moreover, pulmonary involvement (P=0.005) and the presence of ground glass on computed tomography (P=0.01) were also more frequent in SSc group. Regarding follow-up, there was a trend of DM/PM relapsing and also deaths in SSc group when compared to other groups.
Conclusions: In OS, clinical manifestations of DM/PM were identified simultaneously with SSc and RA in majority of the cases, whereas in the SLE overlap they were observed mainly prior or after SLE diagnosis. A higher prevalence of OS was observed in Caucasian women and PM was the most frequent clinical form. Cutaneous and pulmonary involvement were more prevalent in the SSc group that demonstrated a trend of more DM/PM relapsing and deaths.

No conflict of interest (all authors)

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P251

Everyday home and personal product chemical exposure and flare events of Systemic Lupus Erythematosus (SLE).

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Abstract Disclosure Statement: No conflicts of interest related to this abstract or wider project.

Study Sponsor Statement: Abstract represents part of a PhD thesis 'Environmental Determinants of Lupus Flares', supported by the Autoimmune Resource and Research Centre and University of Newcastle Foundation Scholarship.

Study Approvals: Australian health and University research ethics governance committee approvals were obtained ensuring compliance with Declaration of Helsinki (2008).

Introduction and Background: Environmental and intrinsic factors play a pathogenic role in SLE through modulation of immune system regulatory responses. Stimuli such as UV sunlight, hormones, infection and stress are accepted symptom exacerbation effectors, however, reasons for flare occurrence often remain unclear.

Household product chemicals, time spent indoors, and household and personal hygiene practises may increase an individual's potential for environmental chemical exposure (ECE).

This study concentrates on household product usage patterns in 80 SLE participants defined by American College of Rheumatology (ACR) criteria, examining the correlation of product and chemical exposure with flare event days over one year.

Patients and Methods: ECE was established through retrospective self-report questionnaires responses (flare history, home environment, commercial product usage). Questionnaires were analysed to establish counts of SLE flare and ECE days over one year.

Definition and explanatory example of 'Flare' was included in methods to standardise participant understanding of what constitutes a flare.

ECE was estimated after collation of self-reported product/chemical exposure activity. A product and chemical exposure matrix (PACEM) was developed as part of this study: product chemical component groups were assigned using published literature, databases, labelled ingredients and material safety data sheets. Products were coded into 32 product groups and 29 chemical groups.

Product and chemical groups were allocated a binary score (''absence''/''presence''). Weighted scores were not assigned due to insufficient data regarding chemical concentrations within nominated products.

General linear modelling (negative binomial robust link function) was performed for flare, product and chemical exposure day counts adjusted for significant confounders ($p \leq 0.05$).

Results: Paradoxically, the use of immune-modulating therapy indicated an elevated risk of flare activity. Dose-response curves for products (make-up, adhesives and paint) and chemicals (epoxy resin, organotins and pigments) displayed nonlinear non-monotonic responses with consistent patterns within products and some chemical components.

Conclusions: Relative risk increase associated with immune-modulation therapy suggests that participants on therapy have more severe disease with sub-optimal clinical benefit from therapy.

The UV-protective effects of makeup and makeup pigments may reduce the number of flare days in photosensitive lupus patients. The lack of clear correlation between ECE and flares for other chemicals/products may be explained by such factors as small sample size, self-reporting bias, and the lack of accounting for chemical concentration, admixture and chemical multiplicative toxicity. Study size precluded modelling for observed dose-response nonlinear non-monotonicity.

A wider study incorporating biological and environmental sample analysis would strengthen ECE quantification and validate the PACEM tool. This would provide direct assessment of ECE and correlation with lupus flare activity.

Our study suggests that lupus flares reflect complex interactive chemical effects requiring nonlinear modelling.

P252

Supervised physical exercise improves fatigue, aerobic capacity and quality of life without worsening disease activity in patients with systemic lupus erythematosus

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Background: systemic lupus erythematosus (SLE) patients are less physically active, have lower aerobic capacity and exercise tolerance, worse quality of life and more fatigue than healthy controls. The **objectives** of this study are to evaluate the effect of physical exercise training on disease activity, quality of life, fatigue, perceived exertion and ergospirometric test variables in SLE patients.

Patients and Methods: it is a prospective, non-randomized study, in which women with SLE (18 to 45 years old) with availability to perform physical exercise program were allocated in exercise group (EG). Those who were not available were allocated in the control group (CG). Intervention consisted of walking at speed of the ventilatory threshold-1 (VT1) heart rate and monitored by frequencymeter, for one hour, three times a week, for 16 weeks. At baseline (T0) and after 16 weeks (T16), patients were assessed for disease activity by SLEDAI; quality of life by Short Form-36 (SF-36); perceived exertion by Borg scale and fatigue by severity fatigue scale. Exercise tolerance (time duration of the test); at resting, maximum and VT1 heart rate; maximum oxygen consumption (VO2max) and VT1 oxygen consumption (VO2LV1); maximum pulmonary ventilation (VEmax) and maximum and VT1 speed were analyzed in the cardiopulmonary exercise test. Parametric and non-parametric tests were applied according the normality distribution of the variables. $P < 0.05$ was considered significant and P values ≥ 0.05 and < 0.10 were considered as a tendency.

Results: Eighteen patients were allocated in EG and 20 in CG. Both groups were homogeneous and comparable regarding demographic and clinical features. The mean age was 33.2±7.8 years and the mean disease duration was 94.2±80.5 months. After 16 weeks we found significant improvement in exercise tolerance (12.3±2.4min vs 13.4±2.6min, p=0.027), maximum speed (7.7±1.0km/h vs 8.3±1.2 km/h, p=0.027) and VT1 speed (5.6±0.7km/h vs 6.1±0.9 km/h, p=0.005) in the EG. There was a tendency in improving VO2max (25.5±4.4 vs 28.0±4.5, p=0.062) and VO2LV1 (17.3±4.7 vs 19.9±4.9, p=0.052). In the EG, we also observed improvement of functional capacity (64.2±23.0 vs 77.8±18.7, p=0.026), vitality (58.9±21.0 vs 74.2±18.8, $p < 0.001$) and fatigue (3.7±1.9 vs 2.6±1.1, p=0.023) evaluated by SF-36. There was no difference in any of these parameters in the CG. After sixteen weeks, there was no difference in the SLEDAI score in EG (2.0±2.1 vs 2.4±2.3, p=0.196) neither in CG (2.4±2.3 vs 3.1±5.3 p=0.833).

Conclusion: physical exercise is a useful strategy to improving fatigue, aerobic capacity and quality of life without worsening disease activity in SLE patients. Therefore physical exercise program should be offered for SLE patients as a complementary treatment.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 6 Clinical Aspects"

Atlantico A+B+C

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Cutaneous Manifestations in Patients with Systemic Lupus Erythematosus. Data from the Multinational Latin-American GLADEL Cohort

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Introduction: The prevalence of cutaneous manifestations (CM) in systemic lupus erythematosus (SLE) is very high (71 to 85%) and very useful for diagnosis.

Objectives: Assess the prevalence, socioeconomic-demographic, clinical and serological features of SLE patients with CM. Evaluate the association of serology and CM.

Material and methods: SLE patients from 34 centers in nine Latin American countries with a recent SLE diagnosis (≤2 years) had been recruited and followed-up longitudinally for 4.5 years. Socioeconomic-demographic characteristics, clinical manifestations and laboratory were compared between patients with and without CM. The statistical analysis included chi square, test t and Mann Witney test. Was performed logistic regression analysis adjusted for sex, age, SLICC, SLEDAI and time of evolution to compare the type of CM and laboratory. Significant $p \leq 0.05$.

Results: Of the 1480 patients included 1387 had CM (93.7%). 1255/1387 (90.5%) them were women, with a mean (SD) age of onset of SLE of 27.7 (11.7) years. Ninety-one percent (1264/1887) of CM occurred before the diagnosis of SLE. Type of CM: malar erythema 962 (65%), alopecia 943 (63.7%), photosensitivity 880 (59.5%), mucocutaneus ulcers 662 (44.7%), Raynaud's phenomenon 468 (31.6%), discoid rash 192 (13%), livedo reticularis 184 (12.4%), diffuse erythema 112 (7.6%), subacute cutaneous lupus 62 (4.2%), panniculitis 25 (1.7%), bullous systemic lupus 6 (0.4%).

Table one shows the features of patients with / without CM.

Table two shows the significant associations found between laboratory and CM types.

Conclusions: Skin lesions have a high prevalence, mostly as an early appearance in this SLE cohort. The CM are associated with systemic features and musculoskeletal manifestations. Different CM are associated with anti Ro, anti La anti Sm, Anti RNP, and anticardiolipin as previously reported.

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Risk factors for cardiovascular mortality in patients with systemic lupus erythematosus

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Table 1. Sociodemographic, Clinical and Serological Feactures According to Whether or not Cutaneous Manifestations

	With CM (n 1387)	*Without CM (n 93)*	*p*
Female n(%)	**1255 (90.5)**	**75 (80.6)**	**0.002**
Age of SLE onset m (DS)	**27.7 (11.7)**	**33.7 (15.7)**	**< 0.001**
Ethnicity White n (%)	567 (40.9)	39 (41.9)	0.2
Ethnicity White/Indian n (%)	606 (43.7)	39 (41.9)	0.2
Ethnicity African/Latin/American n (%)	171 (12.3)	15 (8.1)	0.2
Ethnicity Others n (%)	43 (3.1)	0	0.2
SES high/medium high n (%)	140 (10.1)	12 (12.9)	0.5
SES medium n (%)	29 (31.2)	398 (28.7)	0.5
SES medium low / low n (%)	52 (55.9)	849 (61.2)	0.5
Systemic Manifestations n (%)	**1152 (83.1)**	**65 (69.9)**	**0.02**
Musculoskeletal Manifestations n (%)	**1297 (93.5)**	**78 (83.9)**	**< 0.001**
Ocular Manifestations n (%)	242 (17.4)	17 (18.3)	0.8
Respiratory Manifestations n (%)	106 (7.6)	8 (8.6)	0.7
Heart Compromise n (%)	**290 (20.1)**	**32 (34.4)**	**0.002**
Ischemic Heart compromise n (%)	86 (6.2)	4 (4.3)	0.4
Renal Compromise n (%)	819 (59)	57 (61.3)	0.6
Neurologic Manifestations n (%)	498 (35.9)	27 (29)	0.1
Hematologic n (%)	1089 (78.5)	79 (84.9)	0.1
ANA positive n (%)	1302 (93.9)	91 (97.8)	0.1
Anti DNA positive n (%)	829 (59.8)	62 (66.7)	0.1
Anti RNP positive n (%)	308 (22.2)	14 (15.1)	0.1
Anti Sm positive n (%)	335 (24.2)	15 (16.1)	0.07
Anti Ro positive n (%)	**330 (23.8)**	**13 (14)**	**0.03**
Anti La positive n (%)	182 (13.1)	9 (9.7)	0.3
Lupus Anticoagulant positive n (%)	90 (6.5)	5 (5.4)	0.6
Anti cardiolipin IgG positive n (%)	347 (25)	16 (17.2)	0.09
Anti cardiolipin IgM positive n (%)	239 (17.2)	15 (16.1)	0.7
Anti BG1 positive n (%)	36 (2.6)	1 (1.1)	0.3
Hypocomplementemia n (%)	810 (58.4)	46 (49.5)	0.09
Antimalarial Use n(%)	**1154 (83.2)**	**60 (64.5)**	**< 0.001**
Death n (%)	82 (5.9)	8 (8.6)	0.2

SES: Socioeconomic status

Table 2. Association Among Laboratory Results and Type of Cutaneous Manifestations by Multivariate Analysis

	Discoid rash *OD(95%CI)*	*Livedo reticularis* *OD(95%CI)*	*Panniculitis* *OD(95%CI)*	*Photosensitivity* *OD(95%CI)*	*Raynaud's phenomenon* *OD(95%CI)*	*Subacute cutaneous lupus* *OD(95%CI)*
DNA +		1.4 (1-2.2)		0.7 (0.5-0.9)		
RNP +			3.4 (1.3-8.7)		2.6 (1.9-3.5)	4.5 (2.5-7.9)
Sm+		1.9 (1.3-2.7)			1.8 (1.3-2.3)	2.4 (1.4-4.2)
Ro +	1.7 (1.1-2.4)			1.1 (1-1,9)	1.6 (1.2-2.2)	2.5 (1.4-4.3)
La +	1.9 (1.2-3)	1.6 (1-2.5)			1.5 (1-2.2)	2.7 (1.5-5)
Lupus Anticoagulant +	0.3 (0.1-0.9)					
Anti Cardiolipin +	0.6 (0.4-0.9)	1.6 (1.1-2.3)				
Hypocom plementemia		2.3 (1.5-3.5)				

Introduction: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder affecting multiple organ systems. Treatment of the disease has contributed dramatically in the long-term survival of the patients. Accelerated atherosclerosis and early coronary artery disease have become important causes of death and hospitalisation in SLE patients. Many cardiovascular risk factors can be considered: disease activity (particularly kidney involvement, hyperlipidemia, antiphospholipid antibodies and many others. Cardiovascular disease is common and a major cause of mortality. Studies on cardiovascular morbidity are abundant, whereas mortality studies focusing on cardiovascular outcomes are scarce. The aim of this study was to investigate causes of death and baseline predictors of overall, non-vascular, and specifically cardiovascular (CVM) mortality in SLE, and to evaluate systematic coronary risk evaluation (SCORE).
Patients and Methods: 249 SLE patients were included between 1984-2010 years.Clinical evaluation, cardiovascular disease risk factors, and biomarkers were recorded at inclusion. Death certificates and autopsy protocols were collected. Causes of death were divided into specifically cardiovascular (ischemic vascular and general atherosclerotic diseases), non-vascular and others. Predictors of mortality were investigated using multivariable Cox regression. SCORE and standardized mortality ratio (SMR) were calculated.
Results: During follow-up 94 patients died at mean age of 47,5 ± 14,3 years. 38 of deaths were caused by CVM. SCORE underestimated CVM but not to a significant level. Age, high cystatin C levels and established arterial disease were the strongest predictors for all - cause mortality. After adjusting for these in multivariable analyses, only smoking among traditional risk factors, and high sensitivity C-reactive protein, anti-beta2 glycoprotein-1 and any antiphospholipid antibody among biomarkers, remained predictive of CVM.
Conclusion: With the exception of smoking, traditional risk factors do not capture the main underlying risk factors for CVM in SLE. Rather, cystatin C levels, inflammatory and endothelial markers, and antiphospholipid antibodies differentiate patients with favorable versus severe cardiovascular prognosis.

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Clinical Description and Outcomes in Second Renal Biopsy in Patients with Lupus Nephritis

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Background: Renal biopsy in Systemic Lupus Erythematosus (SLE) is established for diagnosis of lupus nephritis (LN). Histological features may be associated with poor outcomes. Repeated renal biopsies may be useful in SLE flares and to assess progression or remission of LN.
Objectives: To study clinical and histological features in first and second kidney biopsies in patients with LN as predictors of clinical outcomes.
Methods: Between June 1994 and January 2012, one hundred and eighteen renal biopsies were performed in fifty nine SLE patients with LN. All patients fulfilled the 1997 revised criteria of the American College of Rheumatology. Renal biopsies were classified according to the 2003 ISN/RPS classification of LN. We compared categorical data using the chi square and Mac Nemar test. Continuous variables were analyzed with the Wilcoxon test. A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance. We using the SPSS program (SPSS, Chicago, IL).
Results: Of the 59 patients with LN, 43 (84.7%) were women, mean age at diagnosis 25.4 years (range 7-70). Median time between first and second biopsy was 75.4 months (range 10-324). The class in the first renal biopsy was IV 32 (54.2%), V 11 (18.6%), III 8 (13.5%), II 6 (10.1%), I 1 (1.6%) and IV 1 (1.6%). In the second renal biopsy was IV 32 (54.2%), V 17 (28.8%), II 6 (10.1%), III 2 (3.3%), I 1 (1.6%) and VI 1 (1.6%).

In the second biopsy 20 (33.9%) showed histologist progression to more active forms, 7 (11.9%) to less active forms, and 32 (54.2%) no relevant change. After 6 months of first biopsy, we found partial remission in 43 (73%), complete remission in 9 (15%) and relapse in 7 (12%) patients. After a mean follow-up of 101.9 months five patient have chronic renal insufficiency, one patient underwent renal transplantation and three patients died (5.1%) due to lupus disease activity in 1 (33.3%), sepsis in 1 (33.3%) and cardiovascular disease in 1 (33.3%) patient.

Severe tubular atrophy at the time of first biopsy was associated with subsequent renal flare (p= 0.005).

Table 1. clinical and hystologic data in 1° and 2° renal biopsy

	1 Biopsy	*2 Biopsy*	*p*
SLEDAI M (IQR)	16 (9)	10 (8)	< 0.001
No renal SLEDAI M (IQR)	6 (7)	2 (4)	< 0.001
SLICC M (IQR)	0	1 (1)	< 0.001
Proteinuria M (IQR)	0.9 (0.5)	0.8 (0.7)	0.06
Creatinine M (IQR)	52 (86)	49 (84)	0.8
Creatinine clearance < 60mg/dl n(%)	17 (28.8)	19 (32.2)	0.8

(continued)

Table 1. Continued

	1 Biopsy	*2 Biopsy*	*p*
Ac Anti DNA n (%)	47 (79.6)	22 (37.2)	< 0.001
Low C3 - C4 n (%)	54 (79.6)	22 (37.2)	0.002
Inflammation n (%)	50 (84.7)	51 (86.4)	0.1
Fibrosis n (%)	30 (50.8)	40 (67.7)	0.1
Tubular atrophy n (%)	30 (50.8)	40 (67.7)	1

Conclusions: One third of patients showed renal biopsy progression with increased fibrosis in the second renal biopsy. 8.5% patients had chronic renal issufficiency. Mortality was 5.1% at 8.5 years follow up.

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Neuropsychiatric (NP) manifestations in Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) – Clinical Experience of a Single Center

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Introduction: Despite the clinical criteria of neuropsychiatric involvement in SLE the prevalence is difficult to determine given it's diversity and nonspecific nature. We aimed to describe the clinical experience of the 668 SLE and 76 primary APS patients followed on our center.
Patients and methods: revision of demographical, clinical and laboratory data of SLE and/or APS patients available on our database and clinical charts, who had any neuropsychiatric event or complaints (secondary causes excluded).
Results: We identified 3 subgroups with NP syndromes in a total of 75 patients: 33 NP SLE (5.7%); 22 NP SLE with APS (25%) and 20 NP primary APS (26.3%). The prevalence in the SLE cohort (with or without APS) was 8.2%. Females were more affected. The mean age of neurological presentations was 31.63 years old in SLE, 30.04 in SLE/APS and 42.55 in APS. There was no relation between immunological activity and the neurological event. Anti-P-ribossomal was positive in only 2 of the 22 NP SLE patients tested and in 3 with NP SLE/APS. The first clinical manifestation was neuropsychiatric in 9% of SLE; 27% of SLE/APS and 80% of APS ($p < 0{,}001$). In the SLE subgroup (n=33) the first neuropsychatric manifestation was: seizure disease in 27% (n= 9), aseptic meningitis in 18% (n=6) and 12% (n=4) both in cerebrovascular disease, cognitive dysfunction (dementia) and psychiatric disorder. Peripheral nervous system (PNS) involvement occurred in 2 patients (6%). In SLE/APS (n=22) the first neuropsychatric manifestation was cerebrovascular disease in 54.5% of patients (n= 12), cognitive dysfunction in 9% (n=2) and PNS involvement in 9% (n=2). Demyelinating syndrome, headache, chorea, myelopathy, seizures and psychiatric disorder counts for 4.5% each one (n=1). In the group of primary APS the major first neuropsychiatric manifestation was cerebrovascular disease (60% with n =12), followed by myelopathy in 25% (n=5) and PNS involvement in 10% (n=2). There was only one patient with seizure disorder. 48% of patients with SLE had more than one neuropsychiatric manifestation as well as 55% with SLE/APS and 25% with primary APS. The mean duration of follow up in patients with neurological events was 12.07 years in SLE, 12.41 in SLE/APS and 10.3 years in primary APS. There were 38 patients (5.7%) with neurological complaints (headaches, memory difficulties and peripheral facial palsy) there were not attributed to NPSLE.
Conclusions: In our retrospective study, 8.2 % of SLE patients and 27% of primary APS patients had at least one NP event attributed to autoimmune disease. Our study provided further evidence of the close relationship between NP involvement and APS in SLE (prevalence of NP involvement is 25% in SLE with APS vs. 5.7%). Consistent with previous studies cerebrovascular disease was the most common NP syndrome in patients with APS with or without SLE, while seizure disorder was the most common symptom in SLE patients.

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Drug Perception of Systemic Lupus Erythematosus Patients and Its Association with Quality of Life, Anxiety and Depression

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Introduction: Increasing the quality of life is an important goal of the drugs. However, the perception and belief of the patients about their drugs could be obstacles in their treatment and affect their compatibility. We investigated our SLE patients' quality of life, stress level, drug perceptions and thought for the drugs.
Patients and Methods: 125 SLE with 41 rheumatoid arthritis (RA) patients were included. Clinical and demographical data, disease activity and damage index of the SLE patients were recorded according to SLEDAI and SLICCARC. Subjects fulfilled the approved reliable and valid questionnaires for health related quality of life (HRQoL), beliefs about medication (BMQ), anxiety and depression (HADS). BMQ had 4 subgroup tests. Specific Concern (SC) analysis the negative effects of the drugs, Specific Necessity (SN) evaluates the effectiveness of the drugs in disease control, General Harm (GH) explores the addiction for the drugs and their natural harmful results, General Overuse (GO) inquires prescription of the doctors for their patients from drug users' view. HRQoL has also subgroups of health (1), pain (2), planning (3), close interaction (4), bothering the environment (5), emotional health (6), body image (7) and weakness (8).
Results: Mean age of SLE and RA patients are 37,7 and 39,1 years respectively and without significant difference. BMQ-SC/SN/GH/GO scores were similar to RA group ($p > 0.05$ for all). RA patients had no difference according to their HRQoL and HADS. Subgroup analysis of SLE patients depending on their neurogenic and renal involvement, immunosuppressive drugs or protocol diversities, antibody profiles and disease duration (< 5 or > 5 years) revealed any significant result for BMQ, HRQoL and HADS scores. SLEDAI and BMQ-SC (r=0.296) (p=0.001), -SN (r=0.183)(p=0.039), -GO (r=0.273)(p=0.002) -GH (r=0.234) (p=0.008) and HRQoL -1, -2 and -8 scores had a correlation (r=0.211; 0.232 and 0.232) (p: 0.01, 0.009, 0.009). BMQ-SC and HRQoL 1-,-3 and -8 scores (p= 0.001; 0.018 and 0.007); BMQ-SN and HRQoL -1, -2, and -3 scores (p=0.001; 0.002 and 0.001); BMQ-GO and HRQoL -1; -2; -3 and -6 scores (p=0.001; 0.001; 0.007 and 0.006) and BMQ-GH and HRQoL -1; -2 and -3 scores (p= 0.001 for all) had significant correlation. HADS and BMQ-GO; -GH and HRQoL -1; -2: -3; -4 were also (p=0.002; 0.004; 0.005; -0.008; -0.021; -0.04) correlated. SLICCACR index was relevant with all of the BMQ scores and HRQoL -1; -3; -6; -8 scores (p değerleri < 0.05).
Conclusion: SLE patients' HRQoL scores, anxiety and depression scales were similar to RA group. However diagnosis of depression is associated with anxiety about drugs in both groups. Correlation of these mood scores could also be associated with disease activity and having a chronic disease might be the prominent factor that effecting these patients.

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Premature Cardiovascular Disease in Women with Lupus and Relationship to Premenopausal Status, Disease Severity and History of Eclampsia/Pre-Eclampsia

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Background: Premature onset of cardiovascular disease (CVD) is known to occur disproportionately in women with systemic lupus erythematosus (SLE), but the magnitude of the association has been insufficiently described in the premenopausal age group. Further, specific risk factors for premature onset of CVD in this population remain unclear, particularly the effect of lupus disease severity and history of hypertensive pregnancy complications which are increased in women with lupus.
Methods: Retrospective chart review was performed for 677 predominantly African American (71.9%) women with SLE treated in a single academic medical center. To quantify the degree of excess risk in SLE patients, we used a Z test for proportions with population frequencies from the Framingham study and the National Health and Nutrition Examination Survey (NHANES) database as the comparator and calculated risk ratios (RR) for specific cardiovascular and metabolic diseases among pre and postmenopausal women. We then used chi-square analysis to assess the effect of 2 suspected risk factors (lupus disease severity and pregnancy hypertensive complications [i.e., eclampsia/pre-eclampsia]) on cardiovascular (myocardial infarction [MI], transient ischemic attack [TIA], and chronic hypertension [HTN]) and metabolic (hyperlipidemia [HL] and diabetes mellitus [DM]) disease rates.
Results: Mean age of the cohort was 33 years, 343 (50.6%) were premenopausal, 310 (45.8%) had documented severe SLE, and 25 (3.7%) had pregnancy hypertensive complications. Premenopausal but not postmenopausal state was associated with a greater risk of all CVD (RR = 1.22 for HTN, 4.38 for TIA and 10.6 for MI) and HL (RR = 1.89). Both cardiovascular and metabolic diseases were also more common in patients with severe SLE; however, among those with pregnancy hypertensive complications during pregnancy, an association with only chronic HTN was found.
Conclusions: Compared to non-SLE patients, premenopausal women with lupus are at increased risk for development of cardiovascular and metabolic diseases. Risk appears to be greatest for patients with severe SLE, indicating a potential dose/response relationship.

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Features Associated with the Presence of Renal Involvement in Mexican Patients with Systemic Lupus Erythematosus

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Introduction: Systemic lupus erythematosus (SLE) has been shown to be quite heterogeneous in its clinical manifestations and outcome in different populations around the world and even within the same ethnic group, that is the case for Hispanic patients in the US and Latin America.
Objective: To examine the clinical characteristics of SLE in predominantly mestizo Mexican patients particularly renal involvement defined as the presence of proteinuria or biopsy-proven lupus nephritis (LN).
Methods: SLE patients [American College of Rheumatology (ACR) criteria] of Mexican ethnicity, from three care centers (two tertiary public and one private practice clinic) were included in the study. The association between clinical variables, laboratory and renal involvement, as defined, was examined by univariable (UV) and multivariable (MV) regression analyses.
Results: One hundred twenty patients were included into the study; 90% were women. The mean ± SD age and disease duration were 35.9 ± 10.8 yrs and 8.8 ± 5.9 yrs, respectively. Sixty-five (54%) patients had proteinuria; renal biopsy was performed in 42 patients reporting glomerulonephritis (WHO classification): three type 2, nine type 3, nineteen type 4 and eleven type 5. Univariable and multivariable analyses are shown in Table below.
Conclusion: Low serum complement were associated with renal involvement in Mexican SLE patients. Common and mild clinical features such as malar rash, alopecia, lymphopenia and anticardiolipin antibodies (IgM isotype) were negatively associated with renal involvement.

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TABLE. Variables Independently Associated with Renal involvement in Mexican SLE* Patients by Univariable and Multivariable Analyses (Backward Stepwise Regression)

	Univariable		*Multivariable*	
Variable	*Odds Ratio (95% CI)*	*p value*	*Odds Ratio (95% CI)*	*p value+*
Age	0.960 (0.921-1.001)	0.058		
Gender, female	0.452 (0.098-2.088)	0.309		
Malar rash	0.400 (0.147-1.083)	0.071	0.266 (0.071-0.995)	0.049
Alopecia	0.256 (0.093-0.704)	0.008	0.171 (0.047-0.627)	0.008

(continued)

Table: Cardiovascular and Metabolic Complications in Female Patients with Lupus

Variable n (%)	*Premenopausal n=343*	*Risk ratio*	*p-value*	*95% CI*	*Severe SLE n=310*	*p-value*	*Eclampsia & Pre-eclampsia n=25*	*p-value*
HTN	172 ((50.1%)	1.22	< 0.001	(1.10, 1.36)	244 (78.7%)	< 0.001	22 (88.0%)	< 0.01
TIA	12 (3.5%)	4.38	< 0.001	(2.51, 7.63)	33 (10.6%)	< 0.001	1 (4.0%)	NS
MI	19 (5.5%)	10.60	< 0.001	(2.07, 14.62)	40 (12.9%)	< 0.01	0 (0.0%)	NS
DM	40 (11.7%)	0.99	NS	0.74, 1.33)	70 (22.6%)	< 0.01	6 (24%)	NS
HL	110 (32.1%)	1.89	< 0.001	(1.62, 2.20)	173 (55.8%)	< 0.001	13 (53.4%)	NS

NS=not significant

Table Continued

Variable	Univariable Odds Ratio (95% CI)	p value	Multivariable Odds Ratio (95% CI)	p value+
Lymphopenia	0.428 (0.150-1.222)	0.113	0.085 (0.018-0.095)	0.002
aCL antibodies IgG positive	0.211 (0.056-0.795)	0.022		
aCL antibodies IgM positive	0.291 (0.068-1.239)	0.095	0.037 (0.004-0.359)	0.004
Low complement	2.244 (0.891-5.652)	0.086	3.742 (1.146-12.220)	0.029

*Systemic Lupus Erythematosus; † only p values ≤0.05 are noted

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Study of the disease activity and refractoriness to the treatment in a large spanish multicentric cohort of patients with systemic lupus erythematosus: preliminary data from relesser (registry of sle patients of the spanish society of rheumatology)

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Background: There is little information about activity and refractoriness of SLE in Spain.

Objectives: To study the level of activity and calculate the percentage of SLE patients who are refractory to therapies.

Methods: SLE patients from the RELESSER Registry with active follow-up in a Rheumatology Department.

Variables: a) clinical and analytical activity manifestations and b) past and current treatments.

Methods: Retrospective study of the data collected at the time of the last evaluation of the patient. a) the SELENASLEDAI score is calculated and SLE activity stratified according to it, b) the percentage of refractory cases is calculated according to: inefficacy of cyclophosphamide (CYC), use of rituximab, splenectomy or inefficacy of ≥2 immunosupressors (methotrexate, leflunomide, abatacept, anti-TNF, azathioprine, CYC, mycophenolate mofetil and/or mycophenolic acid).

Results: 583 patients included (88.3% females, mean age: 45.5 years, SLE duration: median 111 months). The most frequent clinical manifestations of activity were mucocutaneous (13.9%) and musculoskeletal (6.3%). Least frequent clinical features: myositis and psychosis (0% both). There was renal or neurological/psychiatric activity in 7.8% and 2.3% of patients. 13.6% had leukopenia. 27 (4.6%) patients had hypocomplementemia and anti-dsDNA antibodies without any clinical manifestation. The median SLEDAI score was: 2 (range: 0-23). 39.4% of patients had a SLEDAI score = 0. SLE disease activity was mild (1-4 points), moderate (5-9) and severe (≥10) in 43.4, 13.2 and 3.9% of patients, respectively.

The table shows the treatments for lupus that received the patients in each activity level group. 59 (10.1%) of the patients presented moderate or severe activity despite corticosteroids and antimalarial treatment.

Conclusions: The level of disease activity is relatively low. An important percentage of patients (10.1%) has moderate-severe lupus activity despite the use of corticosteroids and antimalarials. The percentage of refractoriness of the SLE might be about the 10% of the patients.

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Treatment at the time of the last evaluation	NO activity (SLEDAI=0) n = 230	Mild (1-4) n = 253	Moderate (5-9) n = 77	Severe (≥10) n = 23	P
Corticosteroids + antimalarials	60 (26.0%)	95 (37.5%)	43 (55.8%)	16 (69.5%)	<0.0001
Immunosupressors					
– No	158 (68.7%)	137 (54.1%)	34 (44.1%)	7 (30.4%)	<0.0001
– One	47 (20.4%)	93 (36.7%)	29 (37.6%)	14 (60.8%)	
– Two	2 (1.0%)	5 (2.0%)	5 (6.5%)	1 (4.3%)	

The percentage of refractoriness, according the mentioned definition, was 10.3% of the patients.

Systemic lupus in men. Results from a single center in a cohort of 1048 patients

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Background: eproductive hormones are related to SLE expression and previous researches studying SLE in men in different series and ethnic groups showed that men differed from women in disease expression, in both clinic manifestations and auto-antibodies characteristics.

The objective of this study was to characterize the clinic and laboratory manifestations and the disease evolution of male patients in comparison to female patients in our cohort.

Methods: Of the 1048 SLE patients from a single center (State University of Campinas-Unicamp - Hospital das Clínicas, São Paulo,Brazil),from 1974 to 2012, 80 were male (7.6%) and 968 were female (92.4%).

The clinical manifestations, laboratory profiles and disease prognosis were evaluated and compared in male and female patients.

Results: Malar rash (37.5 % versus 51,5%,p < 0,03), photosensitivity(45% versus 58 %,p < 0,02), alopecia (26% versus 42 %,p< 0,009), and Raynaud phenomenon (14% versus 29 %,p< 0,006) were less common in men with SLE than in female SLE patients.In contrast, general symptoms at onset of disease such as weight loss (55 % versus 35%,p < 0,0005) and fever > 38 ° C (63 % versus 50%,p < 0,0003) were more frequent in male group compared to female group. Concerning to organ involvement, nephritis (66% versus 43%; p <0,00008), pleuritis (29 % versus 16%; p <0,004)and pericarditis (17,5 % versus 9%; p < 0,01) were more commonly found in the

male group. Anti-DNA Antibodies were more frequent in male patients when compared to female (57 % versus 42 %; $p < 0,02$). The number of death was higher in male group with SLE when compared with female group (21 % versus 11%; $p < 0,008$).

Conclusions: These results showed that in our cohort of SLE patients male patients have significantly more fever and weight loss at onset of disease, more nephritis, pleuritis and percarditis, more positive anti-DNA antibodies and higher mortality than female patients. In contrast our male patients have less cutaneous disease (rash malar, photosensitivity and alopecia) and Raynaud phenomenon. Our data confirm the severity of disease in male patients with SLE.

No conflicts of interest

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Hand ultrasound: comparative study between systemic lupus erythematosus and rheumatoid arthritis

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Introduction: Arthritis is one of the earliest manifestations of systemic lupus erythematosus (SLE), with an incidence ranging from 69 to 95%. Most patients exhibit non-deforming, non-erosive arthritis. Erosive arthropathy in SLE (0,01 to 2% of patients) occurs more commonly in the hands and it's similar to that found in rheumatoid arthritis (RA). The use of ultrasound (US) is well established for the evaluation of arthropathy in patients with RA. However, few controlled studies have been conducted on US on patients with other arthropathies and no studies have compared hand US between patients with SLE and those with RA. The aims of the present study were to compare hand ultrasound between SLE and RA patients, compare the correlation between US and disease follow-up variables in these two conditions and correlate an RA-like US pattern in SLE with laboratorial, clinical and functional outcomes.

Results: 2108 and 2040 joint recesses were evaluated in SLE and AR patients respectively. Synovitis was found in 46.8% and 75% of wrists, 83.9% and 86.7% of MCPs and 58.1% and 70% of PIPs in the SLE and RA groups, respectively. More significant ultrasound findings were found in the RA group. The articular cartilage was less consistent statistical associations. SLEDAI was only associated with PD in 2 dorsal MCF. DAS28 had frequent association with PD. Higher values of HAQ were associated mainly to PD in SLE. Lower values in dynamometry were associated with some variables in US. The association between (rheumatoid factor) RF / anti-CCP and the US were uncommon. The only ANA pattern associated with the US was homogeneous pattern. The SLE patients were divided into two subgroups according to presence of erosion on US: SLE1 group, with erosion in any of the joints studied (22 patients/35.5%) and SLE2, without erosion (40 patients/64.5%). No associations were found between SLE1 and the majority of clinical-serologic findings. However, the SLE1 subgroup was associated with hematological involvement and Jaccoud arthropathy (JA). ROC curve and univariate logistic regression showed that US was able to differentiate AR to SLE in US. We observed moderate to good interobserver reproducibility.

Conclusions: Ultrasound of patients with SLE and RA is different specially in wrists. The clinical variable most associated with the ultrasound in lupus was ''puffy hands''. Further studies are needed to assess clinical, serological and ultrasound predictors of erosive arthropathy in SLE and offer a more detailed characterization.

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The new Body Adiposity Index (BAI) in childhood-onset Systemic Lupus Erythematosus

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Background: The body mass index (BMI) is widely used to indicate the weight status of the individual, recently a new index to measure adiposity was developed to estimate the percentage of fat directly. Patients with childhood-onset systemic lupus erythematosus (cSLE) have a high incidence of atherosclerotic diseases and hence the evaluation of body fat is very important.

Objective: To analyze the correlation of the BAI with lipid profile in patients with cSLE

Methods and Patients: We conducted a cross-sectional study with the inclusion of consecutive patients followed in the outpatient pediatric rheumatology at UNICAMP. We evaluated anthropometric measurements (weight, height, waist circumference (WC) and hip circumference (HC)), lipid profile (cholesterol and fractions and fasting glucose) and BAI using the following formula: BAI = ((hip circumference) / ((height)1.5) -18. Patients and controls were compared using the chi square test.

Results: We included 59 patients (56 women, mean age of 17.4 years (SD = 3.7) and 63 controls (54 women, mean age of 17.3 years (SD = 6.4). We observe a WC mean of 79.8 cm (SD = 13.6) in cSLE patients and 76.6 cm (SD = 11.3) in controls ($p = 0.059$); a HC mean was 91.4 cm (SD = 10) in cSLE patients and 92.5 cm (SD = 13.5) in controls ($p = 0.647$). We observe a mean of waist/hip ratio was 0.87 cm (SD = 0.1) in cSLE patients and 0.82 cm (SD = 0.1) in controls ($p < 0.05$). We observed an association between BAI and anthropometric measures calculated between patients with cSLE and controls: height ($p \leq 0.001$), weight ($p < 0.05$), WC ($p < 0.05$) and HC ($p \leq 0.001$). We observe an association of BAI and elevated levels of LDL-c ($p < 0.05$) but no associations were observed between BAI and fasting glucose ($p = 0.32$), triglycerides ($p = 0.17$) HDL-c ($p = 0.35$) and total cholesterol ($p = 0.30$).

Conclusion: Patients with cSLE have a higher prevalence of abdominal fat, abdominal seen by the waist / hip ratio and WC association with the BAI, than the general population. The association between BAI with LDL-c fraction indicates the need for further evaluation of patients seen that oxidation of LDL is the key factor for the onset of atherosclerosis and consequently the development of coronary atherosclerosis

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Contraception in patients with Systemic Lupus Erythematosus

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Objectives: To evaluate the frequency and the different methods of contraception used by patients with systemic lupus erythematosus (SLE).

Methods: We included 345 consecutive SLE patients (>= 14 years) and 118 healthy controls age, sex and socioeconomic status matched. The frequency and the different types of contraceptives used were assessed using a questionnaire developed for this purpose. We excluded 2 (0.58%) homosexual patients, 114 with permanent amenorrhea (33.04%) and 2 pregnant women (0.58%).

Results: In total, 227 SLE patients (mean age 31 years, SD= 7.70, range: 14-45) and 118 controls (mean age 32 years, SD = 7.70, range: 16-51) were included. One hundred and thirty-two (58.15%) and 49 patients (41.52%) controls were married, 71 (31.28%) and 63 patients (53.38%) controls unmarried, 24 (10.57%) and 6 patients (5.08%) controls widows or divorcees. One hundred and sixty-six

(73.12%) and eighty-eight patients (74.57%) controls reported having a sexual partner currently, with only 123/166 (74.1%) patients were using a contraceptive method compared with 76 / 88 (86.36%) controls ($p < 0.05$). Contraceptive containing progestogen was reported in 48/123 (39.02%) patients and 9/76 (11.84%) controls ($p < 0.05$). 3/123 (2.44%) patients and 59/76 (77.63%) controls reported use of contraceptives containing estrogen ($p < 0.05$), 11/123 (8.94%) patients and 3/76 (3.94%) controls reported use of an intrauterine device, 45/123 (36.58%) patients and 31/76 (40.79%) controls used condoms. Withdrawal as contraception was reported by 7/123 (5.69%) patients and 3/76 (3.94%) controls ($p = 0.58$) and 26/123 (21.14%) patients and 7 / 76 (9.21%) controls were using definitive methods (tubal ligation or hysterectomy). 17/123 (13.82%) patients used more than one method of contraception. Use of teratogenic drug was reported by 39/123 (31.71%) patients and 3/88 (3.41%) controls, and only 24/39 (61.54%) and two thirds (66.66%) controls used some regular contraceptive method.

Conclusion: The use of contraceptives in SLE is low when compared to the control group. SLE most often used progestin-containing contraceptives, and the controls used methods containing estrogen. Only 61.54% of patients on teratogenic medications were using adequate contraception. The use of contraceptive methods should be questioned regularly in consultations to avoid unwanted pregnancy, as this can worsen the disease or the course of pregnancy, and the use of teratogenic medications can increase the risk of malformations.

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The spectrum of inflammatory ocular involvement in systemic lupus erythematosus in a multidisciplinary uveitis unit

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Purpose: To describe the inflammatory ocular manifestations of patients with systemic lupus erythematosus (SLE) at a multidisciplinary uveitis unit.

Methods: Retrospective chart review of patients with SLE in a tertiary referral center between 2007 and 2012 was performed. All patients have undergone complete rheumatologic and ophthalmic examination including visual acuity, slit-lamp examination of the anterior segment and fundus examination. Fluorescein angiography and optical coherence tomography were performed if they were required.

Results: Twenty-two patients presented inflammatory ocular manifestations related to SLE. All patients complained of ophthalmologic disturbances with blurry vision and ocular redness as the most common symptoms. A decrease in the visual acuity was detected in 15 patients (68.2%) mostly due to retinal involvement, optic neuritis and anterior uveitis. Anterior uveitis was found in 7 patients (31.8%), intermediate uveitis in 1 patient (4.5%) and diffuse scleritis in 4 patients (18.2%). Changes in retina were found in 7 patients (31.8%); the most frequent was retinal vein occlusion (central retinal vein occlusion in 2 patients and branch retinal vein occlusionin 2 patients) followed by hypertensive retinopathy with serous retinal detachment in 1 patient, occlusive vasculopathy in 1 patient and central serous choroidopathy due to corticosteroids in 1 patient. Three patients (13.6%) showed neuro-ophthalmological symptoms, 1 patient showed rotatory nistagmus related to central nervous system involvement, 1 patient showed optic neuritis and the remaining presented bitemporal hemianopsy.

Conclusions: Ocular manifestations in SLE can affect any structure in the eye. The most visually devastating damage occurs secondary to optic nerve involvement and retinal vaso-occlusion. Anterior uveitis is not an uncommon manifestation of SLE; physicians must be aware of this involvement since it can be treated without serious visual loss.

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Cutaneous involvement in systemic lupus erythematosus. A latent trait analysis

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Background: Cutaneous involvement is one of the most frequent manifestations of systemic lupus erythematosus (SLE); however ethnicity may influence its prevalence and clinical expression. We aimed to evaluate its prevalence and associated factors in a non-Caucasian population.

Patients and methods: Data from a cohort of 310 patients with SLE (ACR 1997 update) who were seen at a single clinical center were analyzed. The cutaneous involvement latent trait (CILT) was constructed using item response theory and two-parameter logistic model which involved the following variables: photosensitivity, oral ulcers, malar rash, discoid lupus, subacute lupus and urticary. CILT was included as dependent variable in a lineal regression model, adjusted for gender and age at onset.

Results: Cutaneous involvement was observed in 88% (n=273) of patients, and was associated with familial autoimmunity (β=0.44, p=0.001), renal involvement (β=0.34, p=0.042), serositis (β=0.32, p=0.009) and immunological criteria (β=0.20, p=0.035). On the other hand, inverse relationship with age at onset (β=-0.01, p=0.027) and leukopenia (β=-0.23, p=0.03) was found. Some interactions were also observed. Among these, patients with polyautoimmunity tended to have a lower CILT than those with lupus arthropathy.

Conclusions: Cutaneous involvement is a common manifestation in our SLE population. Found associations and interactions can help distinguish patients at risk and guide early interventions. Latent trait analysis may be an instrumental tool for the study of subphenotypes in SLE and other autoimmune diseases.

Table 1. Factors associated with cutaneous involvement in patients with SLE.

Characteristic	*β*	*P-value*
Age at onset	-0,01	0,027
Female	-0,27	0,05
Leukopenia	-0,23	0,039
Immunological criteria	0,2	0,035
Serositis	0,32	0,009
Renal involvement	0,34	0,042
Familial autoimmunity	0,44	0,001
Leukopenia:Duration of the disease	0,03	0,017
Serositis:Duration of the disease	-0,02	0,053
Polyautoimmunity (SLE+RA):Duration of the disease	0,06	0,03
Familial autoimmunity:Renal involvement	-0,36	0,055
Serositis:Polyautoimmunity (SLE+RA)	-0,86	0,036

β: Beta coefficient; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis
Multiple R2: 18%

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The relationship between depression, stress and anxiety with disease activity in systemic lupus erythematosus

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Introduction: Patients with systemic lupus erythematosus (SLE) often associate exacerbations or the occurrence of disease with depression, anxiety or stressful events, but evidence for this association are limited. The purpose of this study was to evaluate the relationship between depression, anxiety and stress with activity of SLE.
Patientes and Methods: We evaluated 34 patients who fulfilled the American College of Rheumatology criteria for the classification of SLE and 34 age and sex matched healthy controls. Depression was evaluated by using the Beck Depression Inventory (BDI). Patients with SLE were also evaluated for major life stressful events, daily stress and anxiety by using the Holmes e Rahe's Scale, Hassles Scale and State-Trait Anxiety Inventory (STAI) respectively. SLE activity and damaged were assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2000) and the Systemic Lupus International Collaborating Clinics (SLICC).
Results: The median BDI score was higher in patients with SLE (p=0.001), but not associated with SLEDAI score (p=0.510). Patients with moderate score for state anxiety had lower serum levels of complement C4 [14.6 (±7.4) x 23.4 (±10.2)mg/dl, p=0.008] and higher SLEDAI score [6.2 (± 6.6) x 2.4 (± 3), p=0.035] compared with patients with low score for state anxiety. All patients with active nephritis (p=0.04) and all patients with positive anti-dsDNA antibodies (p=0.002) had moderate score for state anxiety. Daily dose of prednisone and cumulative dose in six months were not significantly associated with depression (p=0.564 and p=0.926) or with state (p=0.071 and p=0.332) or trait (p=0.411 and p=0.670) anxiety.
Conclusion: Depression and stressful events were not correlated with current SLE activity. Patients with moderate score for state anxiety had higher lupus activity than those with low score. One explanation for these results is that patients with higher SLE activity could present higher levels of anxiety due to clinical complications and side effects of treatment. However, we can't rule out that anxiety can be an isolated manifestation of central nervous system pathology caused by the disease activity.

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Association of nail dystrophy with capillaroscopic abnormalities, anti-endothelial cell antibody levels, activity, and chronicity in systemic lupus erythematosus

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Introduction: There is a large variety of nail abnormalities described in systemic lupus erythematosus (SLE) that have been rarely considered a specific sign of the disease. Nevertheless, they have been associated with an increased disease activity. There is little information regarding the association between nail dystrophy in SLE and clinical manifestations, capillaroscopy, and endothelial dysfunction.
Objectives: To evaluate the possible association between nail dystrophy and a greater disease activity, chronicity, capillaroscopic abnormalities, and endothelial dysfunction in patients with SLE.
Methods: Prospective, analytical, and transversal study of SLE patients from a Rheumatology Clinic in a tertiary care hospital. The patients have been divided in two groups, one with, and the other without, nail dystrophy (control group). Clinical, demographic, serologic, and capillaroscopic characteristics, as well as anti-endothelial cell antibody (AECA) levels, activity, and chronicity were compared between groups. Activity was determined by the SLEDAI-2K and chronicity by the SLICC. The AECA were measured by ELISA. The statistical analysis was performed with the Mann Whitney test and the Fisher's exact test accordingly; a less than 0.05 p-value was fixed as significant. The association between variables was assessed by the Spearman rank correlation coefficient (95% confidence interval).
Results: A total of 53 patients were included, 44 (83%) were female. The mean age for the control group was 35±10.2 years and 37±13 years for the nail dystrophy group. Twenty seven (50.1%) patients showed nail dystrophy and 26 did not. A significant association of nail dystrophy with an increased chronicity index was found (p=0.05). Capillaroscopic changes were detected in 40% of the nail dystrophy patients and in 11% of the controls (p=0.02). The most frequent abnormalities in the dystrophy group were capillary dilatations (40%) and tortuosities (11%). There was no association between the serology markers and nail dystrophy; however, the AECA levels showed a direct association with the activity index and an inverse relationship with C3 and C4 concentrations in the correlation analysis.
Conclusions: Nail dystrophy is associated with a greater index of chronicity and with capillaroscopic abnormalities. This might suggest that nail dystrophy is caused by microvascular damage. No relationship was observed between nail dystrophy neither with SLE activity nor with endothelial dysfunction.

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Invasive fungal diseases in systemic lupus erythematosus: the experience of a tertiary public hospital from La Plata, Argentina.

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Introduction: Systemic lupus erythematosus (SLE) is associated to impaired immune function not only related to intrinsic mechanisms but also because of the treatment with steroids and immunosuppressant agents. Infections caused by opportunistic organisms are frequent in these patients, although fungal infections are seldom reported.
Objective: To describe proven invasive fungal diseases (IFD) in patients with SLE.
Material y Methods: Patients with SLE (ACR82-97) and IFD who were admitted to our institution between 1993 and 2012 were retrospectively enrolled. Proven IFD was defined by EORTC/MSG-2008. Demographic, clinical and microbiological features, laboratory data and outcome from episodes at the time of infection were evaluated. Fisher's exact test and Chi- square test were analyzed in SPSS 19. A p value of less than 0.05 was considered statistically significant.
Results: Nineteen patients with episodes of IFD were registered. Women were 79% (ratio 4:1). Mean age was 37 years (18-61). SLE evolution: 78 months (1-264). Disease activity (SLEDAI): 14 (0-45). Renal compromise 79%. Neutropenia: 47%. Mean neutrophils: 397 / mm3 (91-806). Hypocomplementemia: 63%. ICU admission: 47%. Mean daily dose of meprednisone: 46 mg (4-120). Intra venous (IV). Metilprednisolone pulse therapy: 58%. IV cyclophosphamide pulse therapy: 37%. Azathioprine: 32%. Hemodialysis: 32%.

Site of infections: primary funguemia: 5 (26%), meningitis: 4 (21%); disseminated: 4 (21%); pneumonia: 2 (11 %), bloodstream catheter related infection: 2 (11%), abdominal: 1 (5%), skin and soft tissues infections: 1 (5%).

Fungal species: Candida spp.: 7 (37%); C. neoformans: 6 (32%); Aspergillus spp.: 2 (10.5 %); H. capsulatum: 2 (10.5 %); P. jiroveci 1 (5%); H. capsulatum/Alternaria spp. (mixed infection): 1 (5 %). In 12/19 the organisms was from blood culture. Mortality: 58% (11/19). Metilprednisolone pulse was statistically associated with mortality (p 0,024),OR 11 (95%C1,19-106,1) There was no significant association between other variables.
Conclusions: IFD occurred in patients with impaired immune status due to active disease, low level of complement, nephritis, hemodialysis,

immunosuppressant therapy and neutropenia. Candida.spp was found to be the most common organism, followed by C. neoformans. In 63% of the episodes the fungal species were isolated from the bloodstream. The prevalent types of IFD were primary funguemia, disseminated infection and meningitis. Our study supports previous research that has documented a high mortality rate among patients with invasive fungal diseases.

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Histopathologic predictors of poor renal outcome in a Multiethnic group with Refractory Lupus Nephritis

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Introduction: Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus. Although histologic features predictive of poor renal outcome have been described in the literature, few data elaborate on the strength of this association in multiethnic cohorts with refractory LN. In this study, we explored the correlation between renal histopathological characteristics in the first renal biopsy of patients with refractory LN who required subsequent biopsies and the latest available follow-up serum creatinine level as a marker of prognosis in a unique multiethnic population.

Patients and Methods: A retrospective analysis of 40 patients with biopsy-proven refractory LN from the years 1996 to 2006, requiring subsequent re-biopsies was performed. Demographics, laboratory and histopathological characteristics were collected and the association with elevated serum creatinine level (defined a serum Creatinine $>=$ 1.3) at last follow-up visit was tested by logistic regression. A p-value of <0.05 was considered significant.

Results: Baseline clinical, laboratory, and histopathologic characteristics are described in Table 1.

Table 1.

Baseline characteristics	*n=40*
Demographics	
Female gender, no. (%)	35 (87)
Race	
African American, no. (%)	13 (33)
Hispanic, no. (%)	14 (35)
Caucasian, no. (%)	7 (18)
Asian, no. (%)	3 (7)
Other, no. (%)	3 (7)
Mean age at time of LN diagnosis in years	29 ± 13
Laboratory data	
Baseline proteinuria (g/day), median (IQR)	2.3 (1.5-4.4)
Baseline serum Creatinine (SCreat) (mg/dL), median (IQR)	0.9 (0.8-1.3)
No. of patients with baseline SCreat≥ 1.3 (%)	9 (23)
C3 (mg/dL), median (IQR)	55 (36-66)
C4 (mg/dL), median (IQR)	9 (6-12)
CH50 (mg/dL), median (IQR)	14 (4-50)
Ds-DNA Ab titer, median (IQR)	695 (195-2269)
Last follow-up SCreat (mg/dL), median (IQR)	1.2 (0.9-1.9)
No. of patients with last follow-up SCr ≥1.3 (%)	20 (50)
Last follow-up proteinuria (g/day), median (IQR)	0.99 (0.38-2.2)
Renal biopsy histopathologic features	
WHO class at first biopsy	
II no. (%)	2 (5)
III no. (%)	7 (18)
IV no. (%)	6 (15)
III+V no. (%)	12 (30)
IV+V no. (%)	13 (32)
No. of sclerotic glomeruli, median (IQR)	1 (0-4)
Activity index, median (IQR)	8 (4-12)
Chronicity index, median (IQR)	2 (0-4)
Podocytopathy %, median (IQR)	70 (40-100)
No. of crescents, median (IQR)	1 (0-3)
No. of cellular crescents, median (IQR)	0 (0-2)
Thrombotic microangiopathy, no. (%)	1 (3)
Wireloop lesions, no (%)	7 (18)
Tubular atrophy and interstitial fibrosis, no. (%)	33 (58%)
SCreat follow-up time (years)	6.9 ± 3.8

*Values represent mean ± standard deviation unless specified otherwise

We found the presence of tubular atrophy and interstitial fibrosis on first renal biopsy was significantly associated with having a serum creatinine level of ≥ 1.3 mg/dL at most recent follow up after adjusting for gender, race, and length of time after first renal biopsy (OR 5.53; 95% CI: 1.12-27.20; p=0.0356). No significant association was found between anti-ds-DNA titer, complement levels, activity or chronicity indexes or presence of crescents on pathology.

Conclusions: On first renal biopsy in lupus nephritis, the presence of tubular atrophy and interstitial fibrosis was associated with an odds of 5.5 of having an elevated serum creatinine at long-term follow up, adjusting for gender, ethnicity and follow up time.

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Clinical and Immunological profile of a multiethnic Singapore SLE cohort

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Introduction and Aims: Differences in SLE disease manifestations and severity occur between ethnic populations. The aim of this study was to determine the clinical and immunological profile of a longitudinal cohort of Singapore patients with systemic lupus erythematosus.

Patients and Methods: A longitudinal SLE study cohort was started in our Department of Rheumatology, Allergy and Immunology at Tan Tock Seng Hospital in May 2002.SLE patients fulfilling ACR criteria were recruited with their written informed consent. At each study visit, (4-monthly for patients with disease duration <3 years and annually for those with $>$ 3 years of disease) current and past disease manifestations, disease activity(SLEDAI and SLAM-R), damage (SDI), quality of life(SF-36 and SLEQOL), physician and patient global assessments, full blood count, ESR, complement C3 and C4 levels, and anti-dsDNA titres and therapy were recorded according to protocol, and serum stored.

Results: Of the 1005 patients recruited, 91.2% were female, 80.6 % Chinese, 12% Malay, 4.6% Indian and 2.8% of other ethnicity; 90.5% were non-smokers. The mean age at diagnosis was 31.1.years, mean disease duration 110 months(29% with disease of <3 years). The majority had low/inactive disease with SLAM-R scores ≤ 5 (inactive) in 74.5%, >5–≤ 10 (mildly active) in 11.1%, >10–≤ 15 (moderately active) in 2.7% and >15(severely active) in 1.9%.Active

hematological, renal, cutaneous, and nervous system involvement.was present in 60.4%, 31.1%, 17.7%, and 4.5% of patients respectively.he commonest cumulated clinical features since SLE onset were nephropathy(62.3%), alopaecia(59.3%), arthritis(54.6%), malar rash(53.6%) and fever(49.4%). Articular(93.3%) and cutaneous/vascular (92.9%)involvement was more common in females.The mean SLICC score at last review was 0.6. Antibodies to DNA, Ro, RNP, Sm, La and cardiolipin were found in 95.1%, 70.5%,63.3%, 54.8%, 29.2.% and 76.9% respectively. Serum IP-10, TNFα, IL-15 and complement C3 levels correlated with clinSLEDAI(SLEDAI with antidsDNA and C3, C4 omitted), while IP-10, IL- 8, antiDNAab, complement C3 and IL-6 levels correlated with SLAM-R, with IP-10 having the best correlation.

Conclusion: Although this Southeast Asian cohort manifests a clinical profile of greater disease severity, with over 60% with nephropathy and higher prevalence of ENA antibodies, the majority of patients had low disease activity.

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Gastrointestinal manifestations in 1,480 patients with systemic lupus erythematosus (GLADEL cohort).

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Background: SLE is an autoimmune inflammatory disease that can affect various organs and systems. The involvement of gastrointestinal system has been studied in a few cohorts.

Objective: to evaluate SLE patients with gastrointestinal involvement in a large, multiethnic, international longitudinal inception cohort.

Methods: SLE patients from 34 centers in nine countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela) with a recent diagnosis (≤2 years, ACR criteria fulfillment was not required) constituted the GLADEL cohort. Demographic, clinical and laboratory features of SLE patients were stored. Patients who presented peritonitis, chronic autoimmune hepatitis (CAH), primary biliary cirrhosis (PBC) or xerostomia were identified at GLADEL computerized databank. SPSS version 20 was used to analyses the frequency of each manifestation, as well the possible association with autoantibodies, other clinical and demographic characteristics, comparing patients with and without these manifestations. Mann-Whitney test was used to analyses quantitative variables and Chi-square or Fisheŕs Exact test were used to analyses categorical variables. $P < 0.05$ was considered significant.

Results: Among 1,480 patients included in the GLADEL cohort (90% were female), 68 (4.6%) presented xerostomia, 27 (1.8%) peritonitis and only 7 (0.5%) had CAH and 2 (0.1%) had PBC. All gastrointestinal involvement predominated on female gender and no significant difference was found regarding the gender distribution between patients with and without these manifestations. Patients with xerostomia were older than those without xerostomia (35.6±15.8 vs 29.2±12.1 y.o, p=0,001). No differences were found in patients with and without peritonitis regarding age and gender. Patients with xerostomia more frequently presented xerophthalmia ($p < 0,001$), positive anti-Ro/SSA antibodies (p=0.009) and normal C3 levels (p=0.03). They also presented less renal involvement (p=0,002) and glomerulonephritis (p=0.011). For the other hand patients with xerostomia presented higher SLICC at last evaluation (1.5±1.7 vs 1.9±1.7, $p < 0.001$). Patients with peritonitis presented more commonly pleuritis ($p < 0,001$) and pericarditis ($p < 0,001$). Although peritonitis did not be associated to anti-DNA antibody, it was associated with lower C3 (p=0.007) and C4 levels (p=0.038). Patients with peritonitis also presented higher maximum SLEDAI score at follow-up (20.8±8.7 vs 9.8±13.4, $p < 0.001$), higher median SLEDAI score (10.9±11.2 vs 4.9±5.4; $p < 0.001$) and higher SLICC score at last assessment (3.2±2.4 vs 1.5±1.6, $p < 0.001$) when comparing to patients without peritonitis.

Conclusion: Xerostomia and peritonitis were the most common gastrointestinal manifestations in this cohort. Xerostomia was associated with positive anti-Ro antibody and normal complement levels. Patients with xerostomia were older and presented less severe disease and less renal involvement. Therefore the association between xerostomia and higher SLICC score at last assessment was unexpected. For the other hand peritonitis was associated with higher SLEDAI and SLICC scores suggesting that patients with peritonitis had more severe disease and need be treated adequately to improve outcome.

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Pulmonary arterial hypertension in patients with systemic lupus erythematosus. analysis of prevalence in a series of patients by a screening program.

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Background and objectives: Pulmonary arterial hypertension (PAH) is an uncommon manifestation of systemic lupus erythematosus (SLE) that is associated with decreased survival. Reported prevalence is 0'5-14 %, according to echocardiography-Doppler (echoD) based studies that usually consider low systolic pulmonary arterial pressure (sPAP) diagnostic values (> 30 mm Hg) that may overestimate the percentage of patients affected. Moreover, annual screening of PAH by echoD is indicated in patients with scleroderma, another systemic autoimmune disease that is considered a high-risk population. If the reported high prevalence is confirmed in further studies, patients with SLE also should be considered as a high-risk group for developing PAH. The aim of the study was to determine PAH prevalence in our cohort of SLE patients.

Patients and method: A retrospective study that analyzed data of patients from a lupus cohort who were diagnosed with pulmonary hypertension (PH) or assessed in a systematic screening program for PAH developing since 2003. PAH was suspected when sPAP > 35 mm Hg. Patients were monitored if sPAP < 50 mm Hg and they were asymptomatic, and a diagnostic algorithm adjusted to international guides was performed if sPAP ≥50 mm Hg or patients were symptomatic, including right heart catheterism (RHC). We analyzed the prevalence of PH and its various causes, including PAH, as well as the possible association of PAH with demographic, clinical and immunological data.

Result: Three hundred thirty-eight patients were evaluated (94'1 % women). Mean age: 41'1 (13'1) years. Mean time from SLE diagnosis: 12'9 (8'9) years. sPAP was increased in 25 cases (7'4 %): 8 with lupus associated PAH (2 with other associated etiologies: portopulmonary hypertension in 1 and chronic thromboembolic PH in other), 1 with pulmonary capillary hemangiomatosis, 4 with PH secondary to left heart disease, 6 with normal sPAP on a new echoD or RHC and 6 remain on follow-up. Thus, patients with genuine PAH (those included

in groups 1 and 1' of the WHO classification) were 9 (2'6 %) and other 6 patients (1'7 %) had a slightly elevated sPAP value without apparent underlying cause. Association between possible or definite PAH and multiple demographic, clinical and immunological variables was assessed. We only found a statistically significant association with serositis (p 0'026).
Conclusions: The PAH estimated prevalence in our cohort of lupus patients is in the low range of the previously communicated (2'6-4'4 %) and much greater than in general population. Since SLE patients constitute a limited population, we think that echocardiographic screening for PAH, as in scleroderma, is justified.

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Comparing the Diseases Characteristics of Patients with Systemic Lupus Erythematosus inhabiting in two Different Regions of Turkey
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Objective: This study aims to investigate the features of SLE patients followed in two distinct clinics located in South and East Anatolia regions of Turkey.
Material and methods: Sixty-four patients from East Anatolia region (M/F, 9/55, median age 29,9±11,9), and seventy-four patients from South Anatolia region (M/F, 10/64, median age 37,3±11,3) were enrolled into study. A detailed data on file detection has been held for both patient groups recorded. All findings of both groups were compared.
Results: There was statistically significant difference concerning median ages of subjects between south and east Anatolia regions of Turkey (median age 29,9±11,9 vs 37,3±11,3 p=0,000). The was no significant difference concerning the patients' admission age to clinic, median diagnosis age, time between symptoms onset and diagnosis, and family anamnesis. However, symptoms onset age was significantly earlier among the patients inhabiting in east Anatolia (26,7±11,9 vs 37,3±10,6). Clinically, the SLE manifestations including malar rash, discoid rash, cerebral vasculitis, deep vein thrombosis, autoimmune troiditis, livedo reticularis, avascular necrosis, and anti-phospholipids syndrome were similar between the groups. Frequency of the leading manifestations of SLE including photosensitivity, oral ulcers, arthritis, serositis, Raynaud's phonemon, and alopecia were significantly higher among the patients enrolled from East Anatolia region (70,3% vs 24,3% p=0.000, 43,8% vs 10,8% p=0.000, 68,8% vs 22,9% p=0,000, 23,4% vs 4% p=0.001, 48,4% vs 8,1% p=0.000, 23,4% vs 2,7% p=0.000, respectively). Leading laboratory manifestations of both groups including hemolytic anemia, leukopenia, thrombocytopenia, anticardiolipin antibodies (ACA) IgG, IgM ACA, ANA, and anti-dsDNA were not significantly different between south and east Anatolia. However, lymphopenia was significantly elevated among the subjects enrolled from east Anatolia (78% vs 55,4% p=0.007). The concurrent renal involvement among the subject of both groups was very similar and the difference was not significant, however, there was a significant difference concerning the renal classification with renal biopsy. Renal biopsy was initiated to twenty-five patients from east Anatolia and 5 cases were classified as class II (7.8%), 6 cases as class III (9.4%), 12 cases as class IV (18.8%), and 2 cases as class V (3.1%). In south Anatolia renal biopsy was initiated to a total of nine cases; 6 subjects were classified as class IV (8.1%), and 3 subjects as class VI (4%).
Discussion and Conclusion: Geographic location and racial differences may affect the prevalence, clinical and laboratory findings, severity, and incidence of SLE. Therefore, genetic ancestry may play important role in clinical heterogeneity and variation of SLE patients. In our study, the difference resulted from genetic ancestry and geographic differences have been attributed to the socio-economic status of the subjects where especially the patients in East Anatolia are very likely to be delayed until their symptoms became severe and unaffordable.

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Mortality in hospitalized patients with systemic lupus erythematosus and hematologic manifestations: A case-control study
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Introduction: Hemolytic anemia, leukopenia, neutropenia, and thrombocytopenia are the more common hematological manifestations of systemic lupus erythematosus (SLE). These patients are considered good prognosis compared to patients with other major affected organs. Hematological manifestations appears to exert an impact of damage but not on mortality. However, little is known about its clinical course, morbidity and mortality during hospitalization.
Objective: The objective of this study was to evaluate the clinical, prognostic impact and outcome of hospitalized patients with SLE and hematological manifestations.
Patients and methods: We reviewed clinical records of all inpatients with diagnosis of SLE (ACR criteria, 1997) with hematological manifestations (hemolytic anemia, thrombocytopenia and neutrophenia) compared with inpatients without these manifestations, in a period from January 2009 to July 2012. We compared clinical, biochemical and immunological variables, SLEDAI score, organ involvement and causes of death. Statistical analysis included Student's t test, the chi square test and odds ratio (OR) with confidence intervals (CI) 95% were also calculated.
Results: We included 72 patients (83 events) with hematologic SLE (cases) and 123 patients with non-hematologic SLE (controls), most women (84%). The mean SLEDAI in cases on admission was 9.7±6.8 and in controls 11.0± 7.1 (p=NS). The number of organs involved in the cases was 2± 1 and 3±1 control group ($p < 0.01$). The hospital deaths were higher in cases than in controls: 23 (82.1%) vs 5 (17.9%) ($p < 0.01$). The main causes of death in the cases were: disease activity, hemorrhage, pneumonia and sepsis and in controls were diffuse alveolar hemorrhage, infections and kidney failure. The main variables associated with mortality in cases were: hematologic SLE (OR 8.89, 95% CI 3.24-24.5, $p < 0.01$), low C3 (OR 2.97, 95% CI 0.857-10.339, $p < 0.07$) and positive anti-La (OR 3.64, 95% CI 0.969-13.689, p=0.04).
Conclusions: Our study suggests that: 1. In hospitalized patients, hematological SLE have higher mortality in comparison with non-hematologic SLE. 2. The number of organs involved and SLEDAI score at admission had no impact on mortality. 3. The presence of anti-SSB/La and low C3 are factors associated with mortality. Patients with hematological manifestations have good prognosis, however, physicians should consider high risk when they are hospitalized.

P276

Mood disorders, education and beliefs influence adherence to medication in systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease, and multisystem nature of self-immune. O drug treatment in SLE is essential to improving survival rates and quality of life, as well as medical monitoring, which aims reducing inflammation, disease activity and damage. Adherence to treatment is defined as the patient's behavior coincides with medical recommendations in both non-pharmacological treatments as in pharmacological. The major reasons for non-adherence to treatment are forgetfulness, changes in the quantity of pills, prejudices, beliefs, socioeconomic reasons, side effects, lack of symptoms and the use of alcoholic beverage
Objective: To evaluate self-reported adherence to medications and medical recommendation in a cohort of SLE patients and to determine patient, medication and healthcare related factors associated with nonadherence.
Patients and methods: We conducted a cross-sectional study with consecutive patients followed in the outpatient UNICAMP. A questionnaire was developed to assess adherence with demographic information, feel about the disease and treatment, knowledge and proper use of medications and comorbidities. We also analyzed the presence of anxiety and depression questionnaire by HAD/CAGE and socioeconomic status. We performed a retrospective chart review for disease duration, disease activity (SLEDAI), damage index (SLICC).
Results: We included 207 (97.5% women) patients, 134 (67%) in stable..The mean age was 40.3 years and the average education of 9 years (SD = 2.5/variation 1-12 years). 85 (41%) said they were taking the medications correctly > 80% of the time and were considered adherent. Forgetfulness was the main cause of noncompliance identified. Univariate analysis found that nonadherent patients used more drugs, more different pills a day, more people were living in the same house, more children aged < 5 years, greater anxiety, fewer years of schooling, higher disease activity ($p < 0.05$). In multivariate analysis the lack of adherence was associated with anxiety: OR = 4.2 (95% CI = 2.7 to 7.8), depression: OR = 3.6 (95% CI = 1.9-6.3), age: OR = 2.3 (95% CI = 1.2 to 3.2) in children < 5 years: OR = 3.3 (95% CI = 1.8 to 5.2).
Conclusions: Most patients not using medications correctly by forgetfulness. In multivariate analysis nonadherence to this lower education, more children > 5 years, increased anxiety and depression. Identifying these factors may help in developing strategies to improve medication adherence in our service.
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Abnormalities of hippocampal signal intensity predicts hippocampal atrophy in systemic lupus erythematosus

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Objectives: To quantify signal abnormalities in the hippocampus (Hsig) of patients with systemic lupus erythematosus (SLE) and to determine if Hsig predicts hippocampal atrophy (HA) in SLE.
Methods: We screened consecutive SLE patients followed in a longitudinal cohort in the State University of Campinas. We excluded patients with any clinical factors associated with cerebral atrophy or vasculopathy or illiterate patients. We included all SLE patients with 2 magnetic resonance imaging (MRI) done with a minimum of 1 year interval. Healthy age and sex-matched individuals were selected as controls. All underwent a standardized neuropsychological evaluation. Individual results were converted into standard scores and compared to normative data. Subjects with a total score in any of the 8 domains $\leq$2 SD below the normative value were considered impaired. MRI was performed on a Helscint 2 Tessla scanner and T1 inversion recovery and T2 coronal images were used for analysis. The software NIH-Image was used for volumetric and signal quantification. Hippocampal volumes (HV) were determined by standardized protocols. Values diverging by 2 or more SD from the control mean were considered abnormal.
Results: We included 33 SLE patients (29 women; mean age 32.2±11.6 years) and 33 controls (25 women; mean age 34; SD12.9). At study entry, right (mean volume 1981 mm3; SD299.7) and left (mean volume 1910mm3; SD249.6) HV were significantly smaller in SLE patients when compared to right (mean volume 2351mm3; SD 263.6; $p < 0.05$) and left (mean volume 2262mm3;SD261.5;$p < 0.05$) HV of controls. After a mean follow-up time of 16 months (SD 4.2) we observed significantly smaller right and left HV in SLE patients ($p < 0.05$). No difference in HV was observed in controls. At study entry, HA was identified in the left hippocampus in 4 (12.1%) and in the right hippocampus in 5 (15.1%) patients and in no control. In the second MRI, HA was identified in the right hippocampus in 12 (36.4%) and in the left hippocampus in 13 (39.4%). The presence (r=0.66; p=0.01) and severity (r=0.87; p=0.001) of cognitive impairment correlated directly with HV. Hsig abnormalities were found at study entry in 15 (45.5%) patients. Hsig abnormalities in the body and tail of non-atrophic hippocampi correlated with progression of volume loss during the follow-up period (r=0.8 $p < 0.001$). The presence of Hsig in the head of atrophic hippocampi correlated with progression of hippocampal atrophy (r=0.73 p=0.005) during the same period. No correlation of Hsig and disease activity or prednisone dose was observed.
Conclusion: HA is frequently observed in SLE patients and volume loss is progressive in a subgroup of patients. The evaluation of Hsig is an easy tool to determine patients that may have progressive hippocampal volume loss and should be followed more closely with MRI and cognitive evaluation.
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The mosaic of autoimmunity in childhood-onset systemic lupus erythematosus

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Background: Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens and represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems. Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease characterized by varied clinical manifestations. "Mosaic of Autoimmunity" is the combination of factors associated with the induction of autoimmune diseases.
Objective: To determine the prevalence and clinical associations of autoimmune diseases in childhood-onset systemic lupus erythematosus.
Methods: We screened the charts of consecutive childhood-onset SLE patients followed in a longitudinal cohort at the pediatric rheumatology unit at the State University of Campinas. All patients had disease-onset before the age of 16. In all patients we yearly routinely investigate the presence of other autoimmune diseases yearly. Protocol

includes thyroid stimulating hormone and thyroid antibodies, clinical and ophthalmology evaluation and immunology evaluation for common autoimmune disease. Childhood-onset SLE patients were assessed for disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI)] both at study entry and over time.
Results: We identified 61 childhood-onset SLE patients. 57 (95%) patients were women with mean age of 17.85 years [Standard deviation (SD) ±3.89 years; range 10-29]. Mean disease duration was 12.47 years (SD±2.86; range 6-16 years). Other autoimmune diseases were identified in 20 (32.79%) patients; autoimmune thyroiditis in 6, Sjogreńs syndrome in 5, antiphospholipid syndrome in 3, autoimmune diabetes in 2, juvenile idiopathic arthritis in 2, dermatomyositis in 1 patient and primary immune deficiency in 1 patient. Increased TSH in the absence of thyroid antibodies was observed in 15 patients. The presence of thyroid antibodies in the absence of TSH abnormalities was observed in 5 (8%) patients. Five (8%) patients had evidence of streptococcal infections prior to disease-onset, however rheumatic fever was ruled out in all patients. Patients with autoimmune thyroid disease has a more indolent disease over the years, with a significant less number of flares (p=0.01).
Conclusion: We observed concomitant autoimmune diseases in 32% of patients with childhood-onset SLE. Patients with autoimmune thyroid disease had a more indolent disease over time. This elevated prevalence suggests that other autoimmune diseases should routinely been investigated in patients with childhood-onset SLE.
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Neuropsychiatric manifestations in juvenile systemic lupus erythematosus (JSLE)

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Background: The nervous system affects children and adults with systemic lupus erythematosus (SLE); their participation is associated with a worse prognosis and cumulative damage. In pediatric patients the onset and progression of the disease develop neuropsychiatric(NP) manifestations at higher frequencies than adults. The diagnosis of NP SLE is 70% of children, compared with only 28% of adults.
Objective: To analyze the prevalence of NP manifestations in JSLE.
Methods: We conducted a retrospective study including all patients with jSLE with disease onset before 16 years of age. The NP manifestations were analyzed by reviewing medical records, according to the nomenclature and classification of the American College of Rheumatology (ACR). NP manifestations were considered present when they occurred early in the first six months of disease and evolution, as occurred after this period.
Results: We included 71 patients (66 women) with mean age of 18.90 years (SD ± 4.64). At disease onset NP manifestations were present in 49 (69.01%) patients. The most frequently observed events at disease onset were: headache (61.97%), seizures (18.31%), psychosis (7.04%), depression (7.04%), anxiety (4,22%), acute confusional syndrome (1.41%) and movement disorder (chorea) (1.41%). In the follow-up of the disease, NP manifestations were observed in 56 (78.87%) patients. The NP manifestations more frequently observed were headache (59.15%), cognitive impairment (33.81%), anxiety (29.57%), depression (19.71%), seizure (9.85%), psychosis (7.04%), acute confusional syndrome (2.81%), movement disorder (chorea) (1.41%) and polyneuropathy (1.41%). Twelve (16.91%) patients had NP manifestations during the course of the disease and forty-six (64.79%) patients had NP manifestations in both the initiation and evolution (Figure 3). Six (8.45%) patients had recurrent seizures.
Conclusion: The neuropsychiatric manifestations are frequently observed in patients with JSLE.Most jSLE patients had recurrent NP manifestations during the course of the disease.
Grants: FAPESP 2010/136391 and 2008/029170, CNPq 300447/2009-4

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Invasive fungal infections in Systemic Lupus Erythematosus argentine patients

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Introduction: Infections are the leading cause of morbidity and mortality in patients with SLE. Invasive fungal infections (IFI) comprise a group of diseases caused by Cryptococcus, Histoplasma, Aspergillus and Candida. Few studies of IFI have been published in patients with SLE and associated factors have not been completely defined. Our **objectives** were: 1. To estimate the frequency of IFI in patients hospitalized with SLE. 2. To determine the risk factors associated with IFI in patients with SLE. 3. Compare LES + IFI group with control group (LES without IFI).
Methods: The medical charts of patients with IFI (EORTC/MSG, 2008) and SLE (ACR, 1997) admitted to our hospital from June 2001 until June 2012 were reviewed. To identify factors associated with IFI, we developed a case-control study (SLE + IFI vs. SLE alone) in a 1-3 ratio adjusted for sex and age and hospitalized for other reasons. Comparison was made of demographic characteristics, duration of disease and disease activity previous to IFI diagnosis, especially 3 months before infection. We defined severe activity with SLEDAI $\geq$ 8. In case of infection by Candida, was considered only its disseminated form.
Results: Ten cases of IFI were identified in 208 patients with SLE admitted between June 2001 and June 2012. We included 40 patients with SLE (10 with IFI and 30 controls). Of the SLE-IFI patients, 8 were women and the average age was 27.5 years (range, 19-42 years). 8/10 Cryptococcus neoformans, 1 Histoplasma capsulatum and 1 Candida albicans. Sites affected: 5 in peripheral blood, 5 at CNS, 4 in skin/soft tissue and 1 in pleura. Mortality was 40% ($P = 0.002$), with Cryptococcus neoformans being the most common germ. The SLE disease activity was severe in 70% of infected patients and no significant difference with the control group ($P = 0.195$) was found. We also found no association with leukopenia, lymphopenia, complement, anti-DNA, serum immunoglobulin, meprednisone doses > 20 mg/day or intravenous methylprednisolone pulses. The use of general immunosuppressive therapy showed significant association ($P = 0.016$), especially AZA ($P = 0.017$). CY ($P = 0.100$) and MMF ($P = 0.256$) were not significant.
ConclusionL: The frequency of IFI in SLE in our hospital was 4.8%. Cryptococcus neoformans was the most common etiologic agent (8/10) and primarily responsible for the deaths in this cohort (3/4). These data are consistent with publications in East Asia rather than North America where Candida spp. it is more common. Unlike other publications, previous immunosuppression was the only risk factor associated with the development of the infection, not the disease activity and corticosteroids. The latter could be explained by the high doses of steroids used in patients with SLE and organ damage present in the control group. We also found no association with serum immunoglobulin level. IFI should be suspected in hospitalized patients with SLE

and immunosuppression with CNS or atypical cutaneous manifestation in order to start appropriate treatment early and obtain favorable results.

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Outcome of Renal Transplantation in Lupus Patients with Positive and Negative Serology: Survival of the Graft and Patients After Transplant

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Background: To provide an overview of the characteristics of lupus patients with renal transplantation (RT) followed in the Lupus Clinic (1970-2012) and to determine the survival of the graft and patients after RT.

Methods: Patients who underwent RT were identified from the database. RT outcomes included: a) nonfunctional graft requiring dialysis within ≤3 weeks, b) graft failure requiring permanent dialysis after 3 weeks, c) graft survival not requiring dialysis and d) death.

We grouped the patients into graft failure and graft survival. The duration of graft failure was defined as the time between RT and subsequent permanent dialysis. The duration of graft survival was defined as the time between RT and recipient death or the end of the study with functioning graft.

Results: 25 (20 F) of 1645 patients followed in the lupus cohort and of 780 with renal involvement were identified with RT. 2 (8%) patients had a nonfunctional graft, 4 (16%) patients had graft failure (1 patient had failure < 5 years and 3 ≥5 years) and 19 (76%) patients had graft survival (8 had S ≥5 years) (Table 1). Patients with graft survival were older and had longer lupus duration compared to patients with failure at the time of RT. 25% of the graft failures had positive lupus serology (positive anti-dsDNA and/or low complements) compared to 47% in the graft survival 1 year prior to RT. 67% of the graft failures had positive lupus serology compared to 42% in the graft survival 1 year after the transplant.

The time to graft failure (n=4) was 5.75±4.99 years. In the failure group 3 patients died by 6±5.19 years and one patient is still alive. In the graft survival group 3 patients died by 5.6±4.6 years and one patient was lost of follow-up. Cause of death was not related to renal disease in 2 patients and unknown in one patient.

Conclusion: 25 of 780 lupus nephritis patients followed at the Lupus Clinic underwent RT. The persistence of serological abnormalities at the time of RT was not associated with graft failure.

Table 1. Characteristics if graft failure and graft survival patients.

	Graft Failure N=4	*Graft Survival (N=19)*
Sex	F75%	F84%
Age at lupus diagnosis	25.4+7.3	24.4+8.3
Age at transplant	29.8+9.1	40.0+9.5
Lupus duration at 1st clinic visit	5.9+4.0	7.2+7.8
Lupus duration at transplant	4.5+2.1	15.5+7.1
Ethnicity		
Caucasian	1	7
Black	1	6
Asian	2	2
Others	0	4
Positive DNA in 1 year prior	1/4	5/18
Low complements in 1 year prior	1/4	9/19
	1/4	9/19
Positive DNA and/or low complements in 1 year prior	2/3	8/19
Positive DNA and/or low complements in 1 year after transplant		
SDI at transplant	4.0+0 (n=4)	4.6+1.9 (n=17)
Time (duration on dialysis prior to transplant	3.9+2.4 (n=4)	5.8+5.6 (n=6)

(continued)

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Effect of Partial and Complete Proteinuria Recovery in Lupus Nephritis On Long Term Outcomes

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Background: The use of partial proteinuria recovery (PPR) or complete proteinuria recovery (CPR) as a primary endpoint led to more responders compared to CPR alone. The long term outcome of patients achieving PPR at 1 year is not well studied.

To determine the prognostic value of PPR and of CPR at 1 year on long term outcomes.

Methods: Active lupus nephritis (LN) patients registered at lupus clinic since1970 were studied. Proteinuria was defined as > 0.51g/24 hours. Patients with proteinuria and at least one of the urinary sediments (hematuria, pyuria or casts) present at entry into the study and persistent on 2 consecutive visits were enrolled.

CPR was defined as proteinuria <0.5g/24 hours. PPR was a decrease of ≥ 50% in the level of proteinuria from baseline. Proteinuria recovery was identified if present on 2 consecutive visits within 1 year.

Long term outcomes (death, renal failure, dialysis or kidney transplant, atherosclerotic events and severe damage with SDI > 3) by proteinuria recovery at 1 year were studied.: The trend of percentage of long term outcomes between different recovery end points at 1 year were studied using the Mantel-Haenszel test. Time to long term outcomes for different recovery end points was evaluated (Kaplan-Meier curves/Cox proportional hazard models).

Results: 196 patients (84% F) were identified. At 1 year: 24 patients achieved PPR, 26.5% CPR and 49.5% not recovered. 43% of the patients with PPR at 1 year achieved CPR at 2 years. eGFR < 15 was identified in 11% of the patients, dialysis or kidney transplant in 8%, atherosclerotic events is 4%, 11% of the patient died and 21% developed damage (SDI > 3). The trend for death and renal failure goes down in patients with CPR compared to PPR and no response (Table 1). Achieving CPR at 1 year protects against renal failure, accrual of severe damage and death. Achieving PPR at 1 year may protect against renal failure but not severe damage (Table 2).

Conclusion: Proteinuria recovery at 1 year is a predictive factor for long term outcomes. Although complete recovery is ideal, even partial recovery may be protective.

Table 1. Long term Outcome by Proteinuria Recovery @ 1 Year

Long Term Outcomes	*Proteinuria Recovery @ 1year*			*Trend Test*
After 1 year	*No Response n-97*	*Partial n=47*	*Complete n=52*	*p*
Death	15 (15%)	5 (11%)	2 (4%)	0.03
eGFR <15	16 (17%)	3 (7%)	2 (4%)	0.03

(continued)

Table 1. Continued

Long Term Outcomes	*Proteinuria Recovery @ 1year*			*Trend Test*
After 1 year	*No Response n-97*	*Partial n=47*	*Complete n=52*	*p*
Dialysis/Transplant	11 (12%)	4 (9%)	0 (0%)	0.01
Atherosclerotic	4 (4%)	4 (9%)	0 (0%)	0.35
SDI > 3	20 (27%)	11 (28%)	3 (7%)	0.02

Table 2. HR for long term outcomes by Proteinuria Recovery at 1 year.

Long Term Outcomes (After 1-year)	*Partial*		*Complete*	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*
Death	0.63 (0.23,1.74)	0.37	0.23 (0.05, 1.02)	0.05
eGFR < 15	0.38 (0.11, 1.30)	0.12	0.21 (0.05, 0.90)	0.04
Dialysis/Transplant	0.71 (0.23, 2.23)	0.56	No event	
atherosclerotic	2.02 (0.50, 8.07)	0.32	No event	
SDI > 3	0.96 (0.46, 2.01)	0.92	0.20 (0.06, 0.69)	0.01

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Serum Uric Acid is elevated in Lupus Nephritis with normal renal function.

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Background: Uric acid has been recognized as a potential mediator of endothelial dysfunction and kidney disease, however, there are scarce data characterizing the uric acid profile in lupus nephritis (LN).
Objectives: This study was aimed to examine the profile of serum uric acid in LN, by comparing lupus patients with and without nephritis with a normal renal function.
Methods: Thirty nine female patients that fulfill systemic lupus erythematosus (SLE). ACR criteria (1997), aged 18-45 years, were investigated. Patients with creatinine clearance lower than 80ml/min, use of salicylic acid, diuretics, cyclosporin, alcohol or other substances that interfere with serum uric acid were excluded. The SLEDAI was used to evaluate the disease activity. An age-mached normal female group (n=14) was the control group (Co). All individuals were investigated by laboratory assays: serum cretinine (Cr), serum uric acid (UA), urine analisys (U) and 24h proteinuria. SLE patients were separated in subgroups according to renal activity: 28 without (R-) and 11 with nephritis (R+). Data were analyzed by Mann-Whitney, Kolmogorov-Smirnov and Bonferroni tests.
Results: The three groups (Co, R- and R+ respectively) were similar regarding age (30.07+3.52 yrs, 30.61+5.41 and 32.91+7.01, P=0.38), creatinine levels (0.67+0.09 mg/dL, 0.71+0.18 and 0.65+0.20, P=0.53) and creatinine clearance (109.79+14.08 ml/min, 120.57+31.31 and 135.73+39.05, P=0.10). The SLEDAI was significantly higher ($p < 0.001$) for the group with renal activity (8.91+5.17) when compared with that with no renal involvement (1.46+2.59). The uric acid from patients with renal activity (5.43mg/dL+1.35) were significantly higher than those presented by patients with no renal activity (3.65mg/dL+1.09) and normal controls (3.79mg/dL+0.76) $P < 0.001$.
Conclusions: The serum UA are elevated in patients with SLE with nephritis, independently of reduced kidney function.

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The Effect of Disease Damage and Long-term Glucocorticoid on Bone Mineral Density, Microarchitecture and Bone Strength in Systemic Lupus Erythematosus

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Background and Objective: Patients with systemic lupus erythematosus (SLE) are predisposed to fragility fracture. Cumulative inflammation (disease damage) and glucocorticoid (GC) are deemed as two of the major clinical risk factors for bone loss in SLE. Mismatch between decrease in areal bone mineral density (aBMD) by dual-energy x-ray absorptiometry (DXA) and increase in fracture rate was noted in SLE patients and GC users. With the advent of the novel non-invasive 3 dimensional high resolution imaging techniques, alterations of volumetric BMD (vBMD) and bone microarchitecture are able to be measured. The objective of this study is to compare aBMD, vBMD, bone microarchitecture and strength between SLE patients and controls and to assess the influence of GC and disease damage on bone deterioration in SLE patients.
Methods: ABMD was measured by DXA at femoral neck (FN), total hip (TH), lumbar spine (LS) and distal radius, vBMD and bone microarchitecture by high-resolution peripheral quantitative computed tomography (HR-pQCT) at distal radius and micro-finite element analysis estimated bone strength in female SLE patients on long-term GC, SLE patients without GC and healthy controls.
Results: A total of sixty female SLE patients and 60 age-, sex-, body mass index-matched healthy controls were recruited in the study, among whom 30 patients were on long-term GC and 30 did not received GC for at least 10 years prior to study entry, among whom 21 had never treated with GC. The mean age was 46 years old of the entire cohort. Sixty percent of patients were postmenopausal, compared with 35% postmenopausal women in controls. Patients with GC were taking average prednisolone 6mg/d for median duration of 9.5 years with median cumulative dose since disease onset of 19.8 g. Compared with controls, aBMD at FN and TH, cortical area, average and cortical vBMD, cortical thickness significantly reduced in SLE patients after adjusted for menopausal status. Whole bone stiffness, failure load and apparent modulus therefore decreased in SLE patients after adjustment. When divided patients into two subgroups according to GC use, no significant difference in BMD, microarchitecture or bone strength was found between patients with GC and those without GC. No significant correlation between GC use (duration, average dose, cumulative dose and current dose) and bone quality parameters was found among patients with GC. Systemic Damage Index was significantly correlated with reductions of cortical area, D100, CtTh and apparent modulus in all SLE patients.
Conclusion: Bone density, microarchitecture and bone strength were inferior in SLE patients than controls, which may lead to bone fragility fracture. Inflammatory burden, but not GC, was the risk factor for deteriorations of bone quality in SLE.

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Similar initial response to therapy and long-term prognosis of Class III, IV-S and IV-G lupus nephritis: a single center study of 98 new-onset cases

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Objective: To evaluate whether the different ISN/RPS classes of proliferative lupus nephritis (LN) respond differently to first-line immunosuppressive therapy and have a distinct long-term prognosis.
Methods: Since 2001, new-onset ISN/RPS proliferative (III, IV-S or IV-G) LN was diagnosed in 98 patients at our institution. Their baseline renal parameters (including pathology indices) and their primary response to immunosuppression were compared, based on quarterly collected data during the first year. Results of a second biopsy, performed after a mean period of 30 months, were available in 45 patients. Mean clinical followup time was 76 months. Activity (range 0-42) and chronicity (range 0-6) indices were computed according to Morel-Maroger.
Results: As illustrated, mean baseline 24-h proteinuria was higher in class IV-G patients compared to IV-S and III and mean activity index lower in Class III versus IV-S and IV-G. Nevertheless, serum creatinine, serum albumin and 24-h proteinuria improved similarly over the first year in the 3 subsets. No differences were noticed at last followup. Activity and chronicity indices on the second biopsy did not differ between classes. Percentages of patients given cyclophosphamide, mycophenolate mofetil and azathioprine did not differ between groups. The rates of death and ESRD were low and similar between the groups.
Conclusion: These results, obtained in a large series of new-onset LN patients, suggest that subsetting proliferative LN according to the ISN/RPS classification does not provide valuable prognostic information.

24-h proteinuria (g; median/range)	*Baseline*	*Month 3*	*Month 6*	*Month 12*	*Last FU*
III (n=25)	1.9 (0.2-8.6)	1.1 (0.1-4.8)	0.7 (0.0-3.3)	0.3 (0.0-6.5)	0.2 (0.0-7.2)
IV-S (n=23)	1.6 (0.4-5.9)	1.1 (0.0-4.7)	0.4 (0.1-2.9)	0.2 (0.0-4.0)	0.1 (0.0-0.9)
IV-G (n=50)	3.6 (0.4-12.2)*	1.0 (0.1-6.3)	0.6 (0.0-5.7)	0.4 (0.0-4.4)	0.2 (0.0-4.8)

*: $p < 0.005$ vs III and IV-S

ISN/RPS Class		*First Biopsy*	*Second Biopsy*
III	AI (median; range)	4 (2-15)	2 (0-12)
	CI (median; range)	1 (0-4)	1 (0-4)
IV-S	AI (median; range)	9 (1-27)*	3 (0-18)
	CI (median; range)	1 (0-3)	1 (0-2)
IV-G	AI (median; range)	11 (3-22)**	2 (0-19)
	CI (median; range)	1 (0-2)	1 (0-3)

*: $p < 0.01$ vs III; **: $p < 0.0001$ vs III

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Frequency and Risk Factors of Avascular Necrosis in Patients with Systemic Lupus Erythematosus

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Background: Avascular necrosis (AVN) is the death of the bone by the collapse of its architecture. Etiology of AVN is multifactorial and steroid usage is significant factor after the trauma.Systemic Lupus Erythematosus (SLE) is one of the most common underlying disease in the AVN development. We investigate the effect of daily or alternate day steroid treatment on development of AVN in SLE patients
Methods: This study included, 127 SLE patients who were >18 years old and fulfilled 1997 ACR criteria and have been followed in our Rheumatology Department between July 2010 and May 2011. Patient's gender, age, age at the time of diagnosis, disease duration, hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, smoking history; body mass index, anemia, menopause, severe organ involvement other than diagnostic criteria, reynaud's phenomenon, cushingoid body habitus, vasculitis were recorded. Association of antiphospholipid syndrome or lupus anticoagulant and/or anticardiolipin antibody positivity were recorded separately. Glomerular filtration rate, proteinuria, osteoporosis were also recorded. SLEDAI scores estimated by SLEDAI-2K and also were calculated according the situation 6 months before the AVN diagnosis. Steroid usage of the cases were analyzed detailed. High dose steroid usage defined as > 30 mg/day steroid usage at any time. Steroid usage duration, high dose steroid; daily or alternate day, pulse steroid and their combination usage were recorded separately. In the cases that AVN developed, the above factors were examined according to the AVN diagnosis time with radiology.
Results: 11 (8.7%) of 127 SLE cases had AVN. Demographic features of AVN group (11 cases) and non-AVN group (116 cases) were similar. Between the co-morbid situations, only hyperlipidemia was statistically significant in AVN group ($p < 0.008$). Antiphospholipid syndrome, reynaud's phenomenon and vasculitis, SLE disease activity (SLEDAI) score which is evaluated greatly in the previous studies, were similar in the both groups. But, cushingoid body habitus and proteinuria were statistically significant in the AVN group ($p < 0.001$ and p=0,013). All of 11 AVN cases were osteoporotic ($p < 0.02$). High dose steroid usage was more frequent in the AVN group and all cases of the AVN group have used daily steroid (p=0.034 and $p < 0.001$). Although the non-AVN group have used mostly alternate day steroid ($p < 0.001$). Steroid usage duration, total steroid dose, total alternate day, total pulse, mean daily steroid dose were not different; but total daily steroid dose was significantly high in the AVN group (p=0,025). Bilaterally hip avascular necrosis mostly occurred.
Conclusion: In our study, symptomatic AVN frequency in the SLE cases was 8.7%. Hyperlipidemia, cushingoid body habitus, disease activite proteinuria, osteoporosis, high dose steroid, total daily steroid dose and daily steroid intake were the AVN risk factors. But, multivariate analysis showed that daily steroid usage is the sole risk factor for AVN development independent from its dose. The striking hypothesis of our study that not mentioned in the previous studies was the alternate day steroid usage may decrease AVN development.

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Retinal vasculopathy in patients with systemic lupus erythematosus: experience from a Chinese center

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Background: It is well reported that retinal vasculopathy (RV) are not rare and clinical relevant to the other manifestations in patients with systemic lupus erythematosus (SLE). But there is little data on this phenotype in Chinese patients, which might be underestimated the importance in daily practice.
Objective: To investigate the clinical characteristics and significances of RV in Chinese patients with SLE.
Methods: A retrospective case-control study was conducted in Peking Union Medical College Hospital. Twenty-five cases with SLE associated RV diagnosed from 2006 to 2012 were enrolled as study

group. Another seventy-five lupus patients without RV were randomly-pooled as control group. Medical charts were carefully reviewed to collect demographic data, clinical features, laboratory results, SLE disease activity evaluations and ophthalmic examinations for the analysis.

Results: The prevalence of RV was approximately 0.94% in our cluster of SLE patients. The ophthalmic examination revealed cotton-wool spots (10/25), retinal vascular stenosis (13/25), hemorrhages (15/25) and vaso-occlusion (8/25). The ophthalmic episodes occurred at earlier stage in SLE patients with RV compared to the controls (23.2±7.7 vs 74.7±11.5 months, P=0.004). The presence of antiphospholipid antibody was not proven to be associated with RV, but the inverse association of anti-SSA antibody with RV was detected (36% vs 55.3%, p=0.01). RV was found to be associated with neuropsychiatric lupus (NPSLE) (60% vs 26.7%, P=0.002) and the significantly higher SLE disease activity index (SLEDAI) scores (20.1±4.6 vs 10.5±6.2, $P < 0.001$). Although with aggressive treatment, most patients with RV (18/25) had little improvement of visual complications.

Conclusions: SLE associated RV is threatening with poor outcome. Awareness of retinal vascular diseases suggests ophthalmo-fundoscopic detection in active early-stage patients with SLE. Early immunosuppressive interventions might not only improve the prognosis of RV, but also prevent from the development of NPSLE.

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ECG and 24-hour Holter monitoring evaluation of cardiac arrhythmic events in systemic lupus erythematosus (SLE): the beneficial effect of antimalarials

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There are no prevalence studies of arrhythmias and conduction disturbances in a large SLE population determining the influence of disease factors and long-term antimalarial use.

Methods: Three-hundred seventeen consecutive SLE patients (ACR criteria) age > 18 y were evaluated by resting-ECG and 24-hour Holter monitoring (n=142, randomly selected) for arrhythmia, conduction disturbances, heart rate variability, and repolarization parameters. Data were obtained in an ongoing electronic database protocol which consists of an extensive clinical/ laboratorial/treatment evaluation.

Results: The majority was female (91%) with medians of age and disease duration of 40.25 years and 11.36 years, respectively. Renal involvement was observed in 26.2% and hypertension in 18.9%. Antimalarial therapy (minimum of 6 months) was observed in 69% with a mean duration of 8.47 ± 6.74 years. Resting-ECG abnormalities were detected in 66 patients (20.8%): long QT in 14.2%; RightBBB in 1.9%; LeftBBB in 0.6%; 1st degree AV-block in 1.6%; sinus bradycardia in 1.3%; sinus tachycardia in 1.3%, and supraventricular tachycardia in 0.3%. Prolonged PR interval was associated with less chloroquine use (p=0.01), shorter chloroquine treatment duration (1.00±2.45 vs. 6.10±6.88 years, p=0.018) and older age (54.17±7.33 vs. 42.26±13.25 years, p=0.029). Holter monitoring events were observed in 121 patients (85.2%): HR < 50bpm in 31.6%; pauses > 2.0s in 2.8%; atrial tachyarrhythmia in 18.3%; atrial isolated ectopies in 63.4%, ventricular ectopies in 45.7%, and ventricular tachycardia in 2.8%. Tachyarrhythmias were associated with shorter chloroquine treatment duration (7.05±7.99 vs. 3.63±5.02 years, p=0.043) with a trend to less use of chloroquine (p=0.054), and older age (40.19±11.54 vs. 52.50±12.02 years, $p < 0.001$). Clinical and laboratorial variables such as renal and cardiac insufficiency, hypertension, and anti-La/SS-B were not associated with conduction abnormalities ($p > 0.05$), except for anti-Ro/SS-A with an association with supraventricular arrhythmia (p=0.042). Logistic regression model revealed that predictors for supraventricular tachyarrhythmia (AT/AF) were age ($p < 0.001$; OR=1.100; IC95%=1.050-1.154) and shorter antimalarial use (p=0.035; OR=0.921; IC95%=0.853-0.994).

Conclusion: Antimalarials seem to have a protective role in the unexpected high rate of cardiac arrhythmias and conduction disturbances observed in SLE. Further studies are necessary to determine if this anti-arrythmogenic effect is due to the disease control or a direct effect of the drug.

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Evaluation of arterial stiffness by pulse wave velocity in active lupus patients

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Pulse wave velocity (PWV) and echo-tracking device are noninvasive methods to measure arterial stiffness, distensibility, compliance, and elasticity of the arterial wall. The aim of this study was to assess the influence of disease activity on arterial wall in pre-menopausal female systemic lupus erythematosus (SLE) patients with low coronary artery disease (CAD) risk factors.

Methods: Thirty-seven female SLE patients aged < 40 years old and < 10 years of disease duration were selected. Exclusion criteria were smoking, arterial hypertension, diabetes mellitus, obesity, chronic renal failure, secondary antiphospholipid syndrome, and pregnancy or menopause at the time of the study. Patients were divided into ACTIVE (SLEDAI > 4) (n=11) and INACTIVE (SLEDAI < 4) (n=26) and compared to twenty-five healthy female controls. All subjects were evaluated by carotid-femoral pulse wave velocity (PWV) and common carotid echo-tracking device. Serum lipoprotein and apolipoprotein levels were determined as well as homocysteine and CRP.

Results: Age (26.9 ± 6.0 vs. 28.4 ± 5.0 years, p=0.33) and body mass index (BMI) (22.7 ± 3.4 vs. 22.6 ± 3.7 kg/m2, p=0.91) were similar in SLE patients and controls. SLE patients had mean disease duration of 39.3 ± 26.0 months with mean current and cumulative prednisone doses of 20.0 ± 20.1 mg/d and 19.4 ± 12.9 g, respectively. The ACTIVE group had higher levels of SLEDAI compared to INACTIVE (9.67 ± 5.31 vs. 0.52 ± 0.87, $p < 0.001$) and had higher triglycerides, apoB, total and LDL cholesterol levels compared to INACTIVE ($p < 0.05$). Interestingly, the arterial stiffness determined by PWV was lower in the entire SLE group compared to CONTROL (7.52 ± 1.14 vs. 8.14 ± 1.07 m/s, p=0.04). PWV was also significantly different among the three studied groups (p=0.01): ACTIVE group had lower PWV levels compared to INACTIVE (6.89 ± 1.00 vs. 7.79 ± 1.10 m/s, $p < 0.05$) and also to CONTROL (6.89 ± 1.00 vs. 8.14 ± 1.07 m/s, $p < 0.05$). A significant negative correlation was detected between PWV and SLEDAI (r=-0.354, p=0.03) but not with all other inflammatory and lipid measurements. In contrast, the vessel structural evaluation revealed that all carotid echo-tracking parameters were similar among groups: intima-media thickness (IMT) (p=0.50), diastolic diameter (p=0.34), distensibility coefficient (p=0.98), compliance coefficient (p=0.74), and elastic incremental modulus (p=0.87).

Conclusion: This is the first demonstration that lupus activity leads to a striking reduction in arterial stiffness as measured by aortic PWV even in a low CAD risk SLE population. The concomitant association with high triglycerides, total and LDL cholesterol in active disease suggests that this functional alteration may represent an early vessel inflammatory damage of premature atherosclerosis.

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Depression, Anxiety, Anger, Fatigue and Quality of Life in Systemic Lupus Erythematosus: Relationship to the disease activity and damage

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Background: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease in which almost every organ may be affected. Various psychological problems are associated with systemic conditions, but the influence of SLE is still a matter of discussion. We evaluated depression, anxiety, anger, fatigue and quality of life in patients with SLE, compared to healthy controls. We also investigated the relationship between these psychological problems, disease activity and damage in patients with SLE.
Patients and Methods: 108 patients with SLE and 52 healthy controls completed a psychological questionnaire. Psychological parameters were assessed as follows: depression, Center for Epidemiologic Studies Depression Scale (CES-D); anxiety, Hospital Anxiety and Depression Scale (HADS); anger, State Trait Anger Expression Inventory (STAXI); fatigue, the Profile of Mood States fatigue-inertia scale (POM); quality of life (QOL), Functional Assessment Chronic Illness Therapy (FACIT). Disease activity and damage index were measured by the SLE Disease Activity Index (SLEDAI) and the SLE Collaborating Clinics/American College of Rheumatology (SLICC/ACR), respectively.
Results: Patients with SLE showed higher symptoms of depression, anxiety, anger and fatigue ($p = 0.005$; $p = 0.057$; $p = 0.044$; $p = 0.020$, respectively), and lower level of QOL ($p = 0.003$) than normal controls. In the patients with SLE, mood symptoms such as depression, anxiety, and anger were correlated with each other (depression and anxiety: $r = 0.710$, $p < 0.001$; depression and anger: $r = 0.602$, $p < 0.001$; anxiety and anger: $r = 0.546$, $p < 0.001$). Fatigue and QOL were closely correlated with mood symptoms, respectively. The patients with higher prednisolone use (> 7.5 mg/day) showed higher levels of depression, anxiety, anger and fatigue ($p = 0.002$; $p = 0.022$; $p = 0.027$; $p = 0.010$, respectively), and lower level of QOL ($p = 0.001$) than the patients with lower prednisolone use ($\leq$ 7.5mg/day). However, there were no significant differences in evaluating these parameters according to disease activity or damage index.
Conclusions: The patients with SLE had higher levels of depression, anger and fatigue and lower level of QOL compared to healthy controls. Psychological parameters were affected by daily glucocorticoid dose rather than disease activity or damage index. These findings suggested that the comprehensive evaluation of the various psychological problems could be helpful to SLE patients, especially those with higher doses of glucocorticoid, even if disease activity and damage are not severe.

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Depression has only a marginal contribution to cognitive impairment in systemic lupus erythematosus patients

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Objective: The role of depression in cognitive impairment has gained interest in neuropsychiatric research. In systemic lupus erythematosus (SLE), depression and cognitive dysfunction may co-exist. The aim of the study is to define the extent to which depression symptoms contribute to cognitive impairment in SLE patients.
Methods: Clinical evaluation, education, age, Hospital Anxiety and Depression Scale (HADS), and cognitive function were recorded in 82 SLE patients and 22 healthy controls, all Chilean women. Major depression episode (MDE) according to a structured interview MINI-plus was applied in SLE patients. Cognitive function was measured using a neuropsychological battery (CANTABeclipseTM) assessing tests in attention (reaction time, rapid visual processing), visual memory (paired associates learning), executive function (intra/extra dimensional shift, stockings of Cambridge, spatial working memory) and response control domains (stop signal tasks). In order to evaluate the influence of health status (SLE or control), age, education years, and HADS depression and anxiety scores on cognitive outcomes, ANCOVA models with stepwise selection by the Akaike Information Criteria were performed (P value < 0.05). Additionally, multivariate models were protected from overfitting according to the shrinkage method.
Results: MDE was diagnosed in 22% of patients. Cognitive deficit defined by < -2 SD in $\geq$ 2 domains in any subtest affected 16 (20%) patients, and no controls ($P = 0.007$). Multivariate analysis models showed that worse performances in tests of visual memory domain (paired associates learning), and executive function (spatial working memory) significantly associated with SLE and aging, while depression affected significantly only executive function domain Intra/extra dimensional shift subtests.
Conclusion: Depression only marginally contributes to cognitive impairment in SLE, suggesting that different pathogenic mechanisms drive this neuropsychiatric manifestation in this autoimmune disease.
Disclosure: None

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Prevalence of Lupus Nephritis in Argentina Grupo de Estudio de Lupus de la Sociedad Argentina De Reumatología.

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Objective: To analyze the prevalence of Lupus Nephritis (LN), the predominant histological class as well as the demographics, clinics, serological and cumulative damage associated.
Patients and methods: This is a multicentre, observational and transversal study with consecutive SLE (ACR97) patients $\geq$ 18 years age. Data from cases with LN are compared with those without LN. The categorical variables are analyzed with chi test and continuous with Student test.
Results: Between February and November 2012, 649 patients were registered from 24 Argentine centres. 315/649 (48.5%) had current or past LN.

268/566 (47.4%) patients with LN were women and 47/83 (56.6%) men (OR: 0.69, P=0.11, IC: 0.42-1.12). The average age at the time of entering to the study was 36±11 vs. 40±13 years age (NS), the age at SLE diagnosis was 27±10 vs. 33±13 years (NS), the SLE evolution was 114±100 vs. 87±81 months (p=0.0001). 95% were urban residents vs. 98% (NS).

The SLE criteria classification number was 7±1.6 vs. 5±1.4 (NS). The clinical variables associated were malar rash: 70.5% vs. 62.6% (p=0.031, OR: 1.43, CI: 1.02-2.01; serositis: 36.7% vs. 25.7% (p= 0.003, OR: 1.67, CI: 1.18-2.37); cumulative anti-dsDNA antibodies: 67% vs. 47 ($p < 0.001$, OR: 2.27, CI: 1.61-3.20). The SLICC/ACR index was 1.42 ±2.6 vs. 0.68 ±1.26 (NS). 16/315 (5%) patients presented end stage renal disease.

Renal biopsy was done in 266/315 (84.4%) cases. The histological classes were: Class I: 3 patients (1.12%), class II: 39 (14.6%), III: 42 (16%), IV: 153 (57.5%), V: 35 (13%), VI: 2 (0.75%), 2 without results. The main associations were: class III-V: 2, IV-V: 8 cases.

61 cases had a repeated renal biopsy and 8/9 class III switched to class IV or V and 25/33 class IV switched to class V, or IV plus chronicity index.

At the time of entering to the study 98 patients had active LN (Proteinuria > 500mg/24hs). It was associated with the presence of hypocomplementemia (OR: 2.69, p=0.0001, CI: 1.58-4.57) and anti-dsDNA antibody positive (OR: 4.77, $p < 0.001$, CI: 2.63-8.67).

Conclusion: 48.5% of the SLE studied patients presented Lupus Nephritis. They had more frequently malar rash, serositis and anti-dsDNA antibodies positive. The main histological class was class IV. Patients with LN tended to be younger and with longer SLE evolution. Patients who had a second biopsy showed frequent change to a more severe histological class.

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Frank's sign in systemic lupus erythematosus – an old cardiovascular risk factor viewed from a new perspective

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Introduction: Increased prevalence of cardiovascular disease in patients with systemic lupus erythematosus (SLE) cannot be explained simply by the presence of traditional cardiovascular risk factors. The Frank's sign (FS) is a diagonal earlobe crease extending from the tragus across the lobule to the auricular margin. Several studies suggested the role of FS as an independent factor of cardiovascular risk. The aim of this study is to determine the frequence of FS within a sample of patients with SLE and its association with the presence of traditional cardiovascular risk factors.

Patients and Methods: We analyzed 100 SLE and 104 rheumatoid arthritis (RA) patients subsequently examined in the rheumatology outpatient clinic and 110 patients without a diagnosis of systemic autoimmune disease subsequently examined in the traumatology outpatient clinic (control group). Data were obtained by survey, clinical examination and from medical records. Demographic, clinical and laboratory variables were registered. The local ethics committee approved the study protocol and all patients gave appropriate informed consent. Results were analyzed by the Pearson chi-square test and Student t-test, using the software package Statistica (StatSoft, Tulsa, OK, USA).

Results: Frequence of FS was 37/100 in patients with SLE, 66/104 in patients with RA and 33/110 in the control group. FS was more frequent among RA patients compared to patients with SLE and the control group ($p < 0.001$). The mean age of SLE patients with FS (57.89±11.90) was significantly higher than the age of SLE patients without FS (40.79±10.85, $p < 0.001$). Body mass index (BMI) and waist-hip ratio of SLE patients with FS were significantly higher compared to SLE patients without the sign (Table 1). Conversely, anti-Sm antibodies were more frequent in the group of SLE patients without FS (Table 2). No significant difference was revealed between SLE patients with and without FS in the frequence of other traditional cardiovascular risk factors and in the fulfillment of selected American College of Rheumatology (ACR) classification criteria and subcriteria for SLE associated with elevated cardiovascular risk.

Conclusions: This study revealed a higher prevalence of FS among patients with SLE and RA, albeit the observed difference was significant only for the comparison of the RA with the SLE and control group. Further research is needed to elucidate clinical implications of our findings, especially of the higher frequence of FS among anti-Sm negative SLE patients.

Table 1.

Traditional cardiovascular risk factors	*Frank's sign present*	*Frank's sign not present*	*P value*
Body mass index (kg/m^2)	26.23±4.03	23.61±7.77	0.002
Waist-hip ratio	0.89±0.10	0.81±0.12	0.001
Smoking	8/37	22/63	0.161
Arterial hypertension	16/37	23/63	0.505
Hyperlipidemia	9/36	25/63	0.139
Family history of cardiovascular disease	28/37	44/63	0.530

Table 2.

Selected ACR classification criteria and subcriteria for SLE	*Frank's sign present*	*Frank's sign not present*	*P value*
Renal disorder	7/34	17/55	0.286
Immunologic disorder	27/34	51/55	0.064
Anti-DNA	22/29	39/43	0.086
Anti-Sm	3/29	15/43	0.018
Elevated serum anticardiolipin level	14/29	19/43	0.733
Positive lupus anticoagulant test	4/29	3/43	0.338
Positive antinuclear antibody	33/34	53/55	0.859

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Echocardiographic alterations in a series of patients with systemic lupus eruythematosus.

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Background and Objectives: Cardiac involvement is frequent in patients with systemic lupus erythematosus +v(SLE). All the anatomical heart structures can be affected (Libman–Sacks verrucous endocarditis, miocarditis and pericarditis) and epidemiological studies show an increase of cardiovascular events in lupus patients (pts).

Objectives: To describe prevalence and types of echocariographic alterations in a series of patients (pts) wiit systemic lupus erythematosus (SLE).

Methods: A descriptive study based on the assessment of echocardiograms performed on a cohort of patients diagnosed with SLE (ARA criteria) and followed up in a specialized unit in systemic autoimmune diseases at an Andalusian (Spain) third level hospital. Most echocardiograms were performed as part of the screening program of pulmonary arterial hypertension that is being carried out in our unit.

Results: 387 patients (pts) were assessed. Echocardiograpic alterations were detected in 125 pts (37.3%): 1.- Mitral valvulopathy in 38 pts

(9.8%) with insufficiency in 35 (9%, mild in 27 -7.1%- y moderate en 8 -22.9%-) and stenosis in 3 (0.8%, mild in 1 -33.3%- and moderate in 2 -66.7%-). 2.- Aortic valvulopathy in 30 pts (7.7%) with insufficiency in 21 (5.4%, mild 15 -71.5%-, moderate in 5 -23.8%- and severe in 1 -4.7%-) and stenosis in 9 (2.3%, mild in 4 -44.4%- and moderate in 5 -55.6%-). 3.- Tricuspid insufficiency in 37 pts (9.5%, mild in 32, moderate in 3 and severe in 2) and was associated with high systolic pulmonary pressure, only in 19 cases. 4.- Diastolic dysfunction in 27 pts (7%), mild in all of them. 5.- Pericardial effusion in 19 pts (4.9%), mild in16 (84.2%) y moderate in 3 (15.8%). 6.- Other less frequent alterations: atrial dilations in in 7 pts (1.8%, left in 6 -85.7%- and right in 1 -14.3%-), interauricular septum aneurism in 4 (1%), left ventricular (LV) hypertrophy in 3 (0.8%), LV systolic dysfunction in 2 (0.5%), mitral valve prolapse in 1 (0.2%) and segmentary contractile alterations with ischemic myocardiopathy in 1.

Conclusions:The systematic echocardiogram study allowed us to detect a high prevalence of alterations amongst lupus patients.The most frequent alteration was valvular dysfunction, the left side as well as the trycuspid.

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Sleep Quality in childhood-onset Systemic Lupus Erythematosus

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Background: Patients with childhood-onset systemic lupus erythematosus (cSLE) are more susceptible to sleep fragmentation, by factors such as depression, nocturnal episodes of pain without specific origin, associated with neurodegenerative symptoms, shortness of breath, sweating, palpitation, and use of medications such as corticosteroids. Sleep quality and its influence on quality of life of patients with cSLE is poorly studied, and has extreme importance, since a poor sleep quality leads to disorders such as fatigue and diurnal variation of mood.
Objective: To analyze sleep quality and to correlate sleep quality with the presence of mood disorders, inflammatory markers, disease activity and damage in patients with cSLE

Methods and Patients: We conducted a cross-sectional study with the inclusion of consecutive patients followed in the outpatient pediatric rheumatology and a control group of healthy individuals. Sleep quality was assessed using the Index of Pittsburgh sleep quality (PSQI), which is divided into: subjective quality, latency, duration, habitual efficiency, disturbances, use of sleeping medication, daytime dysfunction, anxiety was assessed using the Beck Anxiety Inventory (BAI), depression using the Beck depression Inventory (BDI), disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and damage through the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC-ACR).
Results: We included 48 patients with cSLE (mean age 17 years, standard deviation (SD) = 11.6) and 35 controls (mean age 19 years, SD = 13.1). poor sleep quality was observed in 14 (30%) patients with cSLE and 12 (23 %) controls ($p \leq 0.001$).

In univariate analysis, anxiety was associated with sleep quality ($r = 0.5$ - $p \leq 0.001$), sleep latency ($r = 0.2$ - $p < 0.05$), sleep disorders ($r = 0.4$ - $p \leq 0.001$) and daytime dysfunction ($r = 0.5$ - $p \leq 0.001$). Depression was associated with sleep quality ($r = 0.5$ - $p \leq 0.001$), sleep latency ($r = 0.4$ - $p \leq 0.001$); sleep disorders ($r = 0.5$ - $p \leq 0.001$) and daytime dysfunction ($r = 0.5$ - $p \leq 0.001$). SLEDAI ($r = 0.3$ - $p < 0.05$) was associated with sleep disorders.
Conclusion: Patients with SLE have worse sleep quality than they reported; the PSQI components of sleep quality evaluators were associated with anxiety, depression, and disease activity.
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Prevalence and features of metabolic syndrome in childhood-onset systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a systemic inflammatory disease characterized by periods of exacerbation and remission. Premature atherosclerosis and CVD became one of the major co morbidity in SLE and the effect of metabolic derangement, and in particular the role of metabolic syndrome (MetS), on cardiovascular risk has gained increased attention in SLE.
Objective: To estimate the prevalence and features of metabolic syndrome (MetS) in childhood-onset systemic lupus erythematosus (cSLE) according to different MetS criteria. To determine association between MetS and SLE or treatment features.
Methods: Cross sectional study of 64 consecutive cSLE patients and 54 healthy controls. Controls were matched by age and sex to cSLE patients. All individuals were assessed for anthropometric and MetS features according to World Health Organization (WHO), Adult Treatment Panel III (NCEP-ATP III) and International Diabetes Federation (IDF) criteria. cSLE patients were further assessed for clinical and laboratory manifestations, disease activity (SLEDAI), damage scores (SDI), current and cumulative drug exposures.
Results: Thirty-one cSLE patients [mean age of 14.1 years (SD) ±2.2 years)] and 30 healthy controls [mean age 12.9 (SD±2.7 years)] were <18 years and 33 cSLE patients [mean age of 20.7 years [Standard deviation (SD) ±2.9 years] and 24 healthy controls [mean age 21.7 (SD±1.5 years)] were ≥18 at study entry.

MetS was observed in 2 (6.4%) cSLE < 18 according to WHO, 9 (29%) cSLE < 18 according to NCEP- ATPIII and 8 (25.8%) cSLE < 18 according IDF criteria. Controls < 18 did not meet any criteria for MetS, independently of the definition used.

The prevalence of the MetS in cSLE ≥18 was 9.1% according to both IDF and NCEP-ATPIII criteria. No patients ≥18 met OMS criteria. Controls ≥18 did not meet any criteria for MetS, independently of the definition used.
Conclusions: This study shows a high prevalence of MetS in cSLE patients. With exception for OMS definition, we observed a similar prevalence of MetS when using NCEP-ATPIII and IDF definitions in cSLE. Identification of MetS is very important to indicate preventive strategies and reduce cardiovascular morbidity and mortality in cSLE.
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Late onset systemic lupus erythematosus. Case Study

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Objective: Systemic lupus erythematosus (SLE) is a multisystem disorder that predominately

affects women of the reproductive age. Onset of the disease beyond the age of 50 years is unusual. This study was undertaken to compare retrospectively the clinical and laboratory features between early and late onset (onset of disease beyond the age of 50 years) SLE patients in a Venezuelans population.
Methods: Case records of all SLE patients who attended our rheumatology service (Centro Nacional de Enfermedades Reumáticas. Caracas, Venezuela) between 2005 and 2011 were reviewed. Patients with a disease onset beyond the age of 50 years were identified.

Eleven hundred consecutive SLE patients who had their disease onset before the age of 50 were recruited as controls. The presenting clinical features, autoantibody profile, number of major organs

involved, SLICC/ACR, and the use of steroids and cytotoxic agents in the two groups of patients were obtained and compared.
Results: 22 patients with late onset SLE were identified. All the female patients in the late onset group were postmenopausal. The female to male ratio was 12.2 to 1, compared with 13.3 to 1 in the control group ($p > 0.92$). There were no significant differences in the presenting features between the two groups except for a lower prevalence of malar rash (21% v 9.6%, $p < 0.0001$) and a higher prevalence of rheumatoid factor (52% v 1%, $p < 0.0001$) and Anti-RNP autoantibody (42% v 7%, $p < 0.0001$) in the late onset patients. Found a high association with scleroderma (9% vs. 0.11%, $p < 0.05$) in the late-onset group, whereas in the control patients there was high association with antiphospholipid syndrome (2% v 29.4%, $p < 0.001$), the greatest effect is evidenced in joints and myopathies (89% v 16%, $p < 0.001$) prevalence of late-onset group, nephritis (6.7% v 62%, $p > 0.0001$) in the control group dominance. SLICC/ACR was lower in the group of late-onset SLE ($p < 0.001$).
Conclusion: Late-onset SLE Venezuelans tend to have a more benign course with less involvement of organs and less organ damage (SLICC/ACR). The significantly higher incidence of arthritis in the presence of RF and anti-RNP can help us differentiate (diagnose) earlier in these patients. Milder disease in postmenopausal patients suggests that estrogen may influence disease activity state.

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Increase in Vitamin D Improves Disease Activity and Systolic Blood Pressure in Systemic Lupus Erythematosus

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Background: Vitamin D deficiency has also been associated with different chronic conditions including cardiovascular diseases. In SLE, it may be associated with the interferon gene signature. We investigated whether an increase in vitamin D levels was associated improvement in disease activity and blood pressure in SLE patients.
Patients and Methods: 1006 SLE patients were followed in a prospective observational study for 138 weeks (July 2009 – March 2012). Serum 25-hydroxyvitamin D levels were measured at routine clinic visits. Patients with low 25-hydroxyvitamin D levels (< 40 ng/mL) were supplemented with 50,000 units Vitamin D2 weekly, and Ca/D3 200 units twice daily. Data analysis was done using longitudinal regression models with one-slope model, controlling for race, age, age squared, sex, prednisone, hydroxychloroquine, and date (SAS 9.2).
Results: There were a total of 5935 visits with serum 25-hydroxyvitamin D measurements from 1006 different SLE patients. They were 91% female, mean age was 49.6 (SD = 13.2), 54% Caucasian, 37% African-American and 8% other ethnicity. The number of visits per patient ranged from 1 to 16. 110 (11% had 1 visit, 313 (31%) had 2-5 visits, 517 (51%) had 6-9 visits, and 65 (6%) had 10-16 visits.

Table. Difference in mean disease measure per 20 ng/mL increase in vitamin D based on longitudinal regression models with one slope.

Disease Measure	*Slope (95% CI)*	*P-value*
Physician Global Assessment	-0.01 (-0.03, 0.01)	0.21
SLEDAI-SLEDAI	-0.02 (-0.11, 0.07)	0.65
Systolic BP	-2.13 (-2.79, -1.48)	< 0.0001
Log Urine Protein/Creatinine	-0.02 (-0.03, -0.01)	< 0.0001
Log HSCRP	-0.02 (-0.09, 0.06)	0.64

There was significant improvement in both the PGA and SELENA-SLEDAI in those with low vitamin D (< 40ng/mL), when vitamin D was increased by 20 ng/mL. There was also improvement in systolic blood pressure and urine protein/creatinine.
Conclusions: After a long follow-up in this SLE Cohort, there was statistically significant improvement in disease activity in those with low vitamin D levels, who increased their vitamin D levels. We also found significant improvement in both systolic blood pressure and urine protein/creatinine with increase in vitamin D. This analysis suggests vitamin D supplementation in SLE patients with low vitamin D levels may have beneficial effects on disease activity and on blood pressure, one of the major predictors of accelerated atherosclerosis in SLE.

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Chinese SLE Treatment and Research group (CSTAR) registry: Prevalence and Risk Factors of Pulmonary Arterial Hypertension and Interstitial Lung Disease in Chinese Patients with Systemic Lupus Erythematosus

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Backgrouds: Pulmonary involvements, especially pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), are associated with high morbidity and mortality in patients with systemic lupus erythematosus (SLE), while large-population-based epidemiological data are lacking. The Chinese SLE Treatment and Research group (CSTAR) therefore developed the first on-line registry for Chinese patients with SLE to investigate prevalence and risk factors of these two pulmonary complications.
Objectives: To estimate the prevalence of PAH and risk factors for PAH in a large cohort of Chinese patients with SLE registered in the CSTAR database.
Methods: A prospective cross-sectional study of patients with SLE was conducted using the CSTAR registry. Patients were considered to have PAH when systolic pulmonary artery pressure > 36mmHg through resting transthoracic echocardiography and ILD, valvular disease or cardiomyopathy were excluded. Patients were considered to have ILD when specific features (grand-glass, subpleural reticulo-nodular opacities or symmetric fibrotic opacities) were demonstrated on chest X-ray or high resolution computerized tomography without infective infiltrations or features of PAH. Potential risk factors for PAH and ILD including patient demographic features, organ involvements, laboratory findings and SLE disease activity measurements were tested by multivariate logistic regression analysis.
Results: Of 1980 patients with SLE, 77 (3.9%) met the diagnostic criteria of PAH. 86 (4.2%) out of 2024 patients with SLE were considered to have ILD. In patients with PAH, the incidences of lupus nephritis, pleuritis, pericarditis, hypocomplementemia, anti-SSA and anti-ribonucleoprotein (RNP) were significantly higher than those without PAH ($P < 0.05$). SLE disease activity index (SLEDAI) was significantly higher in patients with PAH than in unaffected patients ($P < 0.05$). When compared with SLE patients without ILD, ILD group had significantly higher incidences of initial renal and respiratory related symptoms, oral ulcer, pleuritis and proteinuria and significantly lower incidence of lupus-specific cutaneous lesions ($P < 0.05$). Similarily, SLEDAI was also higher in ILD patients with statistic significance than those without ILD. Multivariate logistic analysis indicated pericarditis (odds ratio [OR]=4.609), pleuritis (OR=2.834), and anti-RNP (OR=2.229) were independent risk factors for PAH in patients with SLE ($P < 0.05$). As for SLE patients with ILD, oral ulcer (OR=2.007), pleuritis(OR=2.511), proteinuria(OR=1.637) were independent risk factors, while lupus-specific rash(OR=0.529) was independent protective factor.
Conclusion: The prevalence of PAH and ILD was comparatively low in Chinese patients with SLE from CSTAR registry. Pericarditis,

pleuritis, and anti-RNP positivity were associated with PAH, and oral ulcer, pleuritis and proteinuria were associated with ILD, which suggests that higher disease activity may contribute to the development of PAH and ILD in SLE and aggressive immunosuppressive therapy may be warranted.

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Macroprolactinemia and prolactin levels in active and inactive systemic lupus erythematosus

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Macroprolactin (macroPRL), which comprises immunoglobulin G (IgG) or anti-prolactin (PRL) autoantibody-bound prolactin, is one of the causes of hyperprolactinemia. MacroPRL has a high molecular mass and low biological activity that does not need treatment. Hyperprolactinemia is described in systemic lupus erythematosus (SLE) but the role of disease activity is still controversial. In addition, macroPRL could account for the higher PRL levels detected in SLE. The aim of this study was to evaluate serum PRL levels and the presence of macroprolactinemia in active and inactive lupus patients.
Patients & Methods: Seventy-one consecutive SLE patients (ACR criteria) were selected. Exclusion criteria were presence of pregnancy, prolactinoma, hypothyroidism, renal failure, or drugs that raises PRL levels. Patients were divided according to overall clinical activity (SLEDAI index) in: ACTIVE (n=26, SLEDAI > 4) and INACTIVE (n=45, SLEDAI=0). Serum PRL levels were determined by immunofluorometric assay (normal reference 14.5 ng/mL) and macroprolactinemia was identified by gel-filtration chromatography.
Results: The median serum PRL levels for the entire SLE group was 8.2 ng/mL (1.9 – 49.6 ng/mL) and mild hyperprolactinemia was observed in 22.5%. Similar serum PRL levels were detected in ACTIVE compared to INACTIVE [10.3 (4.9 – 38.9) vs. 7.6 (1.9 – 49.6) ng/mL; p=0.15] as well as prevalence of mild hyperprolactinemia (26.9% vs. 20%, p=0.56). Macroprolactinemia was only identified in 3 patients of the INACTIVE group (3/45) but not in ACTIVE (6.6% vs. 0%, p=0.29). This finding explain the significant higher median monomeric PRL levels observed in ACTIVE group [10.3 (4.9 – 38.9) vs. 7.2 (1.9 – 20.6) ng/mL); p=0.022]. However, the apparent higher frequency of monomeric hyperprolactinemia in ACTIVE compared to INACTIVE did not reach significance [26.9% vs. 13.3%; p=0.20].
Conclusion: Monomeric hyperprolactinemia is closely related to active disease and macroprolactinemia seems to be the main cause of hyperprolactinemia in inactive SLE. Further studies are necessary to confirm a possible protective role of macroPRL in this disease.

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Outcome of patients with Systemic Lupus Erythematosus in the medical intensive care unit: Description of a cohort belonging to a fourth level complexity University Hospital

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Background: Infection and acute respiratory distress syndrome (ARDS) are the main causes of death of Systemic Lupus Erythematosus (SLE) patients admitted in the intensive care unit (ICU). The purpose this study was to evaluate the outcome of SLE patients treated in our hospital ICU and identify potential determinants of mortality.
Materials and Methods: A descriptive, retrospective study was conducted, including all patients with SLE over sixteen, transferred to a ICU between January, 2005 and November, 2012. The results were expressed using descriptive statistics.
Results: Population: 47 patients were inclueded. The mean age was 37.12 years (16 -76) and 87.23% were female (35 years, 16 - 76), 12.7% were male (51 years, 27-72). 23% of the patients were transferred to the ICU the first day of hospitalization, 55% between 1 and 7 days, and 22% after 7 days of hospital stay. On average patients had 2.1 previous hospitalizations. The reasons for ICU entrance were: infection (51%), active SLE and infection (34%) and SLE without infection (15%). Respiratory failure was present in 44.6% of the patients at admission (14 due to infectious cause, 6 due to alveolar hemorrhage, and one transient ARDS). 52.7% of patients survived and a APACHE II score higer than 18 was associatd with mortality.

Treatment started in ICU included: mechanical ventilation (65%), transfusion (51%), dialysis (50%), vasopressors (47.8%), methylprednisolone pulses (39%), anticoagulants (21%), cyclophosphamide (15%), rituximab (10.8%), intravenous immunoglobulin (2%), and plasmapheresis (2%)

Table 1. Baseline differences between SLE patients who survived and those who died in the ICU

	Survivors	*Deceased*
Age (years)	35.22 (16 - 60)	40 (17 - 76)
Female	91%	86.4%
Infection	81.8%	86.4%
Infection Triggered Respiratory Failure	22%	81.8%
Alveolar Hemorrage	27%	9%
Baseline Albumin (gr/dL)	2.48 (1.2 - 3.5)	1.83 (1.2 - 2.4)
Thrombocytopenia (< 100.000/mm3)	13.6%	18.2%
Lupus Nephritis	86.4%	86.4%
Neurological Compromise	40.9%	22.7%
Antiphospholipid Syndrome	22.7%	23.8%
Cyclophosphamide (previous use)	40.9%	50%
Antimalarial (previous use)	68%	68%

Conclusion: Infection triggered respiratory failure, prior use of cyclophosphamide and decreased serum albumin were more frequent in patients who died. 85% of patients reported infection, most of them were caused by common pyogenic bacteria.

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Dyslipoproteinemia and its relation with the activity of the disease and its treatment in patients with systemic lupus erythematosus: preliminary data from relesser (registry of sle patients of the spanish society of rheumatology).

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Background: Abnormalities in the lipid profile contribute to the increased risk of early atherosclerosis in SLE patients.
Objectives: To study the dyslipoproteinemia in SLE and the influence of the disease activity and treatments on it.
Methods: SLE patients from the RELESSER Registry with an active follow-up in a Rheumatology Department.
Variables. a) lipid profile: total, LDL/HDL cholesterol, triglycerides and atherogenic index (total/HDL cholesterol), b) SLE activity: SELENA-SLEDAI score, C3, C4 and anti-dsDNA antibodies and c) ongoing treatments. Dyslipoproteinemia is defined as the presence of at least one of: total cholesterol ≥240mg/dl, triglycerides ≥180mg/dl or statins use.
Methods. Retrospective study of the data collected at the moment of the last evaluation of the patient. We calculated the prevalence of dyslipoproteinemia and the correlations between lipid profile and SLE activity and treatments.
Results: 583 patients included (88.3% females, mean age: 45 years, SLE duration: median 111 months). The table shows the results of the analysis of lipid profile.

	n (%)
Cholesterolemia ≥240mg/dl (n = 553)	45 (8.1%)
LDL ≥130mg/dl (n = 303)	68 (22.4%)
HDL ≤40mg/dl (n = 300)	40 (13.3%)
Trygliceridemia ≥180mg/dl (n = 425)	43 (10.1%)
Atherogenic index ≥4 (n = 300)	75 (25.0%)
Statin therapy (n = 500)	89 (17.8%)
Dyslipoproteinemia (n = 409)	146 (35.7%)

The median of the SLEDAI score was 2 (IR: 0-4). 39.4% of patients had a SLEDAI score = 0. The SLE activity was mild (SLEDAI = 1-4 points), moderate (5-9 points) and severe (≥10 points) in 43.4, 13.2 and 3.9% of the patients, respectively. Total cholesterol levels were significantly higher in patients with severe activity ($p = 0.009$). LDL cholesterol and the atherogenic index were higher in that subgroup (p = n.s.). There were no significant differences in the values of the lipid profile in patients with hypocomplementemia or positive anti-dsDNA antibodies.

The percentage of patients on statin therapy was significantly higher in the group of patients with severe lupus activity ($p = 0.05$). The patients on current treatment with corticosteroids or 2 immunosupressors had higher prevalence of dyslipoproteinemia than those without corticosteroids or with ≤ 1 immunosupresor ($p = 0.009$ and $p = 0.04$, respectively). Patients on antimalarials had lower triglyceride levels and lower prevalence of dysliproteinemia than those without that treatment (p close to 0.05).
Conclusions: One third of the Spanish SLE patients had dyslipoproteinemia. Total cholesterol levels and statin requirement are significantly higher in patients with higher disease activity. The use of corticosteroids and a more aggressive immunosupressive regimen are associated with higher prevalence of dyslipoproteinemia.

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IFN-γ is associated with cerebral atrophy in systemic lupus erythematosus

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Objectives: Evaluate cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings in SLE with CNS involvement.
Methods: We included 20 SLE patients (18 women; mean age 30.2± 9.2 years; range 19-45) with CNS manifestations. Neurologically asymptomatic controls were matched for age and sex, recruited during myelography. SLE patients were assessed for disease activity (SLEDAI), and cumulative damage (SDI). All subjects underwent MRI, blood and CSF withdrawal. T2 axial images with 6 mm thick were used to determine brain volume through the program Neuroline®. CSF samples were obtained for the routine determination of CSF leukocyte count, IgG synthesis and oligoclonal IgG bands. IgG and albumin in the CSF and serum were measured by nephelometry (BNII; Dade Behring, Marburg, Germany), and Link Indexes (LI) were calculated according to the literature. IL-12, IFN-γ, TNF-α, and IL-10 were quantified using commercial kits (Biosource International, Nivelles, Belgium).
Results: Increased IL-12, IFN-γ,TNF-α and IL-10 CSF levels in SLE patients were observed. Mild pleocytosis was observed in 8 (66%) SLE patients and intrathecal production of IgG was observed in 2 (10%) of SLE patients. Three (15%) SLE patients had demyelinating lesions, 5(25%) had atrophy and 12 (60%) had ischemic lesions on MRI. In SLE patients, we observed that total lesion count was associated with CNS manifestations and SLICC/ACR-DI scores. We observed a significant cerebral volume reduction in SLE patients compared to healthy controls ($p=0.002$). Moreover, a direct correlation between cerebral volume reduction and IFN-γ was observed ($r=0.5$; $p=0.01$).
Conclusions: MRI abnormalities are frequently observed in SLE patients and are associated with CNS manifestations and cumulative damage. Although we observed immunologic abnormalities in CSF of SLE patients, only IFN-γ correlated with MRI abnormalities.
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P304

Tumor necrosis factor alpha is associated with mood and anxiety disorders in patients with systemic lupus erythematosus

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Objective: To determine if sera TNF-α levels are associated with mood and anxiety disorders.
Methods: We included 153 SLE patients (women 148; median age 30; range 10-62) and 41 healthy (women 38; mean age 30; range 12-59) age and sex matched controls. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory in all participants. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Sera samples were obtained from all participants in the absence of infections. TNF-α levels were measured by enzyme-linked immunosorbent assay using commercial kits. Mann-Whitney Test was used to compare TNF-α concentrations between groups. Multivariate analysis was performed including sex, age, SLE duration, disease activity, and cumulative damage, severity of depression and anxiety and current drug exposures.
Results: Depression was identified in 70 (45.7%) SLE and in 10 (24.4%) controls ($p < 0.001$). Anxiety was identified in 93 (60.7%) SLE and in 17 controls (41.5%) ($p < 0.001$). Sera TNF-α levels were increased in individuals with depression ($p < 0.001$) and with anxiety ($p=0.037$). A direct correlation between the severity of depression and sera TNF-α levels ($r=0.15$; $p=0.023$) was observed. TNF-α levels were significantly increased in patients with active disease (SLEDAI≥3)

(p=0.007) and with current prednisone dosage (p < 0.001). In addition, we observed a correlation between sera TNF-α levels and SLEDAI (r=0.23, p=0.004) and with current prednisone dosage (r=0.18; p=0.031). No association between TNF-α levels and other clinical, laboratory variable and SDI scores was observed. No difference in TNF-α levels was observed between patients with and without hydroxicloroquine or other immunosuppressants. In the multivariate analysis, sera TNF-α levels were independently associated with depression (OR=3.1; 95%CI 1.8-5.6) and with disease activity (OR=4.4; 95%CI 1.3-7.1).
Conclusion: Sera TNF-α levels are elevated in individuals with mood and anxiety disorders. In SLE, sera TNF-α levels were independently associated with depression and with disease activity. The etiology of mood disorders is still debated in SLE, but our findings suggest the presence of immunological basis for depression in SLE.
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Comparison between body mass index and body adiposity index in childhood onset Systemic Lupus Erythematosus (cSLE)

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Background: Body Mass Index (BMI) is a simple index commonly used to classify weight in adults but it have some important limitations. Antropometric measures of waist-to-hip ratio (WHR) is by far the most widely used index of regional adipose tissue distribution and associated with the amount of abdominal visceral adipose tissue. Recently a new index was developed to estimate total body fat, the body adiposity index (BAI) which was validate by dual-energy X-ray absorptiometry (DXA) as gold standard for body fat evaluation.
Objective: The aim of this study was to compare estimates of body fat content, (BAI, BMI and waist and hip circumferences) with respect to their ability to predict the percentage of body fat (PBF), confirmed by dual-energy X-ray absorptiometry (DXA) scans in cSLE.
Methods: We included 64 consecutive cSLE patients and 64 healthy age and sex-matched controls. Anthropometric data, BMI and BAI were calculated for all subjects. cSLE patients were further assessed for clinical and laboratory cSLE manifestations including disease activity, damage, current and cumulative corticosteroid drug exposures. Fat mass, lean mass and PBF was evaluated by DXA.
Results: cSLE patients had a significantly lower height [median 1.56m (1.2 – 1.7)] when compared to controls [median 1.63m (1.15 – 1.8); p=0.01]. A higher WHR [median 0.88 (0.4 – 1.1)] was observed in cSLE patients when compared to controls [median 0.82 (0.59 – 1.33)] (p < 0.001). We did not find differences between BMI (p=0.978 and BAI (p=0.978) classification in cSLE patients and controls. We observed a correlation between BAI and BMI (r=0.48, p < 0.001).

We observed a direct correlation between fat mass on whole body analysis with BMI (r=0.319;p=0.037), BAI (r=0.334;p=0.029), WC (r=0.578;p≤0.001), HC (r=0.434;p≤0.001), WHR (r=0.445;p≤0.001) and a direct correlation between fat percent with adjusted SLEDAI score over time (r=0,402;p=0,008), BMI (r=0,353;p=0,017), WC (r=0,450;p=0,002) and WHR (r=0,474;p=0,001).

Trunk fat mass was direct correlated with WC (r=0.563;p≤0.001), HC (r=0.377; p≤0.001), WHR (r=0.502; p≤0.001); PBF on trunk region was direct correlated with adjusted SLEDAI score over time (r=0,402; p=0,005), WC (r=0,431;p=0,003) and WHR (r=0,515;p < 0,001).
Conclusions: This is the first study analyzing BAI in cSLE patients. Our result shows no difference between BMI and BAI to evaluating the level of fat on cSLE comparing to controls. Considering the importance of overweight in the occurrence of cardiovascular diseases, it is better to use both index in an attempt to benefit patients prognosis.
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P306

Medication Adherence in childhood Systemic Lupus Erythematosus

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Introduction: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by the production of various autoantibodies that diversifies the range of clinical manifestations and affecting preferably women of childbearing age. Studies suggest that childhood systemic lupus erythematosus (cSLE), have a low adherence to medications is that many factors can cause the patient to leave to take medication, intentionally or not. To understand the reasons why patients do not adhere to treatment, it will be necessary to develop strategies, as well as the way of understanding why or how to take prescribed medication, and how it can help the physician to control the disease.
Objective: To assess medication adherence in cSLE and to evaluate factors related to nonadherence.
Methods: We performed a cross-sectional study. A questionnaire was applied to patients with cSLE followed at the Pediatric Rheumatology Unit at UNICAMP. We designed a questionnaire to patients and families that asked about demographic information, feeling about the disease and treatment, knowledge and proper use of medication. Patients were considered adherent if they refered a proper use of medication > 80% of the time.
Results: We included 45 patients, 39 (86.67%) answered the questionnaire properly. The mean age was 16.9 years (SD = 3.2/variation 9-22 years). 42 (93.34%) cSLE patients were female. 29 (64.44%) patients were considered adherent and 13 (28.88%) were nonadherent. In univariate analysis the lack of adherence was associated only with older age at diagnosis (11.8 u 14.9 years, p = 0.015).
Conclusion: Crrently 53.33% of patients refered not taking their medication properly. Older age at diagnosis was the only variable associated with poor adherence in this series. Identifying these factors may help in developing strategies to improve medication adherence in our service.
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P307

Systemic lupus erythematosus (sle) having developed malignant lymphomas. continuing complete remission of lymphoma following high-dose chemotherapy, but not of sle

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The development of malignant lymphomas, generally of the non-Hodgkin type (NHL), and with a preference to diffuse large cell B lymphomas (DLCBL), in systemic lupus erythematosus (SLE), has been proven and analyzed in an exhaustive recent literature. The combination of germline and somatic mutations, persistent immune overstimulation and the impairment of immune surveillance facilitated by immunosuppressive drugs, is thought to be at the origin of the increased lymphoma genesis. However the treatment and course of such affected patients is less known, and prognosis is generally estimated as poor. Out of 450 patients with complete/incomplete lupus and secondary antiphospholipid syndrome (APS) seen and treated as

an outpatient basis between 1982 and 2011, 9 developed lymphomas (4 DLCBL, 1 Hodgkin's and 4 indolent lymphocytic lymphoma). Six patients were treated with high dose chemotherapy (HDCT) and achieved continuous complete remissions (CCR) with a follow-up comprised between 12 and 204 months. Four patients achieved complete remission (CR) of both diseases. In the other 5 lupus serology (ANA, APA) persisted, with occasional lupus flares and vascular complications. While eradication of the last cancer stem cell is tantamount to cure in neoplastic disease, persistent autoantigenic overstimulation may contribute to the refractoriness of autoimmunity. The implications of these results for the increasing utilization of hematopoietic stem cell transplantation for severe autoimmune diseases (SADS), with lupus as a paradigm, are discussed.;

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Prevalence of metabolic syndrome in patients with systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease characterized by varied clinical manifestations. In recent decades, due to the increased survival of patients with SLE, new complications and comorbidities have been recognized. Among these is cardiovascular disease atherosclerosis (CAD). Metabolic syndrome (MetS) is defined by the World Health Organization (WHO) as a set of metabolic alterations that commonly manifest together and are risk factors for coronary artery disease (CAD). Each component by it self, increases the risk of CAD, however, when combined, become more intense. These factors include hypertension, disturbed glucose metabolism, central obesity, and dyslipidemia. MetS contributes to increased mortality 1.5 times and 2.5 times for CAD.
Objective: Analyze the prevalence of MetS in SLE according to the consensus applicable to different populations; correlate the clinical, laboratory and treatment with the occurrence of MetS and to determine the levels of TNF-α in this patient group and verify that the levels of TNF-α are independently associated with presence of MetS in SLE.
Methods: We conducted a review of medical records of patients with SLE followed at the outpatient pediatric clinic of the Hospital de Clinicas - UNICAMP in order to obtain results of tests previously performed by the patients, such as fasting blood glucose and cholesterol and its fractions. On the day of consultation, anthropometric measurements were obtained from patients and weight. MetS was assessed according to criteria established by the Brazilian society of cardiology. SLE patients were assessed for disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)]. TNF-α was measured by standarized ELISA kits.
Results: We included 120 (95% women) patients with a mean age of 41.20 ± 11.87 years and 106 controls with mean age of 36.32 ± 14.26 years (p=0.006). According to the different classifications of METS, we observed the following **results:** According to WHO criteria, 12 (10.10%) patients met criteria for diagnosis of MetS than in controls while the number was only 6 (5.66%) (p=0.229). According to the criteria of NCEP-ATP III, 45 (37.5%) patients were framed while the controls were 11 (10.38%) ($p < 0.001$). Already by the IDF criteria, the number of MetS was affected by 47 (39.17%) patients and in 11 (10.38%) in controls ($p < 0.001$). We found no association between the presence of MetS variables and TNF-α (p=0.902), SDI (p=0.187), SLEDAI (p=0.562), obesity (p=0.514), age (p=0.782) and BMI (p=0.114).
Conclusions: SLE patients have a higher prevalence of MetS than the general population. The higher risk of coronary disease and atherosclerosis makes the evaluation of MetS imperative in SLE patients.
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Ovarian reserve markers in reproductive age women with systemic lupus erythematosus

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Objective: The aim of this study was to evaluate if there are differences in ovarian reserve markers in systemic lupus erythematosus (SLE) patients compared to controls, and explore the relationship of such markers with clinical and treatment features of SLE patients.
Methods: This was a controlled cross-sectional study including 27 women with SLE and 27 controls. All participants were between 18 and 40 years, were eumenorrheic and had not used hormone therapy or hormone contraceptives in the past 6 months. Clinical data were assessed at a regular follow up visit, while serum concentrations of follicle stimulating hormone (FSH) and anti-mullerian hormone (AMH), and antral follicle count (AFC) through transvaginal ultrasound were assessed at early follicular phase of a subsequent menstrual cycle.
Results: Mean age of SLE patients was 30.9 years (SD±4.8) and had 102.7 months (SD±66.7) of disease duration. We found no difference between SLE group and control group at analysis of AFC [median (interquartile interval) 7 (5 – 13) vs. 11 (7 – 12), p=0.076], FSH [6.44 (4.19 – 7.69) vs. 7.5 (6.03 – 8.09) mUI/ml, p=0.135] and AMH levels [1.23 (0.24 – 4.63) ng/ml vs. 1.52 (1.33 – 1.88) ng/ml, p=0.684]. However, AMH serum values in SLE group were more heterogeneous compared to control group. Cumulative dose of cyclophosphamide was individually related to reduced ovarian reserve, by association with lower values of AFC and AMH. At multivariate logistic regression, AMH was associated with lower maximum corticosteroid doses in the follow-up (OR 0.95, 95%CI 0.894-1.000, p=0.05), and AFC was associated with lower scores of SLICC/ACR-DI (OR: 0.14, 95% CI 0.025-0.841, p=0.031).
Conclusion: Eumenorrheic SLE patients had average values of ovarian reserve markers similar to controls. However, AMH had a wide range of values in that group. Ovarian function is more compromised in patients with higher cumulated dose of cyclophosphamide and with higher disease damage scores.

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Neurosensorial hearing loss in systemic lupus erythematosus

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Introduction: Neurosensorial hearing loss is a uncommon condition in systemic lupus erythematosus (SLE) but it can occur as the first manifestation of disease. Some authors have associated this manifestation with Antiphospholipid Syndrome (APS), probably due to thrombosis. In some cases it can be acute, but also can be a progressive manifestation and even subclinic.
Objective: To determine the association between sensorioneural hearing loss and APS antibodies profile, activity of disease, age, time of disease and cardiovascular comorbidities in SLE patients.

Methods: We conducted a cross-sectional study including patients with SLE followed at the Rheumatic Clinic of UNICAMP. We performed in all patients audiometry and clinical otologic evaluation. After, we correlated sensorioneural hearing loss with all variables analysed.
Results: The study included 90 patients, from wich 2 were excluded after clinical evaluation, considering they had tympanic membrane perforation. They were all women with mean age 39,27 years (SD ± 10,96). From 88 patients left, we found neurosensorial hearing loss in 13, representing 14,77%. Significant correlation between hearing loss and age (p=0,015) and hearing loss and triglycerides level (p=0,019) was found, corroborating the association of aging and hearing loss and dyslipidemia as a predictor of vascular disease. No statistical significance was found correlating diagnosticated APS (p=0,092) or the presence of positive APS antibodies in a gap of 12 weeks despite previous thrombosis or fetal loss (p=0,717).
Conclusion: Although uncommon, we found hearing loss in almost 15% of cases studied. Also, we found a positive association with age and triglycerides level, pointing that cardiovascular disease (not only immune) can be responsible for these alterations. We are now performing the same studies in a control group to compare these results.
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Aspirin Resistance in Systemic Lupus Erythematosus

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Background: Systemic lupus erythematosus (SLE) patients are at increased risk of thrombosis and cardiovascular disease. Aspirin is an effective treatment option for this group of patients. The aim of this study was to investigate the presence of aspirin resistance in SLE patients.

Method: We studied 33 SLE patients and 9 healthy controls. Aspirin resistance was determined by MultiplateR impedance aggregometer (Dynabyte GmbH, Munich Germany).
Results: Twenty-six SLE patients were on regular aspirin treatment. General characteristics of patients were shown in table. Aspirin resistance was found in 5(19,2 %) out of 26 patients who were on aspirin treatment. When the tests were performed by adding acetyl salicylic acid in the medium, all of these patients were responsive to the aspirin. SLE disease activity, mean body mass index, smokering status and presence of anticardiolipin antibodies or lupus anticoagulant test were not different in patients with or without aspirin resistance. (p=NS for all).
Conclusion: Our results suggest that there is considerable number of SLE patients with aspirin resistance.

Table: eneral Characteristics of the Patients with Systemic Lupus Erythematosus (n=33)

Age (y)	36,1 ± 12,4
Gender (F/M)	29/4
Disease duration (y)	7,6 ± 5,5
Smokers	33,3 %
Hypertension	12,1 %
Hyperlipidemia	16,1 %
Family history of cardiovascular disease	12,9 %
Photosensitivity	84,8 %
Malar rash	57,6 %
Discoid lupus	9,1 %
Atralgia/Arthritis	81,8 %
Oral ulceration	6,1 %
Serositis	33,3 %
Central nervous system involvement	18,2 %
Hematopoietic system involvement	42,4 %
Renal involvement	42,4 %
Thrombosis*	18,2 %
ANA	100,0 %
ACA (Ig M and/or Ig G)	30,3 %
Lupus anticoagulant	15,2 %

ANA: anti nucleer antibody, ACA: anticardiolipin antibody, Ig: immunoglobulin
*2 arterial, 4 venous thrombosis

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Transaminitis in patients with early Systemic Lupus Erythematosus

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Introduction: a variable number of Systemic Lupus Erythematosus (SLE) patients suffer from transient transaminitis with a good prognosis that is likely to be related to disease activity. The objective of this study is to determine if transaminitis presence observed in early SLE indicates a patient subgroup with different clinical manifestations or short-term prognosis.
Material and Methods: A retrospective analysis of inpatient and outpatient medical records with SLE diagnosis was carried out. All the patients met the 2012 American College of Rheumatology criteria for SLE. Patients were divided into two groups: a) Patients having at least one hepatogram (baseline hepatogram) with aspartate aminotransferase/alanine aminotransferase (AST/ALT) higher than laboratory reference value (transaminitis group) performed in the early disease stage and shortly after the clinical diagnosis of the treating physician. Patients with other active clinical conditions or medications known to increase liver enzymes were excluded from the case group. b) Patients with a normal hepatogram at the time of diagnosis (control group).
Results: 81 patients were included (73 females, 8 males); mean age was 33.4 years and mean SLEDAI was 10.4. Twenty three subjects (28.4%) had transaminitis. All normalized the liver enzymes except for 3 patients: one patient died during the first hospitalization and two patients had elevated AST for 36 and 108 months of follow-up respectively.There were no statistically significant differences in C3-C4 consumption or positive anti-dsDNA (73.9% vs. 54.4%, p 0.2) in the case and control groups respectively. SLE diagnosis was made during hospitalization in 47.8% of patients with transaminitis vs. 29.3% in the control group (p 0.2).

Patients in the transaminitis group had a higher SLEDAI basal mean (12.04 vs. 9.68, p 0.02). Overall kidney involvement was observed in 69.6% of patients in the transaminitis group vs. 53.4% in the control group (p 0.3). During the first-year of follow-up a kidney biopsy was required in 47.8% of patients in the transaminitis group vs. 20.7% in the control group (p 0.03). The outcomes were as follows: LN Class III or IV in 39.1% of patients in the transaminitis group vs. 12.1% in the control group (p 0.01). During the first six months there were no differences in the treatment and corticosteroids and immunosuppressive therapy were directed toward other manifestations of SLE.

A 24- month follow-up was completed by 69.6% of patients in the transaminitis group (1 patient died, 2 Lost to follow up (LFU), and 4 were being followed up at data base deadline) and by 69% of patients in the control group (4 patients died, 7 LFU, and 7 were being followed up).
Conclusions: transaminitis observed in early SLE is associated with higher disease activity. Increased liver enzymes went into remission in most cases within the first months of treatment. Up to 40% of these patients developed LN Class III-IV within the first year of follow-up.

Finding	*II*	*III*	*IV*	*V*	*p value* *
Asymptomatic Hematuria	2 (33)	8 (80)	21 (68)	6 (46)	0.151
Pyuria	3 (50)	6 (60)	16 (52)	28 (23)	0.246
Urinary Casts	0	2 (20)	3 (10)	3 (23)	N.A. **
HT	1 (17)	6 (60)	12 (39)	5 (39)	0.363
Positive Anti-DNA	4 (67)	6 (60)	27 (87)	7 (54)	0.082
Nephitic Syndrome	1 (17)	5 (50)	14 (45)	2 (15)	0.125
Nephrotic Syndrome	1 (17)	2 (20)	15 (48)	6 (46)	0.216
Acute Renal Failure	1 (17)	0	9 (29)	3 (23)	N.A.
Chronic Renal failure	0	1 (10)	2 (7)	2 (15)	N.A.
C3 levels	86 (57-104)	65 (48-90)	77 (54-103)	102 (91-129)	0.064 ***
C4 levels	14 (9-18)	12 (10-20)	12 (9-20)	27 (24-37)	0.010 ***
24-hour proteinuria (mg)	596 (500-702)	1900 (780-2900)	2860 (1545-5934)	1560 (380-7700)	0.07

* Likelihood ratio
** Not applicable
*** Kruskall-Wallis test

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Lupus Nephritis Clinicopathological Relationship in a Third Level University Hospital

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Background: The gold standard method for the diagnosis of lupus nephritis (LN) is renal biopsy; however, there is still controversy over whether there is a relationship between the clinical, serological and histological findings in these patients. The aim of this study was to establish the clinicopathological association in patients with LN in a university tertiary complexity hospital.
Material and Methods: A cross-sectional survey was conducted, which included 77 patients with LN between January, 2007, and October, 2012, confirmed by renal biopsy, using the ISN/RPS 2003 classification. The following variables were assessed: abnormal urinalysis, arterial hypertension (HT), positive anti-DNA, C3 and C4 hypocomplementemia, and frequency of clinical syndromes (acute renal failure, chronic renal failure, nephritic and nephrotic syndromes). Qualitative variables were described by absolute and relative frequencies, and continuous variables as medians with interquartile ranges due to the distribution of data. In order to associate the clinical features with histopathologic findings in patients classified into one specific subtype of LN (n=60) we used the likelihood ratio test, and Kruskall-Wallis test to compare quantitative variables according to subtypes.
Results: Subtypes: I (n = 1, 1.3%), II (n = 6, 7.8%), III (n = 10, 13%), IV (n = 32, 41.6%), V (n = 13, 16.9%), III/IV (n = 1, 1.3%), III/V (n = 8, 10.4%) and IV/V (n = 6, 7.8%). Activity Index: 4 (1-7); Chronicity Index 1 (0-3). Creatinine 1 mg% (0.7-1.3) The only significant clinicopathologic relationship was decreased C4 values with III and IV subtypes (Table). A positive interrelation between Activity Index and nephrotic syndrome (p = 0.005) was reported.

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Cigarette smoking and coffee consumption independently influence the risk of developing cardiovascular disease in systemic lupus erythematosus

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Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). We aimed to determine the prevalence and associated risk factors for this condition in a Latin American population with SLE.
Patients and methods: This was a cross-sectional study in which consecutive patients with SLE (ACR 1997 update) seen on an outpatient basis were assessed for CVD including arterial hypertension, coronary artery disease, peripheral arterial disease, cerebrovascular disease and thrombosis. Factors associated with its occurrence were examined by bivariate and multivariate regression analyses.
Results: Out of a total of 310 patients, 113 (36.5%) presented with CVD. The most frequent condition was hypertension (69%). Dyslipidemia (28% vs. 12%), ever smoking (51% vs. 37%), coffee consumption (70.5% vs. 55.2%) and pleural effusion (32% vs. 19%) were positively associated with CVD (Table). Logistic regression analyses disclosed an independent effect of coffee consumption and cigarette smoking on CVD regardless of gender and duration of disease.
Conclusions: A high rate of CVD was observed in our patient population. Awareness of the observed risk factors should encourage preventive population strategies for CVD in patients with SLE aimed to

facilitate the suppression of cigarette smoking and coffee consumption as well as to the tight control of dyslipidemia.

Characteristic	β	AOR	95%CI	p
Dyslipidemia	0.971	2.64	1.32-5.28	0.005
Pleural effusion	0.751	2.12	1.17-3.84	0.013
Cigarette smoking	0.602	1.83	1.07-3.10	0.025
Coffee consumption	0.559	1.75	1.01-3.04	0.043
Renal involvement	0.476	1.61	0.94-3.84	0.081

β: Beta coefficient; AOR: Adjusted odds ratio; 95%CI:95% Confidence interval.

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Negative body image affects sexuality in women with systemic lupus erythematosus

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Introduction: Women's sexual functioning, in most cases is directly related to sexual satisfaction. Some factors greatly influence the dynamic female sexual pleasure, such as quality of life, the relationship with the partner, and certain individual factors, one being the body image. Sexual satisfaction is related to various aspects of body image, including the concern with body weight, physical condition, sexual attractiveness, and even thoughts on the body during sexual activity. A distorted body image is one of the consequences of the side effects of treatments for patients with autoimmune diseases such as SLE.
Objectives: To evaluate the relationship between body image and sexuality in women with SLE.
Methods: Cross-sectional study including women with SLE followed at the Rheumatology Clinic-Unicamp. The evaluation was performed using sexual Short Personal Experiences Questionnaire (SpeQ), and image data collected through questionnaire body checking body Body Body Questionnaire, and body mass index (BMI).
Results: We included 228 women with SLE (mean age: 35 years, SD: 11.21, Var :14-65). One hundred and thirty-three (58.33%) patients were married, 60 (26.32%) unmarried and 35 (15.35%) patients divorced or widowed. One hundred and fifty three/228 (67.2%) patients reported having sexual intercourse in the last month, however 53/153 (34.64%) rated their sex life as bad. Among the 228 patients with SLE 136 (59.65%) were overweight, with levels of overweight obesity grade III, 85 (37.28%) had a BMI within the normal range (18.5 to 24.9) and 7 (3.07%) patients were underweight. Women who rated their sex life as bad 37/53 (69.81%) had negative body image. The frequency of sexual activity and sexual satisfaction in this group was significantly lower (mean 0-1x per week) than in the group with a BMI within the normal range (average 3x per week) ($p < 0.05$).
Conclusion: There is a positive and significant correlation between sexuality and body image in women with SLE. A negative body image can decrease the frequency and sexual satisfaction, which can lead to a lower quality of life. Assessing the quality of life of patients with SLE is important, including aspects of sexual life, and body image since they are directly related.
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ANALYSIS LUPUS NEPHRITIS IN URUGUAY In representation of the prevention program and treatment of glomerulopathies. UdelaR, Montevideo, Uruguay. Centro de Nefrologia, Facultad de Medicina

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Introduction: retrospective analysis the patients with biopsy proven lupus nephritis, belonging to Uruguayan registry of glomerulopathies, in the period January 1, 1985 to December 31, 2006.
Overall objective: describe the characteristics of the population.
Specific objective: determine the progression factors of lupus nephritis, based on the presence of arterial hypertension, proteinuria, renal insufficiency,at diagnosis period. Determinig patient survival.
Methods: To determine patient's survival, use registration information Uruguayan dialysis and active follow. Its location was established at December 31, 2011.
Results: Included a total of 252 patients, 218 female (86.5%), average age at time kidney biopsy 29.38±11.74 años, mean follow-up time 100 ±78.4 months, range 0 to 319 months, median 92 months, monitoring the summation time of was 24676.

Mean serum creatinine was 1.90 ±0.14 mg/dl, 1.24 mg/dl median. The 50,6% of the population was presented with hypertension. The 55,9% presented nephrotic proteinuria at the beginning. In 48 patients provided data of evolution but not the end of the follow.

Renal and globally survival was analized, 51 patients admitted to dialysis, 22 (8,73%) died.

The overall survival was 80% to five years and 77 % to ten years. Renal survival was 91 % to five years and 84% at ten years. Survival was calculated according to the presence renal failure at onset (creatininemia > 1.5 mg/dl), $p < 0.0001$. The group of patients who debut with hypertension, showed no significant differences, $p = 0{,}201$. Proteinuria was categorized in the presentation based on the presence or absence of nephrotic proteinuria, worse prognosis being the presence of the same, p= 0.028.Was divided into two periods the patient group the 1985-1994 and the 1995-2006, being superior survival for the second group, $p = 0.027$.
Conclusions: It is a historical cohort of patients with lupus nephritis, represented all reported glomerulopathies Uruguayan registration during the period 1985-2006.

The renal survival was 91 and 84% respectively. The renal failure and the nephrotic proteinuria at the presentation, were risk for progression. The survival of patients in the last decade was significantly better, probably due to a combination of possible factors; prompt diagnosis, access to immunosuppressive medication, association of antimalarial and blockers of the rennin angiotensina.

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Quality of Life in patients with neuropsychiatric systemic lupus erythematosus in East Europe

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Background: Neuropsychiatric manifestations in systemic lupus erythematosus (SLE) is an area of scientific interest and important medical and social problem. In the past 15 years has been evoked increasing frequency, which determines expanding clinical manifestations and a reserved prognosis in case of neuropsychiatric involvement. At the modern stage, in literature nervous system impairment in SLE is considered one of the manifestations of the disease, causing reluctant impact on forecast.
The objective: to study neuropsychiatric syndromes in patients with systemic lupus erythematosus and their impact on quality of life.

Materials and methods: We examined 84 SLE patients who met the diagnostic criteria of systemic lupus erythematosus (ACR, Hochberg M., 1997) from Republic of Moldova to complete the study group. Special investigations focused assessment of disease activity, damage index, and evaluating the quality of life by short form questionnaire stratified in eight areas- SF- 36. Results. Patients were divided according to the principle affecting the nervous system SLE -group I (n=54) and without affecting the nervous system -group II (n=30) pts. The data shows the proportion of female/male that is disease specific: 53 (63.10%) women and 1 (1.19%) men in group I and 29 (34.52%) women, 1 (3.3%) men in group II. Analyzing the age of onset, we found that the disease was installed at the age of 13 to 56 years, average age 32 was similar- 32.75 and 30. 03 years in group I and II, respectively. Disease duration gap analysis revealed significantly from one month to 36 years, reiterating 7.81 and 7.95 years in group I and II, respectively. So, the examined patients had an average duration of lupus process about eight years (94.56 months). We found that in patients with nervous system damage in lupus activity was predominantly medium/high at 57. 14%, while in group without nervous system affecting medium/low at 30.95 % of cases. Analyzing the data we detected a low level SLICC in both groups, when a high or very high SLICC was found only in patients with nervous system damage. There were no organic damages in both groups, especially in patients without nervous system involvement. Quality of life was stratified into high (more than 50 points) and low (below 50 points). Lower life quality was linked to both mental and physical health, but mental health dominated in subjects with nervous system manifestations.
Conclusions: Application of SF-36 questionnaire in patients with systemic lupus erythematosus showed that low quality of life is determined by the involvement of the nervous system, primarily though mental health damage.

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Thyroid dysfunction in patients with Systemic Lupus Erythematosus
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Objective: To determine the prevalence of thyroid gland disorders in patients with Systemic Lupus Erythematosus (SLE) and to detect the frequency of autoimmune thyroiditis.
Material and Methods: A cross sectional study was conducted. Between May 2 and July 30, 2012 patients diagnosed with SLE (ACR criteria, 1992) were consecutively evaluated by the Rheumatology Unit. Demographic and clinical variables were analyzed (time of disease progression, SLEDAI, SLICC, background of thyroid pathology and treatment received at the moment of the evaluation, laboratory variables (serum T3, T4 and TSH levels, antithyroglobulin antibodies and anti-thyroid peroxidase antibodies) and ultrasound scan was performed (size and echogenicity of the gland; presence, size and type of nodules; macro- and micro-calcifications, scan and degree of gland vascularization). All patients were evaluated in conjunction with the Endocrinology Unit.
Results: Forty two patients were included in the study: 37 (88%) female, mean age 36.1 ± 11.4 years, time of disease progression: 9.5 ± 8.4 years; with a mean SLEDAI of 3.8 ± 4.2, mean SLICC 0.9 ± 1.2. Twenty nine patients were being treated with a mean glucocorticoid dose of 7.9 ± 9.5 g at the moment of inclusion. The accumulated mean dose of glucocorticoids was 62.6 ± 159.3 g (n=38). None of the patients had been previously diagnosed with thyroiditis. Nine of 42 patients (21.4%) had positive anti-thyroid peroxidase antibodies and 5 out of 37 (13.5%) had positive antithyroglobulin antibodies. Medium size (3.5 ± 5.7mm) thyroid nodules were detected in 16 patients (6.7%): 9 cystic nodules, 11 solid, 6 were unique, and the rest were multiple. Two patients had micro-calcifications in the gland and 1 had macro-calcifications and 3 patients presented pathological Doppler. Hypothyroidism was detected in 20 patients (47.6%), 10 had primary hypothyroidism. Eighteen patients (42.8%) were diagnosed with autoimmune thyroiditis; 6 euthyroid autoimmune thyroiditis, 10 hypothyroidism/ hypothyroid autoimmune thyroiditis (6 with positive and 4 with negative antibodies; one of them with Hashimoto's thyroiditis), 2 patients (4.7%) hyperthyroid autoimmune thyroiditis (1 with positive antibodies). Thyroid dysfunction was not associated to either age (p=0.28) or to SLE progression time (p=0.77). The SLICC score was similar in all types of thyroditis evaluated (p=0.13). There was no association between the current and accumulated glucocorticoids doses and the presence of thyroiditis (p=0.4).
Conclusion: The prevalence of hypothyroidism and autoimmune thyroiditis in our patient population was elevated compared to other series. The study of the thyroid gland should be considered in all SLE patients

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 7 Pregnancy & Contraception"

Atlantico A+B+C

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Evolution of pregnant patients with systemic lupus erythematosus (SLE)
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Objective: To evaluate the effect of pregnancy on the evolution of lupus nephritis (lupus activity), fetal outcome and maternal complications.
Methods: We analyzed 67 pregnancies in 44 women with SLE during a 8- years period. The age of patients was 26 +/- 4 years. All patients met American College of Rheumatology classification criteria for SLE.Lupus nephritis was defined by abnormal urinalysis and/or elevation of the serum creatinine, the diagnosis was confirmed by histopathologic findings on renal biopsy.

Previous manifestations of SLE included: dermatological (32), hematological (11) joints (26), neurological (3) nephritis (LN) in 22 patients.No renal involvement was found in 22 patients. Renal biopsy performed before pregnancy in the 22 patients with LN showed the following classes: 5% in II, 24% in III, 52% in IV and 14% in V and 5% in VI. Before pregnancy they received treatment with inmunosupresive drugs, hidroxicloroquin and corticosteroids. All 22 patients without LN were treated with corticosteroids and hidroxicloroquin. Active lupus nephritis (ALN) was defined as the presence of proteinuria >0.5 g/day and/or active urinary sediment with or without an elevation in serum creatinine, complete remission (CR) was defined with proteinuria <0.5 g in 24 hours without hematuria and normal renal function and exacerbation with an increase of proteinuria and hematuria with or without deterioration of renal function.
Results: At conception, most patients with LN (22) were in complete remission (16) and the remaining with active nephritis (6). Among patients with CR 8 had a reactivation of LN. Among patients with ALN 4 remained unchanged with azathiprine and corticosteroid treatment, 1 patient increased proteinuria and hematuria and impaired

renal function, 1 patient presented with SLE close to pregnancy diagnosis and developed rapidly progressive glomerulonephritis with dialysis requirement.

Of the 22 patients without NL two developed it during pregnancy.

Fetal outcomes were: 47 live births (70%), all with cesarea, 12 spontaneous abortions (18%) and 8 stillbirths (12%), with a mean gestational age of 34.4 weeks and a weight of 2339g. Were found 25% of fetal complications (disturbed doppler, IUGR, oligohydramnios, placental hypoxia.) All required prolonged hospitalization.

Maternal outcomes were: 9 premature rupture of membranes, 8 infections, 7 hypertension, 6 with gestational DBT (all NL group), 3 hyperemesis gravidarum, 2 preclampsias (NL group, one developed HELLP syndrome) and 1 aseptic necrosis hip.

Conclusions: During pregnancy 50% of patients with LN in CR were reactivated, 100% NLA were stable with immunosuppressive therapy and 2 patients without previous nephritis developed it during pregnancy, with rapidly progressive glomerulonephritis.

Patients with LN showed higher incidence of hypertension, gestational DBT and infections.

Pregnant patients with SLE had higher fetal and maternal complications and therefore require family planning and close monitoring.

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Maternal complications during pregnancy in Systemic Lupus Erythematosus

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Introduction: In systemic lupus erythematosus (SLE), flares are higher among pregnant women who are active at conception, stop taking hidroxycloroquine and have poor obstetric history. Our objective was to determine in pregnant patients the maternal outcome and their relationship between the SLEDAI at the beginning of pregnancy.

Patients and Methods: Between January 2005 and July 2012 we identified patients with SLE (ACR 1997) who were followed up in the division of Rheumatology and Obstetric. Retrospective patieńts medical records were reviewed following a pre-established protocol. Maternal outcomes included were: activity at the beginning of the pregnancy by SLEDAI (no activity: 0, low: 1-4, mild: 5-8, high: ≥ 9), flares, antiphospholipid antibodies with or without thrombosis, nephritis, pregnancy induced HTA, preeclampsia, eclampsia and HELLP syndrome and maternal death.

Results: We included 42 patients with a mean age of 26,5 years (16- 39) at pregnancy. In five SLE was diagnosed during pregnancy. The mean duration of SLE in the others was 5,6 years (1-14). Thirty patients were multiparous,12 nulliparous and 25 patients had a poor obstetric history (11 spontaneous abortions/4 stillbirths/5 premature births/4 gestational hypertension /1 preeclampsia). Seven had active lupus nephritis at the beginning of pregnancy. Patients with renal involvement during pregnancy or at the moment of conception didńt improve like non renal manifestations. One patient died.

Maternal Outcome depending upon the activity at conception n° (%):

	No activity SLEDAI 0 n° 10 (%)	*Low activity SLEDAI 1- 4 n°16 (%)*	*Mild activity SLEDAI 5- 8 n° 5 (%)*	*High Activity SLEDAI ≥ 9 n° 11(%)*
HTA	3 (30)	2 (12,5)	1 (20)	5 (45)
Preeclampsia	1 (10)	0	1 (20)	2 (18)
Eclampsia	0	0	0	1 (9)
HELLP	0	0	0	2 (18)
Without HCQ at conception	5 (50)	5 (32)	4 (80)	9 (82)

Serology: Anti Ro+ 19/42 patients, antiphospholipid antibodies + 5/32 (15%) (4 aCL and LAC /1 LAC only). *Treatment:* At diagnosis of the pregnancy 22/ 42 received hydroxycloroquine (HCQ), but 3/22 had discontinued. Corticoesteroids: 19/42 (45%) < 20 mgr, 4 /42(9%) doses between 20- 40 mgr, 10/42 (23%) > 40 mgr. Eight patients had also received azathioprine and 1 cyclophosphamide.

Conclusion: Ours results suggest a relationship between high activity at conception and worst maternal outcome. The presence or development of nephritis at the time or during pregnancy is associated with poor prognosis and response to treatment. Women with severe organ damage or severe disease activity should avoid pregnancy. In our cohort, as is described in the literature, patients without HCQ had high activity in the beginning and evolved worse. Hydroxycloroquine is safe and withdrawal increases flares. A careful planning of pregnancy before conception is essential.

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Maternal autoimmune-mediated fetal heart disorders in a cohort of pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies.

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Background: Maternal autoimmune-mediated fetal heart disorders include a wide spectrum of conduction disturbances that can appear in fetuses of pregnant women with systemic autoimmune diseases, being congenital heart block (CHB) one of the most common and severe manifestations. The pathogenic role of maternal anti-Ro/SSA and anti-La/SSB antibodies has been well established in several studies, independently of whether the mother has systemic lupus erythematosus (SLE), Sjögreńs syndrome (SS) or is asymptomatic carrier of these antibodies. The aim of this study was to describe the characteristics of maternal autoimmune-mediated fetal heart disorders in a cohort of pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies derived from an Autoimmune Diseases Pregnancy Clinic of a tertiary hospital.

Methods: We conducted a retrospective study to describe the prevalence of maternal anti-Ro/SSA and anti-La/SSB antibodies and their relationship with fetal heart disorders in pregnant women referred to our Autoimmune Diseases Pregnancy Clinic between 2009 and 2011.

Results: A total of 104 pregnant women were referred to our clinic. The mean (SD) age was 34 (4.4) years and 93 (89%) were Caucasian. 54 (52%) women had SLE, 20 (19%) primary antiphospholipid syndrome, 8 (8%) primary SS, 20 (19%) had other systemic autoimmune diseases and 2 (2%) were asymptomatic carriers of autoantibodies. Anti-Ro/SSA and/or anti-La/SSB antibodies were detected in 44 (42%) of these pregnant women: 39 (38%) had anti-Ro/SSA and 26 (25%) anti-La/SSB antibodies (both autoantibodies were detected in

21 (20%) women). CHB was detected by fetal echocardiography in 4 fetuses: Complete CHB (third degree) in two fetuses and second-degree CHB in the other two. The mean (SD) gestational age at the time of CHB detection was 21.5 (2.1) weeks. The mothers of 3 of the 4 fetuses were positive for anti-Ro/SSA and anti-La/SSB antibodies and the mother of the other fetus was positive for only anti-Ro/SSA. Two mothers had primary SS and both had previous pregnancies with fetuses having CHB. The remaining 2 women were asymptomatic carriers of anti-Ro/SSA antibodies. Regarding fetal outcomes, two newborns did not require any intervention, one needed a pacemaker and the remaining suffered an intrauterine fetal death.

Conclusions: All mothers of the fetuses with CHB from our cohort presented anti-Ro/SSA antibodies. They represent 10.2% of the pregnant women with anti-Ro/SSA antibodies. Fetal echocardiography allowed the prenatal diagnosis and guided the management of the disease. Early serological and ultrasound screening is strongly recommended to recognize CHB in pregnant women with these antibodies.

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Pregnancy in patients with systemic lupus erythematosus. results of two - years study.

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Objectives: The goal of the current project was to investigate the course of pregnancy in 44 patients with systemic lupus erythematosus (SLE) with or without secondary antiphospholipid syndrome (APS) in years 2010–2012, to describe them by type and severity and to explore their relationship with specific characteristic.

Methods: 44 pregnant women with SLE and/or with sec.APS were evaluated every 3 months by a rheumatologist and gynaecologist During evaluation the basic demographic data were reviewed as well as the duration and type of immunosuppressive agent, corticosteroid dose, presence of autoantibodies, presence of organ involvement and its activity, the number and type of disease flares, thrombosis, the number of abortions and premature labours, new-born weight and presence of comlications as gestational diabetes, hypertension and preeclampsia.

Results: The group had 44 pregnant women with SLE, from witch 6 pts. had secondary APS. Average age of pts. was 27 years. Average duration of SLE was 6 years. 30 pts. were treated with oral corticosteroids, 2 with hydroxychloroquine, 5 with azathioprin and 8 with low molecular weight heparin and/or salicylates. 3 pregnancies were terminated in the first trimester due to missed abortion. 31 patients delivered, 6 of them before 37th week of pregnancy. From this group of 3 pts. all women delivered prematurely due to hypertension or preeclampsia. Preeclampsia was only in one pt. who had chronical proteinuria which was present before conception. 2 pts. had growth retardation of feetus. Average of newborn weight was 2860g. AV heart block of 3rd degree in newborns was not found. No congenital malformations were observed in our group. The higher number of gestational diabetes was found: 6 pts., all in corticosteroid treated group. Hypertension complicated 6 pregnancies, all with a history of lupus nephritis. Lupus activity by SLEDAI score was in the begining of pregnancy on average 4 points, after delivery 4. In group with abortions average SLEDAI was 8 points.

Conclusion: In spite of the fact that women with SLE have high risk for the course of pregnancy, the results of our three years study showed the good pregnancy outcome.

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Antiphospholipid antibodies: pregnancy risk is even higher than in other thrombophilias

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Introduction: antiphospholipid syndrome is one of the most important causes of pregnancy loss. Poor obstetric outcomes include miscarriages, fetal losses and severe preeclampsia. Many other thrombophilias are associated with similar pregnancy morbidity. Our objective was to compare obstetric outcomes in patients with antiphospholipid syndrome and thrombophilias of other causes.

Methods: a retrospective cohort of high risk pregnancies of mothers with diagnoses of antiphospholipid syndrome (APS) or other thrombophilias between 2007-2012 was analized. Medical records were reviewed and data of obstetric outcomes (miscarriages, immature delivery 20-< 28 weeks, premature delivery 28-< 37 weeks and on-time delivery), maternal morbidity (pregnancy hypertension, preeclampsia, eclampsia, HELLP syndrome, thrombosis and maternal death) and fetal morbidity (early fetal loss, fetal death, intrauterine growth restriction, placental abruption and placental insufficiency) were obtained. Patients in the APS group were included in 3 subgroups: APS fulfilling Sapporo's criteria (group 1); patients with clinical events and atypical antiphospholipid antibodies (antibodies against phosphatidyl serine, phosphatidylethanolamine, phosphatidylcholine, prothrombin or annexin 5) (group 2) and those with presence of either typical or atypical antiphospholipid antibodies and no previous clinical event (group 3).

Results: 43 patients were included, mean age 33.1 years. APS group had 24 patients (group 1: 17, group 2: 4, group 3: 7) and thrombophilias' group had 19. Treatments were similar in both groups: low weight heparin (LWH) in prophylactic doses (76% and 78% respectively, p=0.4), anticoagulation with LWH (12% and 0%, p=0.08), aspirin (76% and 84%, p=0.2), prednisone > 5 mg/day (36% vs 21%) and hydroxicloroquine (12% and 0%, p=0.08). Pregnancy results, maternal and fetal morbidity are shown in table 1.

Table 1.

	APS group (n=24)	*Thrombophilias (n=19)*	*P value*
Obstetric results	4 (16.7, CI 4.7-37.4)	0	0.043
– Abortion (< 20 weeks), n (%, CI)	1 (4.2, CI 0.1-21.1)	0	0.2
– Fetal death (> 20 w)	1 (4.2, CI 0.1-21.1)	0	0.2
– Immature delivery (20 < 28w), n (%, CI)	15 (62.5, CI 40-81)	4 (21.1, CI 6.1-45.6)	0.004
– Prematurity delivery (28- < 37w), n (%, CI)	4 (16.7, CI 4.7-37)	15 (78.9, CI 54-93)	< 0.001
– On-time delivery, n (%, CI)			
Maternal morbidity	0	0	0.3
– Eclampsia	2 (8.3, CI 1-27)	2 (8.3, CI 1-27)	0.4
– Preeclampsia	1 (4.2 CI 0.1-21)	1 (5.3, CI 0.1-26)	
– Pregnancy hypertension	0	0	0.4
– Maternal death	1 (4.2 CI 0.1-21)	1 (5.3 CI 0.1-26)	
– HELLP syndrome	0	0	
– Thrombosis			
Fetal morbidity	6 (26.1 CI 10.2-48.4)	3 (15.3 CI 3.4-15.8)	0.2
– Intrauterine growth restriction	1 (4.2 CI 0.1-21)	0	0.2
– Placental abruption	6 (25 CI 9.8-46.7)	0	0.01
– Placental insufficiency			

Conclusions: despite being on treatment, patients with antiphospholipid antibodies had more abortions, premature births and placental insufficiency when compared to thrombophilias of other causes receiving similar medications.

P324

Pregnancy in Mexican patients with systemic lupus erythematosus and antiphospholipid antibody syndrome: report of a tertiary hospital

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Introduction: Systemic Lupus Erythematosus (SLE) and antiphospholipid syndrome (APS) are autoimmune diseases that occur with multiple pregnancy complications for both the mother and the product.
Objective: To determine the clinical and laboratory characteristics of Mexican pregnant patients with SLE or APS in a tertiary hospital.
Methods: All pregnant patients seen in the rheumatology service of the Hospital CMNO/IMSS from October 1, 2011 to October 31, 2012 were included.
Results: We reviewed a total of 34 pregnant patients, 19 (76%) had SLE and 6 (24%) primary APS. In the SLE group the average age was 27 ±5.7 years, while in APS 31 ±5.8. The time from diagnosis to pregnancy was 5.5 ±4.9 and 2.4 ±2.2 years for SLE and APS respectively. In the SLE group 26.3% were planned pregnancies vs 16.7% in APS; 21.1% of patients in the first group debuted in pregnancy, while 16.7% in the second group. 36.8% of patients with SLE were active and 15.8% were on cyclophosphamide pulses when pregnant. A 100% with mucocutaneous manifestations, 63.2% kidney involvement and 42.1% secondary APS. 52.6% of SLE patients were in their first pregnancy, one of which was multiple, 10.5% with abortions in there obstetric history, 5.3% preterm births and 15.8% stillbirths. None of the patients with SLE had a history of previous preeclampsia, while in APS patients it was found in 33.3%. 50% in APS presented abortions as history, 16.7% preterm birth and16.7% stillbirths. In SLE 68% received chloroquine, 84.2% prednisone, 42.1% azathioprine and 42.1% with complete anticoagulation. 100% of the APS patients received anticoagulation. Of the 84.2% of completed pregnancies in SLE patients, 36.8% were in term and 42.1% preterm; 10.6% were abortions. While in APS 66.7%, of which 75% were in term and 25% preterm, without abortions. A 47.4% vs 25% of patients had complications, 31.6% preeclampsia and 5.3% HELLP syndrome, 26.3% requiring intensive care unit. In the APS group only 25% of patients presented preeclampsia. There were 7 stillbirths in the SLE group (31.8%) and none in the APS group. 59.5% of SLE babies with low birth weight, 54.5% with systemic inflammatory response syndrome (SIRS) and 18.2% with sepsis, one baby with a complete atrioventricular block. 22.7% of patients with SLE presented anti-Ro antibodies. In the APS group 25% of the babies with low body weight and 25% with SIRS.
Conclusions: This group of patients with SLE showed high activity during pregnancy and due to that unfavorable results were seen.Meanwhile the APS group presented a more benign course compared with that reported in the literature.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 8 Pediatric Lupus"

Atlantico A+B+C

P325

Impairment of left ventricular systolic and diastolic function in pediatric patients with Systemic Lupus Erythematosus: insights from Myocardial Two-Dimensional Strain Echocardiography

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Introduction: Systemic Lupus Erythematosus (SLE) is associated with high cardiovascular morbidity and mortality in adults. However, the detection of myocardial involvement is difficult since clinical signs and symptoms are nonspecific and standard echocardiographic methods for evaluating ventricular function often lack the sensitivity to detect subclinical impairment.

Myocardial dysfunction in those patients may be caused by inflammation, coronary artery disease due to arteritis and premature atherosclerosis, hypertension, renal failure and medication toxicity. Two-Dimensional Strain Echocardiography is a new, largely angle-independent technique used for evaluation of myocardial deformation that was validated against magnetic resonance. The detection of myocardial damage and ventricular function by this technique is little known in patients with juvenile SLE (JSLE). Our aim was to determine if Myocardial Two-Dimensional Strain Echocardiography can detect subclinical abnormalities of ventricular systolic and diastolic function in JSLE.

Methods: Sixteen JSLE patients without symptoms of heart failure (mean age 13,7 ± 3,4 years) and a matched control group (n = 16; mean age 14,07 ± 3,67 years) were submitted to standard transthoracic echocardiography, colored M mode, as well as Tissue Doppler imaging and Myocardial Two-Dimensional Strain Imaging of left ventricle.

Longitudinal, circumferential, and radial peak systolic strain, peak systolic strain rate, longitudinal displacement of left ventricle, early and late diastolic strain rate values were determined by means of speckle tracking.

Results: Routine standard systolic function parameters such as left ventricle ejection fraction and the S (systolic) wave velocity measured by tissue Doppler at mitral lateral annulus were similar in both groups. Ejection fraction: 71,5 % ± 5,6 (JSLE) vs 69,2% ± 4,7 (controls), p = 0,22; S velocity: 0,14 ± 0,03 m/s vs 0,14 ± 0,03 m/s, p = 0,79. Despite that, JSLE was associated with lower longitudinal displacement (5,5 ± 1,3 mm vs 7,8 ± 1,49 mm, p < 0,0001) and lower peak systolic longitudinal strain values (-19,5 ± 3,6% vs -23 ± 2,7%, p = 0,0047). Moreover, peak systolic radial strain was also reduced in patients: + 32,9 ± 9,9% vs + 49,5 ± 6,1%, p < 0,001. Circumferential peak systolic strain values were not considered different. In agreement with published data, SLE patients had greater left ventricle mass index than controls: 41,9 ± 9,8 g/m2,7 vs 25,5 ± 6 g/m2,7. E/Vp, a classic parameter of diastolic function evaluation, was considered extremely different between groups: 1,7± 0,30 vs 1,17 ± 0,18, p < 0,0001. Reduced strain rate during early diastole in JSLE patients also indicated diastolic dysfunction: 1,53 ± 0,35 s-1 vs 1,86 ± 0,52 s-1, p = 0,0451.

Conclusions: Myocardial Two-Dimensional Strain Echocardiography was able to detect systolic and diastolic dysfunction in JSLE patients without cardiac symptoms. Further studies should be conducted to establish the clinical significance of those abnormalities, regarding therapy and prognosis.

P326

Damage Index in juvenile onset - systemic lupus erythematosus (jSLE)

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SLE mortality has declined significantly in the last decades, although a concomitant increase in damage and morbidity was observed (mainly related to disease activity and drugs toxicity). To identify damage risk factors, should improve the management of these patients. Aims of the study – To assess organ damage jSLE patients - To determine its predictors.

Patients and Methods: Retrospective analysis. SLE patients (ACR '97) under 18 years old and at least 3 years follow-up were included (Period '00-12). Demographic, clinical, serological and therapeutical variables as well as Activity Score (SLEDAÍ92) and Damage Index (SLICĆ96) were evaluated, at 1 yr of follow up and at last visit. Major infections (requiring IV antibiotics) and cumulative steroid dose were determined. Initial aggressive treatment was defined as the use of cyclophosphamide, methylprednisolone and /or Rituximab. Statistical analyses: Descriptive, Chi2, T test. Logistic Regression were used as required.PSS 15.0.

Results: Eighty-eight out 138 patients were included; 72 were female (82%), median age at diagnosis 13.1 years (IQR 11,5-14, 7) and mean time of follow-up was 5.7 (SD ± 2.1 years). At onset a high disease activity level was observed (median SLEDAI score 12, IQR :7,7-15, 2) and the most frequent manifestations were: mucocutaneous 62 patients (75%), musculoskeletal (60 patients (68%), renal in 44 (50%) and CNS involvement in 10 (11.4%). Forty-four patients (50%) received early aggressive treatment

	Damage n (%)	*Slicc mean (r)*	*Organ Damage n (%)*
Firt Year	21 (24)	0,4 (0-5)	Kidney 7(33) CNS 6 (29) Ocular 6 (29)
Last visit	46 (52)	1 (0-7)	Ocular 22 (48) ME 12 (26) Kidney 5 (11)

During the first year of follow-up: renal failure, seizures and cataracts were the most common causes of damage, whereas at last visit (mean time 5.7 ys):uscle atrophy and cataracts were the prevalent. Organ damage was associated to a higher SLEDAI score at onset (p.012), and to corticosteroids cumulative dose (mean value 23.7 gr ± 12.4, p.04) at last visit. Two patients died (2.3%) due to infection and multiple organ failure. No damage predictors were identified in this cohort. **Conclusions:** In our series of pediatric SLE, damage prevalence was 52%, initially associated to increased disease activity at diagnosis (SLEDAI X: p.012) and with a higher cumulative dose of corticosteroids (p. 04) at the last visit.A more aggressive control of the disease,a strict surveillance of co-morbidities and an appropriate corticosteroids use, would contribute to prevent the development of irreversible damage in this young pts.

P327

Regional variations in the pattern of childhood onset Systemic Lupus Erythematosus in Oman.

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Background: While SLE in found world wide, numerous epidemiological studies describe variation in disease prevalence, clinical presentation, disease severity and overall prognosis according to geographical and ethnic differences.

Oman is an Arab country situated in the Middle East with a unique geographical variation ranging from long costal margin, vast desert plains and large mountain ranges. Oman is also known for its wide ethnic diversity reflecting its history and cosmopolitan past. The aim of this study is to describe regional distribution of childhood onset SLE in Oman, a country known for its geographical variation and ethnic diversity. Our objective is to identify and compare demographic and clinical characteristic of disease within different regions of Oman.

Patients & Methods: This is a multicentre study that included all of the Omani children (n=114) with SLE who are followed in both pediatric rheumatology over 15 year period between 1995 – 2010. All children were diagnosed with SLE according to the American College of Rheumatology criteria.

Results: Among all regions of Oman, the Sharqiya region had the highest prevalence of childhood onset SLE. On a population-adjusted basis, the prevalence of childhood onset SLE per 100,000 Omani children from each region was: Sharqiya (12.3/100.000), Dhofar (3.61/100.000), Wusta (3.05/100.000), Dakhiliyah (3.17/100,000), Dhahirah (2.71/100,000), Muscat (2.45/100.000) and Batinah (2.49/100,000).

There were significantly more boys affected with SLE in the Sharqiya region compared to the rest of the country (42% versus 15%; p = 0.002). These children also tended to be younger (10.3 versus 16.5 years; p = 0.001), diagnosed at an earlier age (6.4 versus 9.4 years; p < 0.001) with a stronger family history of SLE (58% versus 33%; p=0.010). These children also had increased incidence of mucocutanous changes (81% versus 62%; p=0.036) and decreased hematological abnormalities (30% versus 51%; p = 0.036). However, disease activity index, as measured by SLEDAI, was not significantly different between the two cohorts (14 versus 14; p = 0.950) and there was no difference in the overall prognosis and mortality.
Conclusion: We identified regional clustering of childhood onset SLE to Sharqiya region in Oman which is associated with unique demographical and clinical features. This region is known to be of purely Arab ethnic background with very little ethnic diversity as compared to other regions. Whether increased prevalence of disease in this region is due to geographical, environmental, ethnic or genetic factors is yet to be determined. However, it is likely to be interplay of known and other unrecognized factors.

Discolsure: nil of interest.

P328

Multiple organ dysfunction syndrome and risk of death in patients with juvenile systemic lupus erythematosus: association with sepsis and early cardiovascular failure

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Introduction: Multiple Organ Dysfunction Syndrome (MODS), defined as the failure of at least two organic systems, is probably the most important factor associated to mortality in children hospitalized in Pediatric Intensive Care Units (PICU). Patients with Juvenile Systemic Lupus Erythematosus (JSLE) are frequently admitted in PICU for disease activity control and treatment of associated infections, with high mortality rates. The presence of MODS had not been studied in this group of patients. The aim of this study was to identify the risk factors associated to the presence of MODS in JSLE patients at PICU admission.
Methods: From January 1994 to June 2009, 58 of 224 (25.9%) patients with JSLE (ACR 1997) followed at the Pediatric Rheumatology Unit of Faculdade de Medicina da Universidade São Paulo were admitted in PICU. Ten of them were excluded due to missing data in medical records, resulting in a total of 48 analysed cases. Based on the information collected on the first 72 hours of PICU admission, the presence of MODS was defined according to Wilkinson (1987) and Goldstein (2005) criterias. A systematic analysis was performed regarding demographic data (current age, gender and disease duration), JSLE disease activity (SLEDAI-2K) and cumulative damage (SLICC/ACR-DI), presence of infection, immunosuppressive treatment, use of vasoactive and antimicrobial drugs, mechanic ventilation and outcome.
Results: MODS was identified in 30 (62.5%) and 34 (70.8%) of 48 JSLE patients according to Wilkinson and Goldstein's definitions, respectively. Moreover the presence of MODS according to both criteria was associated with the presence of Systemic Inflammatory Response Syndrome (SIRS) (100 vs. 72.2, p=0.005; 100 vs. 64.3%, p=0.001), sepsis (100 vs. 66.6%, p=0.001; 97 vs. 64.3%, p=0.005), severe sepsis (96.6 vs. 33.3%, p=0.0001; 94.1 vs. 21.4%, p=0.0001), septic shock (63.3 vs. 0%, p=0.0001; 55.9 vs 0%, p=0.0002) and death (53.3 vs. 11.1%, p=0.005; 47 vs. 14.3%, p=0.04). In contrast, MODS was not associated with demographic data, SLE activity, cumulative damage, and immunosuppressive therapy (p > 0.05). The median of affected organs and systems was higher in deceased patients compared to those who survived according to Wilkinson's and Goldstein's definitions [3.0(1-4) vs. 1.0(0-3), p=0.001; 3.0(1-5) vs. 1.5(0-4), p=0.004; respectively]. Cardiovascular impairment (evidenced in 46% of total cases) analyzed by Wilkinson and Goldstein criteria showed association with death in both evaluations (72.2 vs. 30%, p=0.007).
Conclusions: Patients with JSLE admitted in PICU with SIRS, sepsis, severe sepsis, and septic shock have a higher frequency of MODS, independently of lupus activity and its therapy. The presence of MODS was associated to death, especially on those patients with cardiovascular impairment.

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Neuropsychiatric Manifestations in Juvenile Systemic Lupus Erythematosus

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The prevalence of neuropsychiatric lupus(NPL) in pediatric SLE has been reported in 25-75 %. Data about the usefulness of the new NPL nomenclature (ACŔ99) and outcome of neuropsychiatric events (NPe) has been scarce reported in childhood.
Objectives: 1- to determine prevalence and clinical patterns (NPL) 2- to evaluate NPL outcome in juvenile SLE pts.
Methods: Clinical files of SLE pts (ACŔ97) were retrospectively evaluated. Age at disease onset was ≤ than 16ys (1995 -2011). Demographic, Clinical, Serological and Therapeutical variables as well as Activity Score (SLEDAÍ92) and Damage Index (SLICĆ96) were evaluated.StatisticalAnalysis: Descriptive, X2, t-test, regression analysis were used as required (SPSS15.0)
Results: 43 out of 213 pts with SLE (20.2%) developed 46 NPe (21.6%).Thirty-six pts were female, mean time at SLE diagnosis was 11,2 ys (r 4-17), and to NPe 20 m (r 0-101). Fifty percent of the NPe (n: 23) were observed during the first 6 months of the disease (early event). The prevalence of NPL manifestations was as follows: seizures disorders in 14 pts (32.5%), psychosis in 5 (11.6 %) chorea in 4 (9%), and polyneuropathy in 4 (9 %).Two pts didńt fit for NPL nomenclature ACŔ99 (an intermittent headache and an anguish crisis). Twenty five pts with NPL developed nephritis, 15 (60%)simultaneously. At the NPe, the mean (range) of main variables were: SLEDAI 14,3 (4-35), C3 and C4 levels 72 and 12.9 mg/dl respectively, anti-dsDNA titers 160.4 (r 0-2560) and ESR 59 mm (r4-128). Twelve out of 34 pts (35,2%) were positive for anticardiolipin antibodies (aCL) (>40 u/ml). In the bivariate analysis the presence of aCL was significantly associated with the NPe (p.04). The multivariate model showed a higher age at disease onset and the presence of aCL as predictors of NPe (OR 1.2, p .03 and OR 2.72, p .04 respectively). Regarding outcome, complete recovery was observed in 27/46 events, an adequate educational level in 33/43 pts, and residual organic brain damage in other 6 pts. Eight pts died (17.8%), 3 due to NPL (Intracranial hemorrhage).
Conclusions: In our SLE series, the NPe prevalence was 21.6% (seizures disorders, the prevalent).Fifty percent of the pts developed NPL during the first 6 month of the disease. An older age at diagnosis and an aCL Ab positive where the only risk factors associated significantly to NPe. The majority of these events resolved without sequel.

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Prevalence and phenotype of metabolic syndrome in juvenile Systemic Lupus Erythematosus

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Metabolic syndrome (MS) is a set of disorders that increases the risk of diabetes, stroke and cardiovascular disease. The last one, is the second cause of morbidity and mortality in juvenile Systemic Lupus Erythematosus (jSLE). There is no evidence of MS prevalence in jSLE population. The aim of the study was to determine the MS prevalence and its phenotype in juvenile SLE pts - Patients and Methods Cross-sectional study. Pediatric SLE patients (ACR '97), < 17 years-old, with more than 6 months of disease evolution were included (Nov'11-July'12). Patients with nephrotic range proteinuria, thyroid dysfunction, severe liver disease, diabetes type I, pregnancy or breastfeeding were excluded. Demographic, anthropometric, clinical, laboratory and therapeutical variables were analyzed as well as disease activity and damage by SLEDAI ('06) and SLICC index ('96), respectively. Diagnosis of MS was done according to Cook criteria ('03) Statistical analysis: Descriptive, Chi-square/T-test, logistic regression were used as required. SPSS 15.0

Results: Twenty-two patients were included, 20 were female (86.9%), median age at diagnosis 12.1 years (IQR 10.1-13.7), median age at last visit 15.7 years (IQR 14.7-18.1) and mean time of follow-up 3.9 years (IQR 2.6-5.3). At baseline, the median SLEDAI was 14 (IQR 9.2 -16), and at last visit 55% of patients were still active. The prevalence of MS was 22.7% (5/22 patients). The presence of high blood pressure and central obesity were the main MS phenotype features (100%).

Table compares differences between SLE patients with/without MS

	With MS (n:5)	*Without MS (n:17)*	
Hypertension n(%)	5(100)	6(35,2)	,011
Central Obesity n(%)	5(100)	5(29,4)	,005
Cumulative Corticosteroid dose (gr/kg) Mean (SD)	0,49(±0,1)	0,25(±0,1)	,003

A higher frequency of active patients (4/5 vs 9/17) and a higher cumulative steroid dose (0,49gr/k vs 0,25gr/k; p .003) were observed in the MS group. Corticosteroid dose at last visit appears as the only independent variable associated with MS development (OR 1.16, 95% CI 1.02-1.3, p.03). During disease evolution: 1 of these young SLE pts developed stroke and other two, type 2 diabetes. Two patients required aggressive antihypertensive treatment, 1 metformin and 2 lipid- lowering drugs.

Conclusions: In our jSLE cohort, metabolic syndrome prevalence was 22.7% (5/22 patients), MS phenotype features were hypertension and central obesity. Two patients developed complications (Stroke and diabetes). The presence of MS was independently associated to a higher cumulative steroids dose.n early detection of this syndrome and a rational use of steroids, are strategies that contribute to limit the development of severe cardiovascular and metabolic complications in SLE pts.

P331

Biometrics of spleen and liver in patients with childhood-onset systemic lupus erythematosus

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Introduction: Involvement of the reticuloendothelial system occurs in 20-50% of patients with childhood-onset systemic lupus erythematosus (C-SLE) at disease onset. However, a systematic evaluation of liver and spleen sizes has never been performed in a pediatric population with lupus.

Objectives: To evaluate the spleen and liver measures in C-SLE patients and to assess possible associations between reduced spleen size with demographic data, clinical features, disease activity, cumulative damage and treatment.

Patients and Methods: Twenty four consecutive patients with C-SLE (ACR criteria) followed at the Pediatric Rheumatology Unit of Instituto da Criança HC-FMUSP underwent abdomen sonography to evaluate hepatic and splenic biometrics. The sonographic scanner used was Esaote MyLab 80 with 3-8 MHz convex transducers. The measure of liver and spleen were obtained with the patient supine and pulmonary overexpansion. Liver measure obtained was the craniocaudal diameter of the anterior portion of the right lobe in the midclavicular line, whereas splenic size was quantified through its longitudinal size. Radiologist was blind to disease characteristics. Demographic data, clinical manifestations, disease activity (SLEDAI-2K), cumulative damage (SLICC/ACR-DI) and treatment were also evaluated. Statistical analyzes were performed with the Fisher exact test and Mann-Whitney.

Results: Splenomegaly was observed in 2 (8%), reduced spleen size in 5 (21%) and normal spleen in 17 (71%). Male gender was significantly higher in patients with low compared with normal spleen size (60% vs. 6%, p=0.024), as well as higher median disease duration [8.8 (3-13) vs. 2 (0.4 to 7.4) years, p=0.01] and current age [16 (14.8-17.5) vs. 13.5 (8.9-18) years, p=0.037]. However, there was no statistical difference between the other parameters (age of onset, weight, height, and mucocutaneous, articular, serositis, hematologic, renal and neuropsychiatric involvements) assessed in C-SLE patients with low versus normal spleen size (p > 0.05). SLEDAI-2K scores and SLICC/ACR-DI and treatment were also comparable in both groups (p > 0.05). Furthermore, only 1 (4%) C-SLE patient had hepatomegaly and 23 (96%) normal liver size. The same patient had moderate hepatosplenomegaly with nephrotic syndrome and the SLEDAI-2K was 10.

Conclusions: Reduced spleen size occurred in male pediatric lupus patient with long disease duration, suggesting the possibility of autosplenectomy. Future studies evaluating the splenic function, including a healthy control group, will be necessary. Nevertheless, either splenomegaly or hepatomegaly associated with disease activity was rarely observed.

P332

Demographic, clinical and laboratory features of juvenile systemic lupus erythematosus in Croatia and their association with delayed diagnosis: A 20-year retrospective study of 81 children

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Background: Juvenile systemic lupus erythematosus (JSLE) presents with diverse clinical features and it often presents atypically, which may delay diagnosis. Such a delay is tightly linked to morbidity and mortality.

Aim: To identify predictors of delayed diagnosis and analyze the incidence of JSLE and its clinical and laboratory features in Croatia between 1991 and 2010.

Patients and Methods: Medical records at three university-based tertiary care centers were analyzed retrospectively. A total of 81 children with JSLE (68 girls) were included in the study.
Results: Median time from symptom onset to diagnosis was 2 months (range 0-96). Time to diagnosis was inversely associated with ECLAM score ($P < 0.001$), but it showed no association with age, gender, clinical features or distance from the nearest pediatric center. Mean age at onset was 13.4±2.8 yr (range 6-18), and annual incidence varied from 1 to 15 per million at risk. The most frequent clinical and laboratory features were musculoskeletal symptoms (80%) and increased erythrocyte sedimentation rate (96%). The most frequent immune system anomalies were the presence of antibodies against histones (86%), double-stranded DNA (73%), and Sm protein (64%), as well as low levels of C3 complement (69%). Hematuria was present in 58% of children; proteinuria in 56%; and biopsy-confirmed lupus nephritis, in 43%.
Conclusion: This is the first large-scale, in-depth study of clinical and laboratory presentation of JSLE in Croatia. Among all the demographic, laboratory or clinical features examined, ECLAM score alone was associated with time to diagnosis. This study emphasizes the need of identify other factors delaying diagnosis, to detect children with JSLE early in the course of the disease.

P333

Juvenile systemic lupus erythematosus: a case series depiction in an urban community and a comparison to an adult case series.

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Objectives: to describe clinical and serological features of juvenile Systemic Lupus Erythematosus (jSLE) patients; to compare the main differences between jSLE characteristics and adult SLE (aSLE).
Methods: we detected all our jSLE patients from our database. We collected sociodemographic data and both clinical and serological variables from our jSLE patients' charts at Hospital Sant Joan de Déu, Esplugues (Catalunya, Spain). We defined the following variables: cutaneous disease (as presence of discoid lupus, photosensitivity, and/or malar rash), joint disease (arthritis), hematological disease (anemia, leucopenia, and/or plaquetopenia), renal disease (>0.5g/d proteinuria and, if available, histological WHO class), neurolupus (psychosis and/or convulsions). We collected the following data: age at onset, time disease evolution, and gender. In regarding to serological markers: DNAds positivity through follow-up was recorded. We also collected information from a well-recognised aSLE cohort of 124 patients in the same Mediterranean urban area. We analysed all data in order to depict the type of clinical and serological features for each group of patients.
Results: we assessed charts from 42 jSLE (n=42), and compared to aSLE (n=124). 90% of the jSLE patients were female, compared to a 95% of the aSLE cohort. Age at onset was 12.1 years in jSLE. In the jSLE group of patients: 81% had had cutaneous disease, 62% haematological disorder, 44% arthritis, 40% nephropathy (60% class IV, 20% class III, 10% class II and 10% class V), and 14% convulsions. In the aSLE cohort: 80% had cutaneous disease, 54% haematological disorder, 29% arthritis, 14% nephropathy and 3.2% neuro-lupus. DNAds positivity was 68% in jSLE and 54.8% in aSLE.
Conclusions: jSLE and aSLE are slightly different in our Mediterranean region. Most of cases were women and main features were similar in both groups. Pediatric patients had more frequently nephropathy (most of them class IV-WHO), and DNAds positivity. Further follow-up, in which are already involved, is needed to assess the outcome of our jSLE.

P334

Safety and efficacy of B-cell depleting therapy (rituximab) in childhood lupus at a tertiary hospital

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Objective: To report the safety and efficacy of rituximab in Saudi children with systemic lupus erythematosus (SLE)
Methods: Children with SLE treated with rituximab at King Faisal Specialist Hospital and Research Center, Riyadh are included. They were reviewed for demographic characteristics, age at diagnosis, concomitant treatments, indication of using rituximab and adverse events during the treatment period. Clinical and serologic response parameters included SLE- disease activity index (SLEDAI), complement, anti-ds DNA antibody and ANA levels and cumulative corticosteroid dose as well as Pediatric adaptation of the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (pSDI) were assessed 3 months prior to rituximab infusion course and at 6-month interval thereafter.
Results: Sixteen patients (13 girls) with refractory SLE were studied. The mean age at onset of SLE was 93.2+ 39.3 months while the mean age at diagnosis was 97.3 + 40.6 months, the mean disease duration was 55.8 +37.8 months. All patients were treated with corticosteroid and immunosuppressive drugs. Nephritis (8 patients) was the most frequent indication; other indications including refractory arthritis, thrombocytopenia, severe mucocutaneous lesions and central nervous system involvement. All patients received 2 doses but 4 required 4-6 extradoses. All patients showed improvement in response parameters. There was significant reduction in SLEDAI ($P < 0.0002$), pSDI ($P < 0.003$), and corticosteroid dose ($P < 0.005$). A total of 4 adverse events were notified; 2 developed infusion related reactions. One patient had severe soft tissue fungal infection and other patient had pancreatitis.
Conclusion: Our data showed beneficial therapeutic and steroid-sparing effects of rituximab as adjunctive treatment for children with aggressive SLE including both renal and extra-renal manifestations. Although rituximab was well tolerated by the majority of patients, it may associated with various adverse events

The authors declare that they have no financial or other relationships that could lead to a conflict of interest

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Vitamin D concentrations in juvenile systemic lupus erythematosus

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Background: Vitamin D deficiency has been related to the development of autoimmune diseases, however, there are only a few studies in the literature evaluating vitamin D concentrations in pediatric patients with rheumatic diseases. We evaluated the levels of 25-hydroxivitamin-D (25(OH)D) in children and adolescents with Systemic Lupus Erythematosus (Juvenile SLE [JSLE]) and associated them with disease duration and activity, use of medications (chloroquine and glucocorticoids), vitamin D intake, bone metabolism markers and bone mineral density.
Patients and methods: Through a cross-sectional study 30 children and adolescents with SLE were evaluated and compared to 30 healthy individuals age and gender matched. Assessment of clinical status,

disease activity, anthropometry, laboratory markers and bone mineral density were performed.
Results: Of the 30 patients included in the study, 25 (83.3%) were female, 16 (53.3%) caucasian, mean age of 13.7 years. The mean age at diagnosis was 10.5 years and the mean disease duration was 3.4 years. The mean levels of calcium, albumin and alkaline phosphatase were significantly lower in the patients with JSLE compared with controls ($p < 0.001$, $p=0.006$ and $p < 0.001$, respectively). Twenty-nine patients (97%) and 23 controls (77%) had 25(OH)D levels lower than 32 ng/mL with a significant difference between them ($p < 0.001$). Fifteen patients (50%) had vitamin D levels < 20 ng/ml and 14 between 20 and 32 ng/ml. However those values were not associated to greater disease activity, higher levels of parathormone, medications or bone mineral density. Vitamin D levels were not different related to ethnic group ($p=0.083$), body mass index ($p=0.955$), height to age ($p=0.650$) and pubertal stage ($p=0.524$).
Conclusions: We observed insufficient serum concentrations of 25(OH)D in patients with JSLE significantly more frequently than in controls, however with no association with disease activity, higher levels of parathormone, use of medications or bone mineral density alterations.

P336

Health related quality of life in children with systemic lupus erythematosus and it correlation with clinical measures of the disease. Study in two referral hospitals in Medellín, Colombia

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Introduction: Systemic Lupus Erythematosus (SLE) is a chronic, heterogeneous, multisystemic disease. Between 15% and 20% of patients are diagnosed in childhood, behaving worse, having higher rates of mortality and activity with impact on quality of life (QOL). Health related quality of life (HRQOL) is a central component of the evaluation measures of treatment response. In XXX the generic QOL scale "Kidscreen" was validated, but there arenŕt validated scales in children with SLE. SMILEY (English Simple Measure of Impact of Lupus in Youngsters) is a HRQOL scale designed specifically for children with SLE, so far it was validated in the U.S. and is being validated in other countries in several continents.
Materials and methods: To describe the HRQOL in pediatric patients with SLE evaluated by rheumatologists in two reference centers and evaluate the performance of HRQOL according to time course and severity of the disease, correlating two generic HRQOL instruments (PedsQL and Kidscreen), and a scale measuring physical function (Childhood Health Assessment Questionnaire-CHAQ), with the specific tool for evaluating pediatric HRQOL in SLE-SMILEY.

Social and demographic variables and clinical characteristics (duration, disease activity and damage index, global disease assessment by the physician-PGA) were also analyzed.
Results: 35 children with SLE, aged 13.3 ± 2.09 (range 8-17) years, 80% were female. The disease duration was less than 1 year in 40%, between 1 and 5 years in 45.7% and more than 5 years in 14.3%. Sixty percent of patients had inactive disease as categorized by SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), 5.7% had high activity disease and 20.7% of patients had organ damage determined by SDI (The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index). The CHAQ had a mean of 0.23 ± 0.43 (0-2), 57.1% had no disability at this scale evaluation. The SMILEY mean total score was 68.6 in children $\pm$ 14.5 (35.8 to 90.8) and the average of parents was 67.8 ± 16.5 (32.5 to 100). The group of patients with a longer history (over 5 years) tended to have better scores in all questionnaires. Patients with very high activity of the disease had PGA average of 8, with CHAQ of 1.44; they had no SDI as their disease duration was inferior to 6 months.
Conclusions: The total scores on the different scales of HRQOL were similar, without statistically significant differences. When comparisons were made between the scores on the different scales (SMILEY, Kidscreen and PedsQL) and CHAQ with the degree of disease activity, was demonstrated that patients with very high activity of the disease had worse scores in all domains of the different scales, with higher impact and lower scores on the related with physical activity and in the domain "effects on himself" of SMILEY.

This survey is the beginning phase of validation of SMILEY in our country and has the approval of Dr. Nandini Moorthy (original author of the scale).

P337

Anti B therapy in juvenile-onset systemic lupus erythematosus

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Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that is associated with significant morbidity and mortality. The current therapy to manage SLE involves corticosteroids and immunosuppressive agents, which have potentially side effects.

The role of B lymphocytes has been demonstrated in the pathogenesis of SLE. An important advance in the treatment of SLE has been the B cell targeted therapy with Rituximab (RTX) (a chimeric monoclonal antibody specific for human CD20 that depletes circulating B cells), and belimumab (fully human immunoglobulin G1-λ monoclonal antibody that binds to soluble human BLyS). Use of B-cell targeted therapies in juvenile SLE (JSLE) has not been fully assessed yet.
Objective: To describe the safety and efficacy of anti-B cell therapy in the treatment of JSLE.
Material and methods: This is a retrospective study. We included patients with JSLE (ACR 1997) assessed in a tertiary pediatric center between 2005 and 2012 who received anti B therapy (RTX or Belimumab). We assessed the following data: demographic (age at onset, sex, beginning of anti B therapy), disease activity (SLEDAI score), WHO Class of Lupus Nephritis, complete blood cell count, serum creatinine, erythrocyte sedimentation rate, serum immunoglobulins, urinalysis, C3, C4, anti-double stranded DNA antibody, antiphospholipid antibodies, CD19, CD20; and therapy: current and previous immunosuppressive treatments (IT), dose of corticosteroids, indications, regimen, effectiveness and safety of anti B therapy.
Results: Twelve children with JSLE (58% female) were included: median age at onset 11.1 (9-17) years; median disease duration at biologic administration: 1.85 (0.1-5.8) years. Twelve had hematological abnormalities, ten active nephritis (six class IV), two neurologic compromise and five lung involvement. Eleven patients received RTX and one patient Belimumab. Indications for anti B therapy were: lack of efficacy of IT (7/12), adverse events with previous treatment (3/12), antiphospholipid syndrome (3/12), thrombocytopenia (1/12), SLE-associated Sjögren syndrome (1/12), Neuropsichiatric SLE (1/12), Thrombotic thrombocytopenic purpura (1/12). Eleven patients had received previous IT (7 cyclophosphamide). Eleven patients received concomitant IT with anti B therapy (4 azathioprine, 4 mycophenolate mofetil, 3 cyclophosphamide). Dosage of prednisolone could be tapered from a median of 40 (10–80) mg/day to 20 (6–60) mg/day at six months ($p = 0.008$). There was a reduction of SLEDAI from a median of 14 (4–22) to 6 (0–10) at six month ($p = 0.0025$). No significant changes were found in creatinine and proteinuria levels at six months ($p = 0,81$ and $p = 0,83$ respectively). Four patients on RTX had infections (1 cutaneous Herpes simplex [HS] and sepsis E. Coli, 1 cutaneous HS and cellulitis, 1 Herpetic retinitis, 1 Herpes zoster). Two

patients required IVGG due to hypogammaglobulinemia and infection. All patients on RTX exhibited B-cell depletion which lasted a median of 6 (5-11) months.

Discusion: SLEDAI score, immunological and hematological parameters showed improvement in our cohort. The commonest side effect was HS infection. One patient treated with RTX had a very severe adverse effect (sepsis E. Coli).

P338

Miliary tuberculosis: a severe opportunistic infection in childhood-onset systemic lupus erythematosus patients

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Introduction: One of the main issues in systemic lupus erythematosus (SLE) patients is infection. Of note, SLE patients are susceptible to pulmonary and extrapulmonary tuberculosis (TB), especially described in adult-onset SLE population. However, to our knowledge, this contagious disease was rarely reported in childhood-onset SLE (C-SLE) population, particularly diffuse or miliary TB.
Patients and Methods: From January 1983 to May 2012, 5,682 patients were followed at the Pediatric Rheumatology Unit, Faculdade de Medicina da Universidade de São Paulo and 289 (5%) of them met the American College of Rheumatology classification criteria for SLE. All of our 285 C-SLE patients received the bacillus Calmette-Guérin (BCG) vaccination at neonatal period, as indicated in all Brazilian newborn. These patients were routinely assessed for tuberculosis according to TB household contact history, undergo PPD test and chest x-ray at diagnosis and at follow-up when indicated. The diagnosis of disseminated or miliary TB required involvement of many organs simultaneously, particularly lungs, central nervous system, lymphatic organs and peritoneum, with the identification of Mycobacterium tuberculosis in culture or necropsy.
Results: Four (1.4%) of our C-SLE patients had disseminated TB. All of them were female gender and did not have a history of TB household contact. The median of current age at TB diagnosis and the period between C-SLE and TB diagnosis were 17 years old (range 14-20) and 5.5 years (range 2-7), respectively. All patients developed miliary TB during the course of the disease. The median of SLE Disease Activity Index 2000 (SLEDAI-2K) was 4 (2-16) and the patients were treated with immunosuppressive agents (glucocorticoid, azathioprine and/or intravenous cyclophosphamide). Two of them presented sepsis and TB diagnosis was only established upon autopsy, especially with lungs, central nervous system and abdominal involvements. Anti-TB therapy (isoniazid, rifampicin and pyrazinamide) was indicated in the other two TB cases, however they deceased.
Conclusion: Miliary TB is a rare and severe opportunist infection in pediatric lupus population. This study reinforces the importance of routine searches for TB in C-SLE patients, especially with lungs, central nervous system and abdominal involvements. A multicenter C-SLE registry study to evaluate the risk factors associated with this important contagious disease will be necessary.

P339

Immunogenicity and safety of two doses of a non-adjuvanted influenza a h1n1/2009 vaccine in young autoimmune rheumatic diseases patients

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Introduction: Influenza complications can be avoided in juvenile autoimmune rheumatic diseases (ARD) patients by immunization, however the risk of infection need to be balanced with the adverse effects of vaccine. There are no data regarding the pandemic influenza A H1N1/2009 vaccine in ARD patients younger than 9 years old. The aim of the present study was to evaluate the vaccine immunogenicity and safety in young children with ARD in this age bracket.
Methods: Forty-two juvenile ARD were recruited. Five subjects were excluded: four juvenile idiopathic arthritis patients and one control did not return to receive the second dose. Therefore, 38 juvenile ARD patients (childhood-systemic lupus erythematosus, juvenile idiopathic arthritis, juvenile dermatomyositis, juvenile scleroderma and primary vasculitis) and 11 healthy children received two doses of non-adjuvanted preparation of influenza A/California/7/2009 (H1N1) virus-like vaccine. They were clinically evaluated before and 21 days after the second dose of vaccination and serology for anti-H1N1 antibody was performed by hemagglutination inhibition (HI) assay. Seroprotection (SP) (percentage of subjects with HI antibody titer $\geq$ 1:40) and seroconversion (SC) (percentage of subjects with either a pre-vaccination HI titer $<$ 1:10 and a post vaccination HI titer $\geq$ 1:40 or a pre-vaccination HI titer $>$ 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer) rates, geometric mean titres (GMT) and factor increase (FI) in GMT (GMT of the ratio of titers after and before vaccination) were calculated. All participants received a diary card for adverse events assessment.
Results: Current age was comparable in ARD patients and controls (p=0.55). Pre-vaccination SP rates (18.4 vs. 18.2, p=1.0) and GMT (9.1, vs. 7.8, p=0.63) were comparable between juvenile ARD patients and healthy controls Three weeks after immunization, SP (81.6 vs. 81.8%, p=1.0), SC rates (81.6 vs. 90.9%, p=0.66), GMT (151.5 vs. 282.1, p=0.26) and the FI in GMT (16.7 vs. 36.3, p=0.23) were also alike in patients and controls, with both groups achieving adequate response according to the EMEA and FDA standards. The analysis of the possible factors influencing SC showed no difference in demographic data, leukocyte/lymphocyte counts and immunossupressants use (including prednisone, methotrexate, cyclosporine, leflunomide, azathioprine and anti-TNF agents) between seroconverted and non-seroconverted patients ($p > 0.05$). There were no differences in the frequencies of local or systemic adverse events between juvenile ARD patients and healthy controls. The most frequent reactions were local pain (10.5 vs. 18.2%, p=0.61), fever (10.5 vs. 9.1, p=1.0) and headache (15.8 vs. 0%, p=0.32).
Conclusion: Two doses of influenza A H1N1/2009 vaccination induced an effective antibody response and adverse events were rarely observed, suggesting vaccine recommendation for this group of age.

20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

"Area 9 Antiphospholipid Lupus"

Atlantico A+B+C

P340

Effects of maximal acute physical exercise on prothrombin time in primary antiphospholipid syndrome (PAPS) patients under oral anticoagulation with Warfarin

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Acute and exhaustive physical exercise has an increased potential for coagulation and interferes in the pharmakocinetics of several drugs. Warfarin is the leading oral anticoagulant prescribed for primary antiphospholipid syndrome (PAPS) patients but studies about the influence of physical exercise on coagulation parameters in this disease is lacking. The aim of the present study was to evaluate the effects of maximal acute physical exercise on coagulation in PAPS patients under warfarin therapy and assess safety of acute exercise regarding thrombosis and bleeding risk.

Methods: Eighteen physically inactive women with PAPS (according to Sidney criteria) with exclusive venous events were included. All PAPS patients were under warfarin therapy with PT/INR target between 2.0 and 3.0. Eighteen age-matched healthy sedentary women without thrombosis or bleeding disorders were selected as controls. All subjects performed a maximal exercise test on a programmable treadmill using a ramp protocol with progressive exercise. Capillary blood samples were obtained at rest (baseline), at the end of the test (end), and after one hour (one-hour recovery time) for PT/INR analysis using a portable Coagucheck.

Result: PAPS and controls had similar mean age (31.50 ± 8.06 vs. 29.61 ± 7.05 years; p=0.46) and BMI (24.16 ± 3.67 vs. 24.66 ± 2.71 kg/m2; p=0.65). The comparison of PT/INR values between baseline and end was similar in PAPS (p=1.00) and controls (p=1.00). Eleven of the 18 PAPS patients (61.11%) had an increase in PT/INR after exercise test. PAPS had a significant increase of PT/INR value at one-hour recovery time compared to end (2.33 ± 0.34 vs. 2.26 ± 0.32, p=0.001) and to baseline (2.33 ± 0.34 vs. 2.26 ± 0.29, p=0.001). Most of them (9/11) had an increase of 0.1 units in the PT/INR value, which corresponds to an increase of 4.44% (0.1/2.26). On the other hand, controls had similar PT/INR value at one-hour recovery time compared to end (0.99 ± 0.07 vs. 1.00 ± 0.06, p=1.00) and baseline (0.99 ± 0.07 vs. 1.01 ± 0.07, p=1.00).

Conclusion: This is the first study designed to identify the effect of acute exercise on coagulation in PAPS under warfarin therapy. Despite the slight increase in PT/INR value after exercise, it supports that regular training could be performed by these patients and reinforces the need future studies about safety of chronic training on coagulation parameters.

P341

Are thrombotic events in patients with antiphospholipid antibodies disease related?

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Introduction: Antiphospholipid antibodies (aPL) are present in different medical conditions. Whether the risk of thrombosis in patients with antiphospholipid antibodies (aPL) either primary or associated with rheumatic diseases is different to those without has not been clearly established.

Objective: The aim of our study was to analyze the prevalence of thrombotic events in patients with at least one positive aPL (lupus anticoagulant (LA), IgG and IgM anticardiolipin (aCL) and anti-ß (2) glycoprotein-1 antibodies (aß (2) GPI) according to the underlying disease.

Methods: Patients with a positive aPL in our Hospitaĺs laboratory database between 2002- 2012 were included for analysis. Electronic medical records were randomly selected and reviewed. Data on demographics, antibody type, underlying diseases, and thrombotic events (arterial and venous thrombosis, acute myocardial infarction, stroke, and abortions or premature delivery) were obtained.

Results: 400 patients (mean age: 61.4 years; DS: 20.3) (71% females) were included. Types of antibodies and underlying disease are shown in the table 1. Prevalence of thrombotic events in the different diagnostic categories is shown in table 2. In multivariate analysis the only variable significantly associated with thrombotic events was age (1.01; 95% CI: 1-1.03, for each year of age).

Conclusions: Thrombotic events were frequently seen in patients with antiphospholipid antibodies independently of the underlying disease. Patients with aPL antibodies should therefore be carefully monitored for thrombotic events regardless of underlying condition.

Table 1

Disease category	*Antiphospholipid antibodies*				
	LA	*IgG aCL*	*IgM aCL*	*aß(2)GPI*	*LA + aCL*
Rheumatic diseases (n=73)	52 (71%)	20 (27 %)	28 (38 %)	9/28 (32 %)	23 (31)
Primary antiphospholipid syndrome (n=20)	17 (85 %)	10 (50 %)	3 (20 %)	0/4	9 (45)
Cancer (n=81)	63 (78 %)	19 (23 %)	28 (35 %)	4/21 (19 %)	24 (30)
Infectious diseases (n=15)	9 (60 %)	4 (27 %)	6 (40 %)	-	2 (13)
Others (211)	140 (67 %)	39 (18 %)	70 (33 %)	6/46 (13 %)	33 (15)

Table 2. Disease category Number of patients with thrombotic events (%)

	Venous thrombosis	*Arterial Thrombosis*	*AMI*	*Stroke*	*Abortion*	*Any event*
Rheumatic diseases (n=73)	11 (15)	2 (3)	2 (3)	6 (8)	6(8)	20 (27)
Primary antiphospholipid syndrome (n=20)	9 (45)	1 (5)	0	4 (20)	9 (64)	20 (100)
Cancer (n=81)	17 (20)	0	3 (4)	9 (11)	2 (4)	27 (33)
Infectious diseases (n=15)	2 (13)	3 (20)	0	3 (20)	0	5 (33)
Others (211)	25 (11)	6 (3)	15 (7)	19 (9)	5 (3)	59 (28)
Total	64 (16)	12 (3)	20 (5)	41 (10)	22 (6)	131 (33)

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Association between Nontrombotic Neurological and Cardiac Manifestations in Patients with Antiphospholipid Syndrome

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Objectives: The aim of this study was to investigate association between nontrombotic neurological and cardiac manifestations in patients with antiphospholipd syndrome (APS) as well as their connection with type and level of antiphospholipid antibodies.
Methods: Our prospective study comprises of 333 patients: 218 with primary and 115 with secondary APS. Antiphospholipid antibody (aPL) analysis included detection of aCL(IgG/IgM), ß2GPI(IgG/IgM) and LA and served to evaluate associations with distinct neurological manifestations.
Results: Presence of aCL IgG was more common (p=0.001) in SAPS and LA in PAPS patients (p=0.002). High ß2GPI IgM levels (>100PLU/ml) were more common in epilepsy (p=0.00001) in PAPS, and in transient ischemic attack (p=0.029) in SAPS. High ß2GPI IgG levels (>100PLU/ml) were more common in epilepsy (p=0.035) in SAPS. Chorea, migraine and epilepsy occurred more often in SAPS and headache and depression in PAPS. We revealed statistical significance considering the presence of aCL IgG and acute ischemic encephalopathy in SAPS, aCL IgM and epilepsy in SAPS, aCL IgM and migraine in PAPS, ß2GPI IgG and chorea in SAPS and ß2GPI IgM and TIA and epilepsy in PAPS. LA was linked to depression, transient global amnesia and migraine in PAPS. Patients with non stable angina pectoris were more likely to develop TIA in both PAPS and SAPS, epilepsy and transient global amnesia in PAPS and acute ischemic encephalopathy in SAPS. Patients with valve vegetations were more prone to epilepsy and depression.
Conclusion: Certain aPL type and levels are associated with distinct neurological nontrombotic manifestation, suggesting their predictive role. There is strong link between some nontrombotic neurological and cardiac manifestations in APS patients, suggesting complexity and evolutionary nature of APS.

P343

Impaired aerobic exercise capacity and cardiac autonomic control in primary antiphospholipid syndrome

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Introduction: Primary antiphospholipid syndrome (PAPS) is associated with increased risk of cardiovascular disease and mortality. Aerobic capacity and cardiac autonomic control are also associated with these risks. The aim of our study was to assess aerobic capacity and cardiac autonomic control in PAPS patients.
Patients and Methods: Thirteen women with PAPS and 13 healthy controls matched for age, gender, and body mass index were enrolled for the study. Both groups were sedentary and were not under chronotropic, antidepressants and hypolipemiant drugs. All subjects performed a treadmill graded maximal exercise. Aerobic capacity was assessed by peak oxygen uptake (VO2peak), time at anaerobic ventilatory threshold (VAT) and respiratory compensation point (RCP), and time-to-exhaustion, whereas cardiac autonomic control by chronotropic reserve (CR) and heart rate recovery of the first and second minutes after graded exercise (HRR1min and HRR2min, respectively).
Results: All aerobic capacity indexes were reduced in PAPS patients than healthy subjects: VO2peak (30.2 ± 4.7 vs. 34.6 ± 4.3 ml.kg^{-1}.min^{-1}, $P = 0.021$), time at LAV (3.0 ± 1.5 vs. 5.0 ± 2.0 min, $P = 0.016$), time at RCP (6.5 ± 2.0 vs. 8.0 ± 2.0 min, $P = 0.050$), time-to-exhaustion (8.5 ± 2.0 vs. 11.0 ± 2.5 min, $P = 0.010$). HRR1min (22 ± 9 vs. 30 ± 7 bpm, $P = 0.032$) and HRR2min (33 ± 9 vs. 46 ± 8 bpm, $P = 0.002$) were delayed in PAPS patients compared to healthy controls but CR was not significantly different ($P = 0.272$).
Conclusion: In conclusion, an impaired aerobic capacity and cardiac autonomic control was identified in PAPS.

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Early detection with MSCT-angiography of lower limbs arterial lesions in patients with primary antiphospholipid syndrome

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Background: Antiphospholipid syndrome (APS) is an autoimmune disease which is characterized by arterial and venous thrombosis, fetal loss, and the presence of antiphospholipid antibodies in the serum (aPL). It is a challenge for modern medicine, in the ways of early detection and prevention of the consequences of this disease.

Imaging Findings or Procedure Details: Pan-aortography and arteriography were done using the 64-multi slice computed tomography (64-MSCT).The patients were divided into group with primary antiphospholipid syndrome (PAPS-50 pts.), and a control group (30 patients). The data was analyzed using quantitative peripheral angiography, a computer system that measures the degree of lesions (stenosis and obstruction diameter). By using angiographic examination, peripheral blood vessels were included.

There were 70 newly discovered blood vessel lesions in the patients with PAPS and 43 lesions in the control group ($p < 0{,}001$). Most frequent lesions were found on right common iliac artery (30pts vs. 10pts,$p < 0{,}01$), left common iliac artery (13pts vs. 6pts, $p < 0{,}01$), and on the left superficial femoral artery (6 pts vs. 0 pts, $p < 0{,}01$).The newly discovered lesions were more frequent in patients with PAPS ($p < 0{,}05$),with the only exception- arteria poplitea (left and right),where the lesions were more frequent in the control group (2pts vs. 6pts;1pts vs. 5pts, $p < 0{,}05$).
Conclusion: 64-MSCT angio is the method of choice for diagnosing and monitoring the patients with PAPS. This enables timely treatment of these patients with drugs or interventional radiology procedures

P345

Antiphospholipid Syndrome Patients with and without Concomitant Systemic Lupus Erythematosus: Clinical and Laboratorial Features

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Introduction: Antiphospholipid syndrome (APS) can be classified as primary (PAPS) or secondary (SAPS), according to the presence of an autoimmune disease, mainly systemic lupus erythematosus (SLE). However, few studies have compared the features of these two APS groups. The aim of this study was to analyze the clinical and laboratorial characteristics of APS patients with and without concomitant SLE.

Patients and Methods: One hundred and seventy consecutive patients who fulfilled APS Sydney criteria, followed in a single APS outpatient clinic, were enrolled. Data were obtained from an ongoing electronic database protocol, established in January 2000, that was carried out for all patients at 1- to 6-month intervals and consisted of an extensive clinical and laboratory evaluation including those relevant for this study. Lupus anticoagulant (LA), anticardiolipin (aCL), anti-beta-2 glycoprotein 1 (aB2GP1), antiprothrombin (aPT), anti-annexin (aA) and anti-phosphatidylserine (aPS) were measured by standards techniques, with cut-off values according to Sydney criteria.
Results: Of 170 APS patients, 43% were SAPS (n=73) and 57% were PAPS (n=97). SAPS and PAPS patients had similar age (41±10 vs. 43±13, p=0.44), age at diagnosis (29±10 vs. 32±12, p=0.11), disease duration (10±7 vs. 11±7, p=0.40) and frequency of female gender (87 vs. 78%, p=0.15). The frequency of LA was similar in both groups (76 vs. 76%, p=1.0), but the frequency of any positive APS related antibody was higher in SAPS than in PAPS patients (83 vs. 68%, p=0.03). The frequencies of autoantibodies in SAPS and PAPS patients were respectively: aCL (72 vs. 53%, p=0.01), aB2GP1 (50 vs. 39%, p=0.16), aPT (23 vs. 18%, p=0.56), aA (7 vs. 11%, p=0.57) and aPS (45 vs. 32%, p=0.31). The frequencies of clinical manifestations in SAPS and PAPS patients were respectively: any thrombotic event (82 vs. 91%, p=0.10), venous thrombosis (68 vs. 60%, p=0.30), arterial thrombosis (35 vs. 47%, p=0.13), stroke (31 vs. 35%, p=0.74), obstetric morbidity (39 vs. 43%, p=0.75). The frequency of patients with multiple events was similar in both groups (45 vs. 44%, p=1.0). SAPS patients had higher frequency of thrombocytopenia (42 vs. 24%, p=0.01) and lower frequency of livedo reticularis (4 vs. 27%, $p < 0.01$).
Conclusion: In our cohort, patients with concomitant SLE presented higher frequency of APS related antibodies without a concomitant increase in the frequency of thrombotic or obstetric events, probably due to similar frequency of LA. However, thrombocytopenia was a more important concern in SAPS.

P346

The role of the MSCT-angiography in early detection of visceral arterial lesions in patients with antiphospholipid syndrome

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Background: Antiphospholipid syndrome (APS) is an autoimmune disease which is characterized by arterial and venous thrombosis, fetal loss, and the presence of antiphospholipid antibodies in the serum. It is characterized by accelerated atherosclerosis. Increased tendency towards thrombosis leads to the occurrence of various vascular events.
Objective: The objective of our study was to determine if there are sub clinical changes on visceral arteries in APS patients and what the best diagnostic choice for their establishment is.
Methods: In this study we analyzed 50 patients with primary antiphospholipid syndrome (PAPS) and 50 patients with Systemic Lupus Erythematosus and APS (SAPS). The results were compared to 30 controls. The groups were comparable with respect to age, gender, and traditional risk factors except for the lipid status, since controls had significantly higher levels of cholesterol and triglycerides. Study was conducted on 64-multi-sliced computed tomography (64-MSCT) and only the new changes that have not been verified until this exam were taken into analysis.
Results: There were 20 newly discovered visceral blood vessel lesions in the patients with APS and 5 lesions in the control group. There was significantly higher incidence of overall visceral arterial changes comparing to controls since in PAPS patients the sum of 10 and in SAPS the sum of 5 arterials stenosis compared to 5 in control group was detected ($p < 0.001$). Significant changes in PAPS and SAPS patients comparing to controls were detected on celiac artery (10pts vs.3pts vs. 3pts; $p < 0.05$), superior mesenteric artery (6pts vs. 2pts. vs. 0pts; $p < 0.05$) and right renal artery (4pts vs. 0 pts. vs. 2pts; $p < 0.05$).

Conclusions APS patients suffer from accelerated atherosclerosis and the 64-MSCT angiography is the method of choice in monitoring disease progression. It is safe, with minimal risk and the lowest degree of error.

P347

Antiphospholipid Antibodies In Patients Diagnosed With Systemic Lupus Erythematosus In A Rheumatology Department Of Buenos Aires Argentina

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Objectives: Antiphospholipids antibodies (aFL) are found in 2% of the healthy population. A third of patients diagnosed with systemic lupus erythematosus (SLE), have positive titers of aFL, but not all of them develop antiphospholipid syndrome (APS). Anticardiolipin antibodies (aCL), are positive in 80% of patients with APS, Lupus anticoagulant (LA) only in 20% and both together in about 60% also associated with clinical manifestations such as thrombotic events and recurrent abortions.

The aim of the present study was to analyze the prevalence of antiphospholipid antibodies in patients with SLE and describe the inmunologic and clinical manifestations associated.
Materials and Methods: Retrospective study of medical records of patients who met the 1997 American College of Rheumatology criteria for SLE, and were followed in the Rheumatology Department of Rivadaviás Hospital since 1980 to June 2012.
Results: Ninety eight (68.5%) (CI 95% 58.8-76.8) of 143 patients with SLE, were positive for aFL: anticardiolipin antibodies were present in 85.7% of patients (CI 95% 77.4-91.3) with IgG aCL in 45,9% (CI 95% 36,4-55,6); lupus anticoagulant was found in 37,7% (CI 95% 28.8-47.5) with IgG LA in 25,5% (17,9-34,8) and beta2 glycoprotein1 in 9.1% (CI 95% 4.6-16.5). For IgG aCL and IgG LA the first determination was in higher titers compared with the second determination twelve weeks later. A hundred and twelve patients (78,3%)(CI 69,2-85,3) had high titers of ANA antibodies, 51 patients (35,6%)(CI 26,9-45,7) had low C3; 62 (43,3%)(CI 34,1-53,1) had low C4; 75 patients (52,4%)(CI 42,7-61,9) had anti ds-DNA antibodies.

There were three cases of upper limb deep vein thrombosis confirmed by Doppler (2.09%) (CI 95% 0.16-7.5), one in a male patient with positive LA and two female patients with aCL/LA.There were 16 patients who had abortions (11.1%) (CI 95% 6.2-19), some of them with more than one aFL antibody:9 patients (56.2%) (CI 95% 46.4-65.52) had aFL antibodies; 8 (50%) (IC 95% 40,3-59,6) lupus anticoagulant; 7 patients (43.7%) (CI 95% 34.3-53.4) anticardiolipin antibodies and 1 patient (6.2%) (CI 95% 2.6-12.9) presented beta2 glycoprotein1.
Conclusions: In this retrospective study, we found that more than half of our SLE patients showed moderate to elevated titers for antiphospholipid antibodies at least once throughout their disease, as well as the common findings in the laboratory such as low complement, ANÁs and ds-DNA p. The clinical manifestations were present in small proportion, being more frequent in women however, similar to international cohorts.

P348

What do we know about the new anticoagulants in Antiphospholipid Syndrome?

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Introduction: To prevent thrombotic complications in patients with the antiphospholipid syndrome (APS), current recommendations stand

that they should be treated with antiplatelet and/or anticoagulant drugs. Treatment of thrombosis is the same used in thromboembolism in general population (heparin, low molecular weight heparin and coumarins). Novel oral anticoagulants, including the direct thrombin inhibitor dabigatran etexilate and the direct factor Xa inhibitors such as rivaroxaban, may have potential role in thrombotic APS treatment.

Our objective was to describe and analyze current evidence regarding treatment of APS with the recently approved anticoagulants, dabigatran etexilate and rivaroxaban.

Methods: We searched Pubmed database for articles involving APS and new anticoagulants until 11/ 2012, by using the preferred terms ''antiphospholipid syndrome'' and ''rivaroxaban'', ''dabigatran etexilate'', ''ximelagatran'' or ''betrixaban''. We complete our search using the two clinical trials databases: clinicaltrials.gov and clinicalregister.eu.

Results: Only 4 publications were retrieved from Pubmed Medline database. Two of them were letters to the editor describing the interference of rivaroxaban in lupus anticoagulant (LAC) detection (1,2). One reported the results of false positive LAC testing in 21 patients randomized to rivaroxaban in a clinical trial. The other described the interference of rivaroxaban in different assays for the detection of LAC in plasma samples. Both concluded that rivaroxaban can change the results of LAC determinations leading to false positive results. The other two publications were reviews about antithrombotic treatments in APS but only described the pharmacology of dabigatran etexilate and rivaroxaban (3,4)

Two randomized clinical trials were registered in the European clinical trials database. Both of them have as primary objective to determine the no-inferiority of rivaroxaban compared with vitamin K antagonists (warfarin and acenocoumarol) in patients with thrombotic APS.

Conclusion: No clinical evidence is published regarding treatment with new anticoagulants in APS. Two randomized controlled clinical trials are actually on-going to compare the efficacy of rivaroxaban vs vitamin K antagonists in patients diagnosed with thrombotic APS.

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20/04/12

08:00 - 19:30

Poster Sessions & Tours 2

''Area 10 Lupus Treatment''

Atlantico A+B+C

P349

Methylprednisolone pulse as a risk factor for endemic infections in systemic lupus erythematosus

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Background: Infections are commonly identified in the course of systemic lupus erythematosus (SLE). However, endemic and opportunistic infections in these immunocompromised lupus patients are poor analyzed, despite case reports or small series. Therefore, the aim of the present study was to assess endemic infections and possible risk factors associated to these infections in SLE patients.

Patients and Methods: This is a single center retrospective cohort study from 2001 to 2012 that evaluated 1,364 SLE patients (ACR criteria, 1997) regularly followed. The main inclusion criteria were the identification of one of these infections: toxoplasmosis, cryptococcosis, atipic mycobacterium, pneumocystis, aspergilosis, actinomycosis, leishmaniasis, phyeoifomycosis, listeriosis, cytomegalovirus and hanseniasis. SLE patients with infections were age-, gender-, age at SLE onset-, interval time between infections and SLE diagnosis-matched to SLE patients without infections (ratio 1:2), in the same period. Data were obtained from the ongoing electronic database protocol carried out for all SLE patients at 1-3 month intervals, including those relevant for this study. Cumulative clinical and laboratorial features of SLE patients were recorded for analysis.

Results: Twenty SLE patients with infections (1.5%) patients were identified in our cohort. Groups with and without infections had similar mean age at SLE onset (25.0±9.0 years) and comparable predominance of female gender (75%). Infections were observed 3.5 years (interquartile: 2.0-11.5) after SLE diagnosis. Clinical SLE manifestations and SLEDAI were similar among groups ($P > 0.05$). SLE patients with infections had higher frequency of anti-dsDNA (45% vs. 20%, P=0.043) and anti-P ribosomal (30% vs. 10%, P=0.05) compared to control group. Regarding therapy, immunosuppressive and prednisolone doses at the time of infection, immunosuppressive used 3 months prior to infection, and cumulative prednisolone doses 3 months prior to infections were also comparable between both groups ($P > 0.05$). On the other hand, use of methylprednisolone pulse (1g/day for 3 consecutive days) 6 months prior was strongly associated to infections (30% vs. 2.5%, $P < 0.001$).

Conclusions: Methylprednisolone pulse seems to increase the risk of endemic infections in SLE which emphasize the importance of epidemiological history and monitoring infections in patients after this therapy.

P350

Immunoadsorption in lupus nephritis: three different high affinity columns are equally effective in inducing remission

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Background: Pathogenic autoantibodies and immune complexes are a hallmark of SLE. They can effectively be removed by extracorporeal procedures such as immunoadsorption (IAS). We previously reported that IAS performed with columns using sheep IgG as ligand (Ig-Therasorb®) reduces proteinuria, global disease activity and pre-treatment dsDNA levels in highly active SLE with renal involvement and contraindications or refractoriness to standard cyclophosphamide and/or MMF therapy (Stummvoll 2005). Meanwhile, three different high-affinity IAS columns using different adsorbing ligands are in use for lupus patients.

Objective: We now atempted to answer the question which column should be preferred in the treatment of (a) active, refractory lupus nephritis and for (b) maintenance therapy once disease activity has been reduced.

Patients and methods: We retrospectively analyzed all patients with histologically proven lupus nephritis with immunoadsorption (n=26)

and analyzed the effects of IAS induction therapy within the first 3 months on global disease activity and renal outcome. Patients were grouped according to the column used to perform IAS: (i) IgG-group (ligand=sheep IgG, Ig-Therasorb®, n=16), (ii) ProtA-group (ligand=staphylococcal protein A, Immunosorba®, n=5), and (iii) Gam-group (ligand=synthetic peptid Gam146, Globaffin®, n=5). Patient characteristics are given in the table.

When low/moderate disease activity was stably achieved, 8 consecutive patients where switched from IgG-columns to either ProtA (n=6) or Gam columns (n=2) while the rest of the therapy and the IAS protocoll was kept constant.

Results: In highly active, refractory SLE patients, all types of columns significantly lowered the serum levels of IgG, IgM, and anti-dsDNA. Serum-creatinine decreased in all groups and stabilized in near-normal range after three months of treatment (table). Proteinuria significantly decreased in all groups within one month, with a reduction of 55%, 59% and 60%, respectively, while serum-albumin increased accordingly. All groups presented with comparably high disease activity scores (SIS, SLEDAI) at the start of IAS and achieved a significant reduction of overall disease activity within one month and a steady increase in serum complement levels. No severe adverse event (allergic reaction, critical hypotension) occurred.

In stable, lowly/moderately active patients a column-switch from IgG to either ProtA or Gam did not affect parameters of renal function or global disease activity.

Conclusion: Immunoadsorption reduces disease activity and proteinuria in highly active, refractory lupus nephritis, leading to improved renal function. In our retrospective analysis, no column offered clear advantages, neither during induction nor for maintenance therapy. Thus, it is primarily not the type of the ligand, but the successful removal of autoantibodies that is pivotal for reducing SLE activity. Our findings may facilitate future attempts for randomized controlled trials on IAS in lupus nephritis.

	IgG (n=16)	*ProtA (n=5)*	*GAM (n=5)*
age (years)	30.5	34.2	27
female (%)	86	100	100
# of IAS treatments	23.4	18.2	18
steroid treatment (mg/day)			
start of IAS	42±35	50±25	52±28
1 month	35±27	26±17	34±27
3months	26±25*	20±17*	25±16*
serum-creatinine (mg/dl)			
start of IAS	1.72±1.02	2.07±1.69	1.87±1.22
1 month	1.54±1.31	1.67±1.31	1.55±1.0
3 months	1.48±1.17	1.54±0.86	1.19±0.71*
proteinuria (mg/dl)			
start of IAS	8.8±5.0	5.7±2.9	4.0±2.4
1 month	5.9±3.7**	1.39±0.9**	2.6±2.0*
3 months	4.0±3.2**	2.32±2.0*	1.6±1.7*
serum-albumin (g/l)			
start of IAS	24.4	28.2	27.1
1 month	27.6**	31.3	29.8
3 months	30.6**	32*	34.8**
SIS			
start of IAS	13.9	14.2	14.4
1 month	6.3**	6.2**	5.6**
3 months	5.6**	6.2**	5.2**
SLEDAI			
start of IAS	17.7	18.8	18.4
1 month	6.3**	3.6**	3.6**
3 months	4.5**	9.2*	2.4**
C3c complement (mg/dl)			
start of IAS	60	42.4	54.2
1 month	74.7*	49.3	58.2
3 months	86.5**	50.2	67.5

* = $p < 0.05$ and ** = $p < 0.01$ as compared to start of IAS all values displayed in mean±SD;

P351

Does the infection risk in SLE patients increases after rituximab therapy?

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Introduction: Immunosuppressive and biologic therapies can involve a considerable risk of infection. A number of open-label studies have suggested the potential benefit of rituximab (RTX) in systemic lupus erythematosus (SLE). However, clinical trials have shown conflicting results regarding the association of RTX with infections in SLE patients.

Objective: To evaluate frequency, severity and sites of infection in SLE patients pre- and post-6 months of RTX therapy.

Methods: Prospective single-center observational study of SLE patients treated with rituximab 375mg/m2 X 4 infusions. Patients were evaluated during 6 months-period prior and after RTX infusion for the following parameters: mild/moderate infection and severe infection (intravenous antibiotic therapy and/or hospitalization), SLEDAI score, concomitant immunosuppressive drugs. Gammaglobulins were assayed before rituximab infusion and every 2 months.

Results: 17 patients were included, 15 females, mean age 39.5 ± 12.3 years and disease duration of 12.5 ± 9.7 years. At baseline the mean SLEDAI score was 6.3 ± 5.5. Renal, hematologic, cutaneous and/or articular involvement were 35%, 30%, 35% respectively. Overall 24 infections in 13 patients were recorded (16 mild/moderate and 8 severe infection) and most of the post rituximab 5/11 (45%) occurred after 4 months of treatment. Comparing patients during de 6 months-period prior and after RTX infusion no difference was observed in number of patients that developed infection [10 (59%) vs. 9 (53%), p=1.00] and rates of mild/moderate infection [12 (50%) vs. 7 (29%)] or severe infection [1 (4%) vs. 4 (17%)], p=0.142, respectively. Of note, 3/4 (75%) RTX treated patients with severe infection required intensive care treatment whereas this complication did not occur before the treatment (p=0.093). Respiratory tract infections were the most common (33%) followed by cutaneous (16.5%) and urinary tract infection (16.5%), with comparable site distribution pre and post-treatment ($p > 0.05$). Regarding therapy at baseline, all patients were receiving prednisone (mean dose: 34.1 ± 20.8 mg) and 11 (65%) were under concomitant immunosuppressive agents other than hydroxychloroquine. The IgG and IgM gammaglobulin concentration did not decreased significantly between baseline and after rituximab treatment ($p > 0.05$) and no difference was observed in patients that developed infection and not infected patients overtime ($p > 0.05$).

Conclusion: Rituximab therapy did not seem to increase infection rate in SLE patients nor have a specific pattern of organ involvement in the first six months of therapy. Further studies are necessary to determine the long-term risk of infection in these patients.

P352

Therapeutic response in hospitalized patients with hematologic manifestations of systemic lupus erythematosus

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Introduction: Patients with systemic lupus erythematosus (SLE) can present with moderate, and severe hematological manifestations including hemolytic anemia, thrombocytopenia and neutropenia requiring hospitalization and intensive treatment with steroids, immunosuppressants and splenectomy with varying results.

Objective. To analyze the effectiveness of therapy in hospitalized patients with SLE and hematologic manifestations.

Material and methods: We reviewed medical records of hospital admissions of patients with SLE (ACR 1997) and active hematologic manifestations (hemolytic anemia, thrombocytopenia and neutropenia) in the period January 2009 to July 2012. We recorded the clinical, laboratory and immunological variables, administered treatments, with 3 months follow-up. Complete remission was defined as platelets $>100{,}000/mm3$, hemoglobina >10 g/dL and neutrophils $>1{,}500/mm$. Statistical analysis included descriptive statistics, chi square and ANOVA Friedman.

Results: Of 594 hospitalizations, 431 were for SLE and 84 per hematologic manifestations (72 patients) including thrombocytopenia (54%), hemolytic anemia (23%) and neutropenia (23%). The mean age at admission was 33.3± 14.2 years and duration of SLE 61.8±86.9 months. Thrombocytopenia was severe ($\leq$30,000/mm3) in 28 patients (62.2%), severe neutropenia ($\leq$500/mm3) in 6 patients (36.5%) and severe hemolytic anemia ($\leq$7g/dL) in 17 patients (89.4%). Inpatient treatment included high-dose steroids, methylprednisolone, dexamethasone, IV immunoglobulin, plasmapheresis and transfusion support. The changes of cell counts are shown in table 1. At discharge, 70% of patients were receiving immunosuppressive drugs mainly azathioprine, cyclophosphamide or mycophenolic acid. At discharge, complete remission was achieved in 18 patients (36.7%) with thrombocytopenia, 10 (52.5%) with neutropenia and 1 (5.2%) with hemolytic anemia, and at three months, 27 (55.1%), 7 (36.8%) and 10 (52.6%), respectively. Twenty three patients died from multiple complications such as disease activity, hemorrhage, pneumonia, and sepsis.

Conclusions: Therapeutic efficacy of high-dose steroid for hematologic manifestations in hospitalized patients with SLE is variable and temporary. It determines the use of immunosuppressive therapy from the beginning and continue long term in order to prevent relapse, subsequent hospitalizations, and mortality.

Table 1

x/ mm3	*Basal*	*Discharge*	*One month*	*Three month*	*p*
Platelets, n=45	9,911±17, 291	45,068± 66,902	92,363± 129,264	83,806± 118,948	>0.004
Neutrophils, n=19	624±288	2,889± 2,418	3,569± 2,642	3,343 ± 2,506	>0.001
Hemoglobin, n= 19	5.68 ±1.72	8.92 ± 2.10	10.8 ± 2.31	12.8 ± 2.05	> 0.001

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Effects of Tetra-arsenic tetra-sulfide on BXSB lupus-prone mice: A pilot study

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Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology that affects multiple tissues and organs. Arsenic trioxide (ATO) has been used in lupus-prone mice and showed regulatory effect on abnormality of immune system. Tetra-arsenic tetrasulfide (As4S4), a traditional Chinese medicine, which is effective in the treatment of acute promyelocytic leukemia with mild side effects than ATO. In this study, we conducted a pilot study and investigated the effects of As4S4 on the lupus-prone BXSB mice. As4S4 treatment resulted in a marked improvement of monocytosis ($p<0.05$) in spleen, followed with significantly decreased serum IL-6 ($p=0.0277$). These changes did not affect the level of serum anti-dsDNA IgG. As4S4-treated mice exhibited amelioration of skin, liver and renal disease. Histological analysis revealed that As4S4 suppressed immune complex deposition, mesangial proliferation and inflammatory cell infiltration in kidney and reduced inflammatory infiltration in liver of BXSB mice with mild side effects. Our study support that As4S4 selectively suppresses cutaneous lupus and nephritis in BXSB mice; As4S4 might be a potential treatment for SLE.

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Periodontitis treatment improves systemic lupus erythematosus response to immunosuppressive therapy

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Periodontal disease (POD) may affect rheumatic diseases severity but there are no data regarding the effect of its treatment on disease activity in SLE patients under immunosuppressive therapy. The aim of this study was to assess periodontitis treatment in SLE patients under immunosuppressive therapy and its possible influence in disease activity.

Methods: Forty-nine consecutive SLE patients (ACR criteria) under corticosteroid and cyclophosphamide pulse therapy (IVCYC) were selected. All patients underwent blinded odontological evaluation by the same dentist to identify periodontitis according to: bleeding gingival index (BGI) determined by the percentage of bleeding teeth after periodontal probing, probing depth (PD) evaluated by the mean distance from the free gingival margin to the bottom of the pocket, and probing attachment level (PAL) determined by the mean distance from the cemento-enamel junction to the bottom of the pocket. Inclusion criteria were presence of POD defined as BGI > 1 and active disease defined as SLEDAI > 2. At entry, SLE patients were assigned to groups according to the availability of odontological intervention in: TREATED (n=32) and NOT TREATED (n=17). Clinical evaluation, POD parameters, SLEDAI, CRP, and ESR were performed in all subjects at entry and 3 months after odontological treatment.

Results: Age, female gender, and race were alike among TREATED and NOT TREATED ($p>0.05$). Both groups had also comparable disease duration (10.7±6.8 vs. 11.0±6.6, p=0.83), IVCYC number (5.8±4.8 vs. 4.5±4.8, p=0.17), SLEDAI (5.9±4.2 vs. 6.3±4.3, p=0.73) as well as POD parameters [BGI (40.8±31.0 vs. 40.7±36.2%, p=0.89), PD (1.7±1.8 vs. 1.5±0.60mm, p=0.80), and PAL (2.5±1.9 vs. 1.9±1.1mm, p=0.18)]. At the end of the study, TREATED group had a significant improvement in SLEDAI (5.9±4.2 vs. 3.4±3.3, p=0.04) with a paralleled reduction in BGI

(40.8±31.0 vs. 15.2±17.2%, p < 0.01), PD (1.7±1.8 vs. 1.1±0.3mm, p < 0.01), PAL (2.5±1.9 vs. 1.7±0.9mm, p < 0.01). CRP and ESR were comparable pre- and post-treatment in TREATED (4.7±4.6 vs. 4.7±5.7 mg/dl, p=0.8 and 20.7±2.9 vs. 16.3±13.2 mm/h, p=0.6; respectively) and also in NOT TREATED (4.1±5.9 vs. 4.3±5.0 mg/dl, p=0.4 and 23.4±21.9 vs. 17.3±15.5 mm/h, p=0.4; respectively). SLEDAI (6.3±4.3 vs. 6.0±5.5, p=0.40) and POD parameters [BGI (p=0.33), PD (p=0.91) and PAL (p=0.39)] remained largely unchanged in NOT TREATED group.

Conclusion: Periodontal disease treatment seems to have a beneficial effect in controlling disease activity in SLE patients under immunosuppressive therapy and management of this modifiable risk factor is strongly recommended.

P355

Efficacy and safety of double filtration plasmapheresis therapy in severe lupus nephritis

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Objective: To investigate the clinical efficacy and safety of double filtration plasmapheresis (DFPP) accompanied with corticosteroid in patients with severe lupus nephritis(LN).

Methodology: 31 patients (19 females and 12 males, average age 24.4±10.9) with severe LN including class IV (n=19), III (n=1), V+IV (n=8), V+III1 (n=2) and V (n=1) were studied. Among them, 22 cases showed rapidly progressive glomerulonephritis(RPGN) with elevated serum creatinine (SCr) (3.42±2.11mg/dl) and 11 of them needed renal replacement therapy. DFPP was performed with two-fold plasma volume on each session using membrane type plasma component separator (EC50W and EC20W, Asahi Kasei Kuraray, Japan).

Results: 1) Clinical efficacy Each patient received DFPP treatment for 2.6 times(1~3). SLE-DAI was reduced significantly from 15.96±3.45 to 9.70±1.47 (P < 0.01)and SCr decreased from 3.42±2.11 to 2.75±1.91 mg/dl (P < 0.05)after DEPP. 6 patients were free from dialysis respectively; Gross hematuria disappeared in 4 patients and no change was founded in proteinuria. 2)Immunologic parameters Serum IgG decreased from 10.9±5.2 to 4.6±2.0 g/L (P < 0.01). The titers of anti-dsDNA and anti C1q antibody were significantly declined after DFPP, while the levels of complement C3 and C4 had no change. 3)Follow up study 31 patients were followed up for 1~29 months(10.1±6.4). 6 patients achieved complete remission, 18 had partial remission and 6 received dialysis. 4)Adverse effect 1 patient had catheter infection during DFPP treatment.

Conclusion: DFPP can rapidly and effectively eliminate autoantibodies in severe LN, thus improving renal function. Although DFPP accompanied with corticosteroid is an effective therapeutic method for severe LN, it needed to be investigated deeply.

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Intravenous immunoglobulin G in the treatment of patients with lupus nephritis: clinical experience lasting 25 years

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Introduction: Kidney disease is one of the most serious manifestations of systemic lupus erythematosus (SLE). Despite the improvement in the medical care of SLE in the past two decades, the prognosis of lupus nephritis (LN) remains unsatisfactory. In order to improve the prognosis of LN further, newer strategies with better efficacy, but with lower toxicities are necessary.

Patients and Methods: In our study we collected data on 124 patients with biopsy-proven lupus nephritis who were treated with high doses of Intravenous immunoglobulin G (IVIG). Nephrotic syndrome had been observed in all patients. 43 patients had renal failure (serum creatinine up to 504 μmol/l) and 102 hypertension. 101 patients were previously for a long time treated as induction immunosuppression with corticosteroids (CS), immunosuppressors (IS) and anticoagulants without effect. IVIG had been applied in a dose of 85 mg/kg/24 h three times every other day. Depending on the clinical improvement afterwards (in case of therapy resistance or relapse) these boli had been repeated in 98 patients after 1 month (and every 3 months for maintenance of remission) to 15 years. In 33 patients maintenance therapy comprised prednisolone (P), IVIG, azathioprine (AZA) or cyclophosphamide (CYC) or mycophenolate mofetil (MMF), in 37 - prednisolone and IVIG, in 26 - prednisolone and AZA or CYC and in 28 – only IVIG. In 26 patients IVIG was part of the initial therapy.

Results: Proteinuria disappeared and full remission occurred in 41 patients. Partial remission was present in 49 patients. 34 patients went into end-stage renal failure and/or died (28 of them of a nonrenal cause). In 24/43 patients with impaired renal function serum creatinine levels go back to normal after treatment. CS-IS-IVIG group showed better relapse-free survival than CS-IVIG group and CS-IS group (76% vs 73% vs 56% respectively at 5 years; 69% vs 64% vs 32% respectively at 10 years; 54% vs 50% vs 28% respectively at 15 years). Patients treated with IVIG for more than 10 years had better relapse-free survival than those treated for CS-IS (62% vs 32%; P < 0,001). A progressive clinical improvement was observed in 90 patients, associated with increases complement protein levels and decreases in auto-antibodies, and marked improvements in renal function and reducing necessary corticosteroid doses and proteinuria. Most patients with lupus nephritis tolerated their IVIG therapies.

Conclusion: Long-term treatment with IVIG from induction to maintenance phase in LN patients is associated with relatively favourable long-term outcome. Lupus nephritis flares are independently associated with an increased risk of deterioration in renal function; prevention of renal flares might, therefore, also decrease long-term morbidity and mortality. Appropriate maintenance therapy with IVIG might lead to a decrease in the occurrence of renal and extrarenal flares in patients with SLE. Our results suggested that IVIG therapy may be recommended in patients unresponsive to aggressive conventional treatment.

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PRIMARY AND SECONDARY CENTRAL NERVOUS SYSTEM VASCULITIS: CLINICAL MANIFESTATIONS, LABORATORY FINDINGS, NEUROIMAGING, AND TREATMENT ANALYSIS

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Introduction: Primary central nervous system vasculitis (PCNSV) is a rare condition of unknown cause that affects the brain and spinal cord only. PCNSV is a challenging clinical problem due to its non- specific signs and symptoms, inaccessibility of the central nervous system (CNS) tissue for pathologic examination, lack of efficient non-invasive diagnostic tests and the relative rarity of it presentation. Secondary central nervous system vasculitis (SCNSV) occurs in association with autoimmune rheumatic diseases (ARD) especially systemic lupus erythematosus (SLE), infections, lymphoproliferative diseases, drug abuse, and systemic vasculitis.

Objective: To compare the initial clinical, laboratory and imaging features in primary central nervous system vaculitis (PCNSV) versus secondary central nervous system vasculitis (SCNSV) and follow-up after

treatment with intravenous cyclophosphamide (IV CYC) plus methylprednisolone (MP).
Patients and methods: Neurological (focal and non-focal manifestations), laboratory (cerebrospinal fluid and immunological tests) and neuroimaging findings were analyzed in PCNSV and SCNSV patients. Both groups received at onset MP plus IV CYC during 6 months, followed by bimonthly IV CYC plus oral glucocorticosteroids (CGS) for 12 months. All the patients were followed for 36 months.
Results: The inclusion criteria were: 1) Patients over 16 years of age. Diagnosis of PCNSV according to the Calabrese criteria. 2) Diagnosis of ARD: i.e., SLE, systemic sclerosis (SSc), Sjogren syndrome (SS), systemic primary vasculitis according to The American College of Rheumatology criteria.Thirty patients were included (12 PCNSV and 18 SCNSV). Focal and non- focal manifestations were similar in both groups (p=NS); headache being the most frequent manifestation in both groups. Fatigue, myalgias, arthralgias, neuropathy low leukocytes and platelets, elevated erythrocyte sedimentation rate, positive ANA, anti dsDNA, ANCA, low complement, and rheumatoid factor were more frequent in SCNSV ($p < 0.05$). In cerebrospinal fluid (CSF) pleocytosis and proteins were higher in PCNSV ($p < 0.05$). Periventricular and subcortical hyperintense lesions were observed in cranial magnetic resonance imaging in both vasculitides. Only one out of 12 PCNSV patients (8.3 %) had a relapse at one year of follow up. In contrast, 8 out of 18 SCNSV patients (43.7%) showed a relapse after 9 months of follow-up. Time to relapse since initial treatment in PCNSV was 12 months versus 9±1.15 months for SCNSV. The cases with relapse were the following: SLE (5), SSc (1), Wegener Granulomatosis (1), and Behcet Disease (1). Cerebral angiography and angioresonance showed narrowing of vasculature in both groups. After treatment, Kaplan-Meier survival curve showed higher relapse free survival in PCNSV ($p < 0.05$).
Conclusion: There are significant differences in the clinical manifestations, laboratory, and CSF findings between PCNSV and SCNSV. After treatment with IV CYC and GCS patients with PCNSV had higher relapse-free survival than SCNSV

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Prednisone therapy is an independent cause of damage in systemic lupus erythematosus

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Objectives: To analyse the association of prednisone therapy with damage at 5 years in an observational cohort of systemic lupus erythematosus (SLE).
Material and Methods: Demographic and clinical variables were extracted. Prednisone doses were calculated from the medical records. Two prednisone-related variables were constructed: the mean daily dose received by the 5th year after the diagnosis and a categorical variable based on the mean daily dose, with the following categories: no prednisone, up to 7.5 mg/d (low dose), up to 30 mg/d (medium dose) and over 30 mg/d (high dose). Damage was calculated at year 5 using the SLICC damage index (SDI). Activity was measured using SLEDAI.
Results: 249/283 (88%) of patients were women. The mean age (SD) at diagnosis was 36.5 (16) years. 59 (21%) patients had accrued damage within 6 months after the diagnosis of SLE. The mean (SD) SDI score increased over time: 0.26 (0.59) at 6 months, 0.34 (0.72) at 1 year and 0.67 (1.05) at 5 years. The mean daily dose of prednisone was significantly higher in patients with any damage at year 5 (10.3 vs. 5.8 mg/d, respectively, $p < 0.001$). Likewise, there was a significant association between the mean daily dose of prednisone and the SDI score at year 5 ($p < 0.001$). The mean daily dose of prednisone and the SDI variation between year 0 and year 5 were also statistically associated ($p < 0.001$). Damage at year 5 was seen in 9/45 (20%) of patients taking no prednisone, 31/104 (30%) of patients taking low doses, 48/90 (53%) of patients taking medium doses and 3/5 (60%) of those receiving high doses ($p < 0.001$). Significant differences in SDI scores and SDI variations between baseline and year 5 were seen in patients taking medium doses vs. those taking low doses (p=0.018 and 0.021, respectively) and vs. those taking no prednisone (p=0.003 and 0.005, respectively). However, no differences were seen between patients receiving low doses and those not taking prednisone (p=0.77 and 0.89, respectively). The effect of the mean prednisone dose on the absolute SDI score at year 5 and on the SDI score variation 0-5 persisted after adjusting for gender, age at diagnosis, calendar year of diagnosis, baseline SDI, mean maximum SLEDAI, class III or IV lupus nephritis and time on antimalarials (p=0.003 and p=0.002, respectively). The results did not change when the categorical prednisone variable was used (p=0.009 and p=0.008, respectively).
Discussion: Irreversible organ damage is a major predictor of morbimortality in SLE. The effect of glucocorticoids on organ damage has been suggested. This study confirms that prednisone is an independent predictor of damage within 5 years after diagnosis, including new damage accrued after the diagnosis of SLE. Our results also point to the safety of low prednisone doses (defined as those lower than 7.5 mg/d).

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Evaluation of Treatment Success in Systemic Lupus Erythematosus Clinical Trials: Development of the British Isles Lupus Assessment Group-Based Composite Lupus Assessment Endpoint

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Background: Evaluation of disease activity in SLE trials is challenging due to the multi-organ presentation of SLE, interindividual variability, unpredictability of disease course, medication effects, and interobserver rating differences. Composite endpoints have been used in other disease areas, but single disease activity indices (DAIs) have been standard in SLE. This abstract reports the development of a composite responder index for use in SLE trials.
Patients and Methods: An expert panel was reviewed DAIs commonly used in SLE trials. These included the British Isles Lupus Assessment Group index (BILAG-2004), the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the Physician's Global Assessment (PGA). Characteristics considered included basis of scoring and the number and types of items assessed. Following this review, the BILAG-based Composite Lupus Assessment (BICLA) was developed as a composite of multiple DAIs based on early epratuzumab clinical trial data. The BICLA requires patients to meet response criteria across three assessment tools.
Results: BICLA responders must achieve BILAG disease activity improvement with no worsening in BILAG or other DAIs and no treatment failure at any time point (Table). The BICLA was used to evaluate response in the EMBLEM™ phase II study (SL0007), a 12-week, randomized, double-blind, placebo-controlled study that

recruited 227 patients with moderate to severe SLE. BICLA was sensitive to epratuzumab treatment response (epratuzumab 600mg QW 45.9% response at 12 weeks; epratuzumab 1200mg EOW 40.5%; epratuzumab 2400mg cumulative dose 43.2%) with a limited placebo response rate (21%; p = 0.02 vs 2400mg at 12 weeks). The use of BILAG as the primary component of the BICLA requires simultaneous improvement across all body systems with severe or moderate disease activity at baseline. BILAG gives balanced weight to all affected body systems and can reflect incremental improvements within a body system. The BICLA is also the 48-week primary efficacy variable in the EMBODY™ phase III studies (SL0009 [NCT01262365] and SL0010 [NCT01261793]) of epratuzumab in patients with moderate to severe SLE.

Conclusions: The BICLA index is a sensitive, clinically meaningful composite measure of SLE disease activity which has discriminated between placebo and treatment responses in a phase II clinical trial. BICLA response requires disease improvement across all body systems with moderate or severe baseline activity without worsening or change in background medication. The three DAIs included in the BICLA require clinical assessment, physician assessment, laboratory assessment, and recording of medication use. Further analysis of data from studies using the BICLA composite endpoint may help to guide the design of future trials in SLE.

Role of the study sponsor: The development of the BILAG-based Combined Lupus Assessment was funded and supported by UCB. Epratuzumab was licensed from Immunomedics, Inc.

Table: Definition of BICLA treatment response. All criteria must be met.

Improvement	1. ALL BILAG level A scores at study entry improved to B/C/D *and* 2. All BILAG level B scores at study entry improved to C/D
No worsening	1. No single new BILAG A and no > 1 new BILAG B scores *and* 2. No worsening of baseline SLEDAI total score *and* 3. No worsening in PGA (< 10% relative to baseline)
No treatment failure	Treatment failure was defined as non-protocol treatment, e.g. new or increased immunosuppressants or antimalarials, no requirement for other prohibited medications

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Predictors of response to induction therapy in lupus nephritis

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Introduction: Several prognostic factors have been described in lupus nephritis, which vary depending on the population studied. Few studies have examined these factors in relation to different stages of treatment.

Objective. To identify prognostic factors associated with response to induction therapy in LN according to the stages of treatment.

Patients and methods: We performed a retrospective case-control study nested in a cohort of patients with systemic lupus erythematosus (SLE) with biopsy-proven lupus nephritis period from January 2001 to December 2008. Lupus nephritis was classified according to WHO. All patients received induction therapy remission and had a minimum follow-up period of two years. For analysis patients were divided into 2 groups, those with response (complete and partial) and non-responders. We analyzed 18 clinical and laboratory variables that potentially have predictive value for response to therapy inlcuding age, gender, duration of SLE, time course of lupus nephritis, histologic class of lupus nephritis, delay in treatment, and biochemical (serum creatinine, urinary active sediment, creatinine clearance, proteinuria) and immunological parameters (complement C3, C4 and anti-dsDNA antibodies). We identified predictors of therapeutic response at 6, 12 and 24 months by univariate and multivariate analysis; odds ratios (OR) with confidence intervals (CI) 95% were also calculated.

Results: We reviewed clinical records of 168 patients, 141 of female (84%), with average age at diagnosis of lupus nephritis of 30.4±10.6 years, the mean time of evolution of SLE until lupus nephritis diagnosis was 28.0±48.8 months. Lupus nephritis was inicial manifestation in 94 (56.5%) patients. Renal biopsy revealed WHO class II lupus nephritis in 33 patients (19.6%), class III in 28 (16.6%), class IV in 92 (54.7%), class V in 7 (10.2%) and a combination in 7 (10.2%). One-hundred and thirteen (67%) patients received pulses of cyclophosphamide as induction therapy, the response rate was 69% at 6 months, 86.9% at 12 months and 79.7% at 24 months. Multivariate analysis with lack of therapeutic response as the dependent variable are shown in the table.

Conclusions: The main predictor of poor therapeutic response at 24 months is the delay in treatment. At 12 months is low creatinine clearance. Patients younger than 25 years and microhematuria are the best responders to treatment at 6 months. Unlike other studies, male gender and elevated creatinine and hypocomplementemia were not factors of poor therapeutic response. Early treatment of lupus nephritis is associated with favorable response to two years.

	OR	*IC 95%*	*P*
6 months			
Age > 25 years	0.22	0.10-0.48	0.00
Male gender	2.08	0.81-5.34	0.13
Creatinine > 1.4 mg/dL	2.29	0.91-5.78	0.08
Eritrocituria	0.35	1.28-11.43	0.02
12 months			
Male gender	2.67	0.90-7.93	0.08
Creanitine clearance < 30 ml/min	3.82	1.28-11.43	0.02
24 months			
Nephritis III/IV	0.28	0.09-7.93	0.02
Treatment delay	5.36	1.36-21.14	0.02
Eritrocituria	2.49	0.72-8.57	0.15
Low C3	0.34	0.12-0.99	0.05

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Manteinance treatment with mycophenolate sodium in an argentinian lupus nephritis cohort

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Introduction: The aim of the induction therapy in lupus nephritis (LN) is to achieve long-term remission and, for maintenance, to prevent relapse and progression to end-stage renal disease. Mycophenolate has been proposed as an effective treatment for both induction and maintenance. We evaluated efficacy and safety of mycophenolate sodium (MPA-s) as maintenance therapy in patients with LN in an Argentinean cohort.

Patients and Methods: We included 21 patients with SLE (ACR criteria 1997) with nephritis (class II, III, IV ISN/RPS 2003). All received 6 or more pulses of intravenous cyclophosphamide (CY) [0,5-1 g] plus

intravenous methylprednisolone (MP) [3-6 g] followed by MPA-s as maintenance therapy assessed at twelve and twenty four months. Renal evolution was evaluated according the following parameters: Complete remission: creatinine 1.1mg/dl female 1.3mg/dl male, proteinuria < 0.5 gr/d and urinary sediment with dysmorphic RBCs < 5 without cylinders. Partial remission: creatinine increased < 50%, proteinuria > 0.5 < 2.9 gr/d or reduction > 50% in baseline proteinuria > 3,5, GR < 10. No response (> 3gr/d) creatinine increased > 50%, GR dysmorphic > 10. Data were analyzed using SPSS 17.0.

Results: 19/21 (90.5%) were women. Mean age 37.43 (SD 11.17). Histological classes: IV 11 (52.4%), III 5 (23.8%), II 3 (14.3%), mixed III-V and IV-V 2 (9.6%). Median months from biopsy to MPA-s: 8 months (1-105, IQR:22). Patients who responded to MPA-s vs. non-responders did not differ with respect to age, sex, median months from biopsy to MPA-s, histological classes, C3, C4, CH50, DNA positivity and proteinuria.

After induction therapy: 2/21 patients (9.5%) had complete remission criteria, 6/21 (28.6%) partial remission, 13 (61.9%) no response. *At 12 months:* 3/20 (15%) had complete remission, 8/20 (40%) partial remission, 9/20 (45%) no response. One patient discontinued treatment due to severe adverse event. *At 24 months:* 2/18(11%) patients had complete remission, 14/18 (78%) partial remission and 2/18 (11%) no response. Two were lost follow up.

Adverse events: 11/21 gastrointestinal symptoms, 4/21 urinary tract infections and one pulmonary and nodal tuberculosis.

n (%)	*Complete/ Partial remission*	*Non response*	*Lost follow up*	*Low C3*	*Anti DNA(+)*
Baseline	8/21 (38)	13/21(62)	0	11/21(52)	15/21(71)
12 months	11/20(55)	9/20(45)	1/21(4,8)	4/20(20)	7/21(33,3)
24 months	16/18(89)	2/18(11)	2/20(10)	4/17(23)	6/18(33,3)

Conclusions: Maintenance therapy with MPA-s in our cohort evidenced greater efficacy at 24 months suggesting the importance of sustaining the long-term treatment.

Our results also suggest that serological markers of activity decreased at 12 months and remain low at 24 months of treatment with MPA-s.

Adverse events were mild in most patient, gastrointestinal symptoms were the most frequent as those reported in the literature. Only one patient discontinued treatment due to tuberculosis.

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Combination of mycophenolate mofetil and tacrolimus for refractory lupus nephritis: a 12-month open-labeled trial

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Objectives: To evaluate the efficacy and tolerability of a combination of mycophenolate mofetil (MMF) and tacrolimus (Tac) for refractory lupus nephritis

Patients and methods: Patients with refractory lupus nephritis were recruited. Inclusion criteria: (1) Active nephritis documented by renal biopsy within 24 months of entry; (2) Failure to respond to >=2 regimens which consisted of high-dose corticosteroid combined with another non-corticosteroid immunosuppressive agent. Each regimen should be used for >=4 months at the maximally tolerated dosage of the drugs; (3) Serum creatinine(Scr) < 200umol/L. While prednisolone (< 10mg/day), ACE inhibitors/ARB and hydroxychloroquine were continued, other immunosuppressive agents were replaced by the current regimen, which consisted of MMF (1g/day) and Tac (4mg/day) in two divided doses. Patients were followed prospectively at least 2-monthly for the primary end-point (clinical response) at 12 months and adverse events.

Results: 21 patients (95% women) were studied. The mean age of these patients was 35.8+/-9.2 years and the mean SLE duration was 111+/-51 months. The ISN/RPS histological classes of lupus nephritis were: class IV/III (33%), pure V (33%), V+III/IV (33%). Previous treatment regimens were: high-dose prednisolone (100%), CYC (pulse/oral) (38%), AZA (90%), MMF (90%), CSA (33%) and Tac (38%). Previous ineffective immunosuppressive regimens received by these patients were: high-dose prednisolone (>=0.75mg/kg/day for >=6 weeks) (100%), CYC For The median number of immunosuppressive protocols failed in these patients was 2 (inter-quartile range 2-2). The mean SCr, CrCl, uP/Cr, 24-hour proteinuria and serum albumin was 89.9+/-42umol/L, 82.4+/-33ml/min (< 90ml/min in 57%), 3.27+/-1.5, 3.13+/-1.3g and 30.1+/-5.9g/L, respectively. Thirteen (62%) patients had active urinary sediments and 17(81%) patients had active lupus serology.

After 12 months, 8 (38%) patients had very good response, 1 (5%) patient had good response and 5 (24%) patients had partial response. Seven (33%) did not respond to the protocol and required salvage treatment. For patients who responded to treatment, significantly improvement in uP/Cr, serum albumin, anti-dsDNA titer and complement C3 level was observed from baseline to month 12 ($p < 0.05$ in all). CrCl in these patients did not change significantly ($p=0.14$). The renal SLEDAI and extra-renal SLEDAI score also improved significantly after treatment. Ten (71%) patients had complete resolution of urinary sediments whereas 4 (29%) patients had improvement of urinary sediments to < 5/HPF. 33 adverse events were reported in 18 patients: major infection (6%), minor infection including herpes zoster (36%), diarrhea (12%), cramps (9%), dyspepsia (6%), transient increase in serum Cr (6%), alopecia (4%), facial twitching (3%), tremor (3%) and diabetes mellitus (3%). None of these led to protocol withdrawal.

Conclusions: Combined MMF and Tac is a viable option for refractory lupus nephritis, with 61% patients improves after 12 months without significant adverse effects.

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Membranous Glomerulonephritis: Response Rate to Therapy After Five Years of Follow-up

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Introduction: It is estimated that pure membranous (class V) glomerulonephritis encompasses 10 to 20% of the lupus related nephritis. Treatment response may vary according to histologic findings observed at biopsy.

Materials and methods: We analyzed the data from 20 SLE (ACR 1997 criteria) patients with biopsy proven Class V glomerulonephritis to evaluate the five years response rate. The treatments used for induction and maintenance therapy were: cyclophosphamide (oral and IV), mycophenolate mofetil (MMF), azathioprine and methylprednisolone, isolated or in combination. Response rate was evaluated by the ACR criteria.

Results: The average age was of 32+10 years at the time of glomerulonephritis diagnosis. Before the treatment the average serum creatinine level was of 1.0+0.5mg/dL. Three patients presented serum creatinine levels higher than 1.5mg/dL. After six months, no patient had serum creatinine levels higher than 1.5mg/dL and the average creatinine level decreased to 0.8+0.2mg/dL. After 6 months and 5 years of treatment, respectively, the average creatinine was of 0.86+0.22mg/dL and 0.68+0.1mg/dL in the IV cyclophosphamide plus methylprednisolone group (n=10); 0.94+0.08mg/dL and 0.9+0.1mg/dL in the MMF group (n=2); 0.55+0.35mg/dL and

0.77+0.04mg/dl in the oral cyclophosphamide group (n=2) and 0.77+0.2mg/dL and 0.8+0.1mg/dL in the azathioprine group (n=6). The average protein urinary loss before the start of treatment was 5.2+3.8g/24hs. After 6 months and 5 years of treatment, respectively, the average 24 hour protein urinary loss was 2.2+3.5g and 0.27+0.3g in the IV cyclophosphamide plus methylprednisolone group; 0.81+0.8g and 0.06+0.02g in the MMF group; 1.44 +0.79g and 0.8+0.4g in the oral cyclophosphamide; 1.19+1.9g and 1.5+3.4g in the azathioprine group. After five years, the average protein urinary loss was 0.4+0.4g/24hs. At the end of two years, thirteen patients had complete remission (one partial remission and no remission). At five nine patients had complete remission, two patients had partial remission and two patients had no remission.

Conclusion: In this retrospective study we found that after six months all patients showed improvement in serum creatinine and urinary protein loss. However, the response rate in two and five years, disclosed an absence of complete response in two and four patients, respectively. The data from this study are similar to the literature with respect to good initial clinical response in patients with Class V lupus nephritis, however we noticed long-term remission is not universal possibly due to superposition of more severe forms of glomerulonephritis.

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