Myositis-Specific Antibodies and Myositis-Associated Antibodies in Patients With Idiopathic Inflammatory Myopathies From the PANLAR Myositis Study Group

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Background: Dermatomyositis (DM) and polymyositis (PM) are forms of idiopathic inflammatory myopathies (IIMs), which are associated with the production of autoantibodies that are useful in the diagnosis and prognosis of the disease.

Objective: The aim of this study was to determine the frequency of antinuclear autoantibodies (ANAs), myositis-specific autoantibodies (MSAs), and myositis-associated autoantibodies (MAAs) in 6 Latin American countries.

Methods: Two hundred ten patients with IIM were included in this cross-sectional study from 2014 to 2017: 112 from Mexico, 46 from Colombia, 20 from Peru, 16 from the Dominican Republic, 10 from Argentina, and 6 from Guatemala. Antinuclear autoantibodies were detected by indirect immunofluorescence on HEp-2 cells. MSAs and MAAs were tested by a line immunoassay method. Mann-Whitney U and χ^2 tests were used for statistical analysis.

Results: Of the 210 IIM patients, 139 (66.2%) had DM, 59 (28%) PM, and 12 (5.7%) juvenile DM. The mean age was 43.5 (6–79 years); 158 (75.2%) were female, and 52 (24.8%) were male. The overall frequency of ANA was 60%. The most frequent patterns were fine speckled (AC-4) (78.3%) and cytoplasmic (AC-19) (6.45%). The most frequent MSA were anti–Mi-2 (38.5%) and anti–Jo-1 (11.9%). Anti–Mi-2 was more frequent in patients from Colombia (40.1%). The MAA more frequent were anti–Ro-52/TRIM21 (17.6%) and anti–PM-Scl75 (7.5%).

Conclusions: This is the first study of ANA, MSA, and MAA in patients from 6 countries from the Panamerican League against Rheumatism myositis study group. We observed a general prevalence of 60% of ANA. In relation to MSA and MAA, anti–Mi-2 was the more frequent (38.5%).

Key Words: antinuclear antibodies, myositis-specific antibodies, myositis-associated antibodies, idiopathic inflammatory myopathies, PANLAR myositis study group

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Idiopathic inflammatory myopathies (IIMs) are a rare group of systemic autoimmune diseases that are distinguished by the presence or combination of weakness and progressive muscle pathology, altered muscle enzymes, electromyographic findings suggestive of a myopathic pattern, muscle biopsy with the characteristic pathological features, and finally the presence of pathognomonic dermatological alterations such as heliotrope rash, Gottron's papules, Gottron's sign, V-sign, and Shawl sign.[1]

As in other autoimmune conditions, IIMs are characterized by the production of autoantibodies detected in the serum of patients. Within the spectrum of IIM, the autoantibodies are classified into 2 important groups: myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs).[2–4]

Myositis-specific antibodies are divided in 2 subgroups: anticytoplasmic antibodies and antinuclear antibodies. Within the group of anticytoplasmic antibodies is another subgroup of antibodies directed against different types of aminoacyl tRNA synthetases (ARSs),[5] the most common antibody being the one directed against histidyl-tRNA synthetase (anti–Jo-1), which is detected in 25% to 30% of patients with myositis.[6–9] The other MSAs directed to tRNA synthetases that belong to the ARS subgroup are collectively detected in 3.5% of cases[10]

Another MSA subgroup of anticytoplasmic antibodies, originally described in a polymyositis (PM) patient, are those directed against the signal recognition particle (SRP)—a macromolecular complex of 7SL RNA and several proteins including 72, 68, 54, 19, 14, and 9 kD, proteins that regulate the translocation of proteins across the endoplasmic reticulum.[8,11] Anti-SRP is detected in less than 4% of myositis patients and is associated with necrotizing myopathy and characterized with a poor prognosis.[12]

Antinuclear antibodies (ANAs) are present in approximately 60% of myositis patients' sera. Anti–Mi-2 antibody is the only MSA localized in the nucleus,[13,14] detected in 5% to 10% of patients and is associated with both adult and juvenile dermatomyositis (DM). Less frequently, other MSA detected include anti–MDA-5/CADM-140, anti-155/140 (TIF1-γ/α), anti–MJ/NXP-2, anti-PMS1, anti-SAE, and anti-HMGCR.[15–23]

The MAA most commonly found in myositis patients and overlap syndromes include anti–U1-RNP present in 10% of

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patients with overlap syndromes and in virtually all patients with mixed connective tissue disease; anti-SSA/Ro in more than 35% of patients with IIM and ILD, anti–PM-Scl present in patients with PM-systemic sclerosis overlap,[24] and anti-Ku antibodies are found in PM-SLE overlap (20%–30% in Japanese patients) and can be frequently associated with corticosteroid sensitive IIM and severe, corticosteroid-resistant ILD.[25,26]

In the present study, we evaluated the presence of ANA, MSA, and MAA in the sera of IIM patients from rheumatology clinics in 6 Latin American countries that participate in the Panamerican League against Rheumatism (PANLAR) Myositis Study Group. The aim of our study was to determine the frequency and profile of MSA and MAA in Latin America as well as to individually assess the frequency of autoantibodies in each country.

SUBJECTS AND METHODS

Patients

Two hundred ten serum samples from both incident and prevalent patients with IIM were included in this cross-sectional study, from 2014 to 2017. The diagnosis was made according to Bohan and Peter's criteria.[27–29] The regional distribution of the patients included 112 from Mexico, 46 from Colombia, 20 from Peru, 16 from Dominican Republic, 10 from Argentina, and 6 from Guatemala.

The researchers participating in this project made a commitment to respect and work according to the principles expressed in the Declaration of Helsinki, as well as adherence to current good clinical practice standards. All patients signed an informed consent, which was approved by an ethics committee in each participating center.

ANA Detection

Antinuclear antibodies were detected by indirect immunofluorescence (IIF) in HEp-2 cells (Antibodies Inc, Davis, CA) as previously described.[30] Briefly, we included as screening both dilutions 1:160 and 1:320. We considered a positive test for ANAs a dilution of 1:320 or higher.

Myositis-Specific and Myositis-Associated Antibodies

The MSAs and MAAs were performed by a line immunoassay method (Euroline Myositis Antigens Profile 3; Euroimmun, Luebeck, Germany)[31] to identify the following antibodies: Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, SSA/Ro52, PM-Scl100, PM-Scl75, and Ku. All strips were scanned with a densitometer, and the results expressed as optical density units. An optical density unit value higher than 10 was considered as a positive test.

In Colombian patients, the MSAs and MAAs were performed with a qualitative enzyme immunoassay kit "DIA Spot Polymyositis/Scleroderma IgG" (DIASource-Belgium), to identify the following antibodies: Jo-1, PL-7, PL-12, SRP-54, Mi-2, Ku, PM/Scl, and ScL-70. Quantitative results were considered as positive or negative based on control sera included with the assay kit.

Anti-HMGCR Antibodies

Anti-HMGCRs were detected with an addressable laser bead immunoassay (ALBIA Luminex) as previously described.[32] A value higher than 20 median fluorescence units was considered positive.

Statistical Analysis

Descriptive statistics tests were performed for the data. For the comparison of medians, Mann-Whitney U test[33] was performed. χ^2 Tests[34] were used for the comparison of frequencies. A $p < 0.05$ was considered statistically significant. All the analyses were performed using the GraphPad Prism 6.

RESULTS

Of the 210 IIM patients, 158 (75.2%) were female and 52 (24.8%) were male. Their mean age was 43.5 (6–79 years). According to the diagnosis, 139 (66.2%) had DM, 59 (28.1%) PM, and 12 (5.7%) juvenile DM (Table 1). Also, PM showed significant differences between the countries ($p = 0.02$); Guatemala was more frequent (83.8%), followed by Argentina (40%) and Colombia (34.8%).

The seronegative frequency was 21.0%, with a significant difference between the countries ($p = 0.003$). The most frequent was Guatemala (66.7%). The ANAs' frequency was 60%, being more frequent in Colombia 89% (Table 2). These frequencies showed significant difference between the countries ($p = 0.02$). In particular, the frequencies of positivity of ANAs of Colombia obtained significant differences when compared them with

TABLE 1. Clinical and Demographic Data of Patients With IIM in 6 Latin American Countries

	Total n = 210	Mexico	Colombia	Dominican Republic	Peru	Argentina	Guatemala	*p* value
Demographics								
Patients, n (%)	**210 (100)**	112 (53.3)	46 (21.9)	16 (7.6)	20 (9.5)	10 (4.8)	6 (2.9)	NS
Female, n (%)	**158 (75.2)**	91 (81.3)	32 (69.6)	12 (75)	9 (45)	8 (80)	6 (100)	NS
Male, n (%)	**52 (24.8)**	21 (18.7)	14 (30.4)	4 (25)	11 (55)	2 (20)	0 (0)	NS
Age, n [range]	**43.5 [6–79]**	40.7 [6–69]	47.2 [20–72]	37.3 [8–68]	52.1 [20–73]	48.4 [21–79]	46.7 [10–76]	NS
Ethnicity								
Mestizo, n (%)	**187 (89.0)**	112 (100)	46 (100)	0 (0)	19 (95)	5 (50)	5 (83.3)	NS
Native, n (%)	**1 (0.5)**	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	NS
Mulatto, n (%)	**16 (7.6)**	0 (0)	0 (0)	16 (100)	0 (0)	0 (0)	0 (0)	NS
Caucasian, n (%)	**6 (2.9)**	0 (0)	0 (0)	0 (0)	1 (5)	5 (50)	0 (0)	NS
Diagnostic								
DM, n (%)	**139 (66.2)**	74 (66.1)	30 (65.2)	13 (81.3)	15 (75)	6 (60)	1 (16.7)	NS
PM, n (%)	**59 (28.1)**	26 (23.2)	16 (34.8)	3 (18.7)	5 (25)	4 (40)	5 (83.3)	0.02
JDM, n (%)	**12 (5.7)**	12 (10.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NS

JDM indicates juvenile dermatomyositis; NS, not significant.

TABLE 2. Frequency of ANA, MSA, and MAA in 6 Latin American Countries

	Total	Mexico	Colombia	Dominican Republic	Peru	Argentina	Guatemala	*p* value
Patients, n	210	112	46	16	20	10	6	NS
Seronegative	44 (21.0)	23 (21.0)	1 (2.2)	5 (31.3)	8 (40.0)	3 (30.0)	4 (66.6)	0.0003
ANA + n (%)	126 (60)	62 (55)	41 (89)	7 (43)	9 (45)	5 (50)	2 (33)	0.002
MSA, n (%)								
MI-2	81 (38.5)	45 (40.1)	29 (63.0)	1 (6.5)	3 (15)	3 (30)	0 (0)	NS
HMGCR [144 SS]	4 (2.0)	1/98 (1)	ND	3 (18.8)	0 (0)	0 (0)	ND	NS
JO-1	25 (11.9)	19 (17.0)	5 (10.9)	0 (0)	0 (0)	1 (10.0)	0 (0)	NS
PL-12	8 (3.8)	5 (4.5)	1 (2.2)	0 (0)	2 (10)	0 (0)	0 (0)	NS
SRP	13 (6.2)	9 (8)	0 (0)	2 (12.5)	1 (5)	1 (10)	0 (0)	NS
PL-7	4 (1.9)	3 (2.7)	1 (2.2)	0 (0)	0 (0)	0 (0)	0 (0)	NS
OJ [164 SS]	2 (1.0)	2 (0.9)	ND	0 (0)	0 (0)	0 (0)	0 (0)	NS
EJ [164 SS]	2 (1.0)	1 (0.9)	ND	0 (0)	0 (0)	1 (10)	0 (0)	NS
MAA, n (%)								
RO52/TRIM21	39 (18.6)	28 (25.0)	3 (6.5)	3 (18.8)	1 (5)	4 (40.0)	0 (0)	0.01
PM-SCL75 [164 SS]	15 (7.1)	12 (10.7)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NS
KU	13 (6.2)	11 (9.8)	0	1 (6.25)	1 (5)	1 (10.0)	0 (0)	NS
PM-SCL100	3 (1.4)	3 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NS

respect to other countries: Mexico ($p = 0.0005$), Dominican Republic ($p = 0.0025$), Peru ($p = 0.002$), Argentina ($p = 0.03$), and Guatemala ($p = 0.014$), respectively. The most frequent patterns were nuclear fine speckled (AC-4) in 78.3% serum samples and cytoplasmic (AC-19) in 6.45%.

Myositis-Specific Antibodies

The overall frequency of MSA was Mi-2 (38.5%), Jo-1 (11.9%), SRP (5.7%), PL-12 (3.3%), HMGCR (2.0%), PL-7 (1.9%), EJ (1.2%), and OJ (0.6%). The most frequent MSA, anti-Mi-2, was more frequent ($P \leq 0.05$) in serum samples from Colombia (40.1%), Mexico (38.5%), and Argentina (30%), when compared against those sera samples from Peru (15%) and Dominican Republic (6.3%). Anti–Jo-1 was present in 17% of serum samples from Mexico, and in patients from Colombia and Argentina, it was present in 11% and 10%, respectively. Nevertheless, anti-Jo1 was not detected in the sera from Peru, Dominican Republic, and Guatemala individuals (Table 2).

Myositis-Associated Autoantibodies

The overall frequency of MAA was anti–Ro-52/TRIM21 in 17.6% of the serum samples and then PM-Scl75 in 7.5%, Ku 3%, and PM-Scl100 0.6%. The most frequent MAA, Ro-52/TRIM21, was detected in 30% of the Argentinian patients, 24% of Mexican patients, 18.8% of Dominican Republic patients, and 5% of Peruvian patients. However, anti-Ro52/TRIM21 was not detected in sera of any of the patients from Guatemala (Table 2).

Autoantibodies and Groups of Seropositivity and Clinical Variables

An analysis of positive and negative autoantibodies was performed, and groups were stratified accordingly to the number of positive autoantibodies and to a negative result.

Four groups were identified: those who were negative, those who had 1 positive autoantibody, those who were positive to 2 autoantibodies, and those who were positive to 3 autoantibodies. Once the groups were formed, the group that did not show positivity to any of the autoantibodies was the most frequent, corresponding to 47.6% (MSA group) and 73.3% (MAA group), followed by those positive to 1 autoantibody (Fig. A, B).

Likewise, a global analysis was made where we included positivity for ANA, MSA, and MAA, and 8 groups were identified, from negative to up to 7 positive autoantibodies. In this case, the most frequent group was the one positive to 1 autoantibody 31.4% (Fig. C). Once the groups were evaluated, they were stratified according to the type of myositis and there were no significant differences.

DISCUSSION

This study describes the serological autoantibodies profile related to IIM patients from rheumatological centers in 6 Latin American countries who are participating in the PANLAR Myositis Study Group.

In this study, the cumulated frequency of ANA in IIM patients from the 6 Latin American countries was almost 60% with the highest frequency of 86% in Colombian IIM patients and the lowest frequency of 33% in patients from Guatemala ($p \leq 0.05$). Consistent with previous reports, the specific autoantibodies observed in our IIM cohort were also usually reported in a large proportion of myositis patients in other geographic locations (50%–80%).[35]

The frequency of DM in our IIM cohort varied from 16% in Guatemala, 60% in Argentina, 65% in Colombia, 66% in Mexico, 75% in Peru, and the highest frequency was in 81% of Dominican Republic patients. The frequency of this type of IIM that presents pathognomonic skin changes can be relevant because it could support previous associations of ultraviolet exposure at different geographical latitudes.[34–36] With the exception of Guatemala, DM predominated in the rest of the Latin American countries, the most frequent being the Dominican Republic. Nevertheless, the presence of anti–Mi-2 antibodies was higher in Colombian patients as compared with Dominican Republic patients (37% vs 6.7%, $p = 0.03$); despite the frequency of DM in these patients (65% vs 81%), this was nonsignificant ($p = 0.35$). In Mexico and Argentina, the frequency of anti–Mi-2 of approximately 30% is consistent with a previous study in Mexico that reported a high prevalence of anti–Mi-2 (35%) and a low prevalence of anti-synthetase antibodies (4%) in PM/DM.[14] In this same study, the prevalence of anti–Mi-2 was 35% in PM/DM but was higher at 45% in DM.[14] The correlation of UV radiation and its possible role in the pathogenesis of DM and production of anti–Mi-2 antibodies as previously reported[37] needs to be taken into consideration.

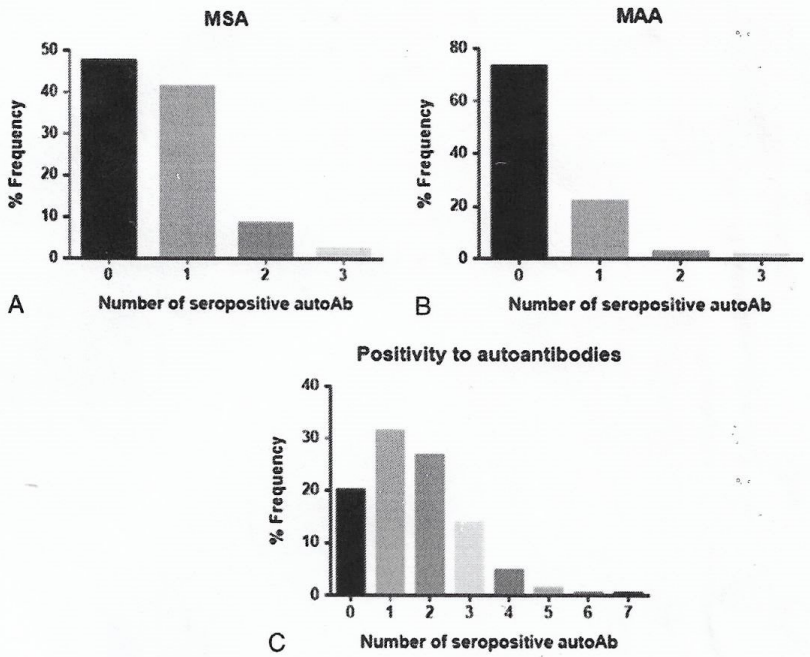

FIGURE. Groups of seropositivity to autoantibodies (A) MSA, (B) MAA, (C) ANAs, MSA, MAA. Groups of seropositivity, the numbers show the amount of autoantibodies to which each patient was positive. The data show the % frequency of groups of individuals seropositive to autoantibodies.

Most studies worldwide agree in pointing to anti–Jo-1 as the most common antisynthetase antibody found in IIM with a prevalence from 15% to 30%.[38] Patients with antibodies to Jo-1 and other tRNA synthetases have been classified as antisynthetase syndrome characterized by high prevalence of myositis, interstitial lung disease, arthritis, Raynaud phenomenon, mechanic hands, and other clinical features.[6–9,26,39] It deserves special attention that, in our current study, a frequency of 11.9% for anti–Jo-1 antibody was identified, clearly lower than described in other studies: 33% included as a synthetase group,[7] 11% to 21%,[26] 15% to 30%[38] with the highest frequency of 17% in Mexico, followed by Colombia with 10.9% and Argentina with 10%. Anti–Jo-1 was not detected in patients from Peru, Dominican Republic, and Guatemala, although PM predominated in Guatemala. However, we must mention that this is a limitation of the study because the number of patients included from Guatemala was very low.

Anti-HMGCR is detected in approximately 62% of statin-related immune-mediated necrotizing myopathies.[21–23] Our results shown a high frecuency of anti-HMGCR (18.8%) only in patients from Dominican Republic with DM diagnosis.

The most prevalent MAA in myositis is directed against Ro52/TRIM21 and was detected in more than 30% of patients frequently coexisting with anti-ARS antibodies or other MAA.[40,41]

Latin America is a heterogeneous region with different demographic characteristics in its population as well as cultural, ethnic, genetic, and geographical variations, which can contribute to the differences found in autoantibodies.[42] Although environmental factors are poorly characterized, significant differences in genetic background can contribute to the development and presence of myositis-specific and myositis-associated autoantibodies.[42] Moreover, there is a lack of information regarding the role of several factors that could modulate the autoimmune response, such as the miRNAs[43] and posttranslational modifications.[44]

Limitations

Due to the low frequency of patients in some countries, it is difficult to establish an association within all regions. Because the patients included in this study were predominantly from Mexico and Colombia, some of the results, including proportion of positivity, may not be generalizable.

CONCLUSIONS

This is the first study of ANA, MSA, and MAA from the PANLAR Myositis Study Group. In relation to MSA and MAA, anti–Mi-2 was the most frequent, a finding that contrasts with studies in other geographic areas in which antisynthetase antibodies tend to be more common, mainly anti–Jo-1 antibody.

However, the frequency of anti–Jo-1 antibody in this study was 11.9% probably related to the DM frequency. Anti-Ro52/TRIM21 antibody was the most frequent MAA. In conclusion, our results describe the frequency of these autoantibodies in patients from 6 centers of latinoamerican countries. We think it is important to continue these studies and the detection of these autoantibodies in order to have a better understanding of the implication and association with the various phenotypes of the inflammatory myophaties in different populations.

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