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Disease activity in patients with idiopathic inflammatory myopathy according to time since diagnosis and positivity to antisynthetase autoantibodies: data from the Myo-Spain registry

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Abstract

Objective To evaluate the main outcomes of disease activity and their association with other measures of activity, damage, and quality of life in patients with idiopathic inflammatory myopathy (IIM) according to time since diagnosis and positivity to antisynthetase autoantibodies (ASAs).

Methods Cross-sectional multicenter study within the Spanish Myo-Spain registry. Cases were classified as incident (≤ 12 months since diagnosis) and prevalent. The main outcomes of disease activity were the Myositis Disease Activity Assessment visual analogue scale (MYOACT), the Manual Muscle Test 8 (MMT-8), physician global activity (PhGA), and extramuscular activity. Other measures of activity, damage, and quality of life included patient global disease activity, MYOACT muscular, creatine phosphokinase, Health Assessment Questionnaire, physician and patient global

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damage, global damage of the Myositis Damage Index, and the 12-item Short-Form Health Survey (SF-12). We analyzed associations using a multivariate generalized linear model and a simple linear regression model.

Results A total of 554 patients with different diagnostic subgroups of IIM were included (136 incident and 418 prevalent cases), with 215 ASA-positive patients (58 incident and 157 prevalent cases). All measures of disease activity were higher in the incident cases ($p < 0.05$), except for MYOACT muscular and creatine phosphokinase, for which no differences were recorded in ASA-positive patients. No differences were found between incident and prevalent cases for measures of damage. Values for the physical component of the SF-12 were higher in the prevalent cases ($p < 0.05$). The multivariate model was initially significant overall for the main activity outcomes. Positivity to ASAs was positively and negatively associated with the MYOACT index and MMT-8, respectively ($p < 0.05$), although no association was recorded with PhGA and extramuscular activity. Prevalent cases were negatively associated with the main outcomes of activity, except with MMT-8, for which the association was positive ($p < 0.05$).

Conclusions The main activity outcomes validated in polymyositis and dermatomyositis could also be used in other subtypes of IIM, such as antisynthetase syndrome. Recent diagnosis is associated with greater disease activity, as assessed based on these activity outcomes. PhGA and extramuscular activity are not modified by ASA positivity, thus supporting their preferred use for assessing treatment response in IIM with ASAs.

Keywords Idiopathic inflammatory myopathies, Antisynthetase, Autoantibodies, Activity, Damage

Introduction

Idiopathic inflammatory myopathy (IIM) comprises a heterogeneous set of systemic autoimmune diseases in terms of both presentation and clinical course. Evaluation of disease activity is complex owing to the diverse nature of the clinical manifestations, which are not limited to skin and muscle involvement. A core set of measures and tools for assessment of the activity of dermatomyositis and polymyositis have been put forward by the International Myositis Assessment and Clinical Studies (IMACS) group [1, 2]. These measures were subsequently adopted by several groups [3] and incorporated in the validated response criteria for dermatomyositis and polymyositis [4], which have been used in various clinical studies [5] and evaluated as measures of response in clinical trials [6].

Several tools for assessing activity in IIM and their association with other measures of activity and damage have been investigated [7, 8]; however, there has been no research into disease activity measures in recently diagnosed patients. It is also important to note that advances in our knowledge of the pathogenesis of IIM and identification of new autoantibodies have made it possible to define new subgroups of IIM [9]. Previous studies on activity and damage included patients diagnosed with dermatomyositis and polymyositis but did not take into account the presence of antisynthetase autoantibodies (ASAs) [10, 11]. This is important, since it has been shown that patients with IIM and ASAs have a similar phenotype—irrespective of the whether they develop the characteristic skin lesions of dermatomyositis [12]—and that the histologic characteristics of their muscle tissue biopsy differ from those of patients with dermatomyositis [13]. Furthermore, the gene expression profiles in muscle biopsies of patients with ASAs are homogeneous, differing from those of other IIMs, including dermatomyositis [14]. Based on these arguments, it has been suggested that patients with ASAs constitute another subgroup of IIM.

Therefore, we consider it would be useful to evaluate the patients we see in daily clinical practice, to assess the behavior of the various instruments and measures of disease activity validated for dermatomyositis and polymyositis in recently diagnosed IIM and, specifically, in the subgroup of patients with ASAs. The objective of this study was to evaluate the main outcomes of disease activity and their association with other measures of activity, damage, and quality of life in patients with IIM according to time since diagnosis and positivity to ASAs.

Methods

Study design

Multicenter cross-sectional study of data from the baseline visit of the Spanish registry of patients with IIM (Myo-Spain). The methodology of the registry is detailed elsewhere [15].

Setting

The Myo-Spain registry of the Spanish Society of Rheumatology is a prospective database of cases enrolled from daily clinical practice at 30 hospitals in 11 of the 17 Spanish Autonomous Communities. The hospitals were selected based on the clinicians' expertise in the field of IIM. The baseline visits were held between June 9, 2019 and June 14, 2021.

Population

The study population comprised patients diagnosed with IIM in standard follow-up in the rheumatology departments at the participating centers. Patients were classified as incident (≤12 months between diagnosis and the baseline evaluation) or prevalent (>12 months since diagnosis). Irrespective of age and disease subtype, we included patients in active follow-up with a clinical diagnosis of IIM according to the criterion of the attending physician. We excluded patients who were unable to attend the visits or complete the forms, patients with non-inflammatory myopathy (toxic, infectious, or neuromuscular), patients whose data were insufficient to enable them to be classified, and patients with an unclear diagnosis. Disease subtypes were assigned, as follows: polymyositis, dermatomyositis, clinically amyopathic dermatomyositis, inclusion body myositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, overlap myositis syndrome, and non-classifiable myositis.

Variables and measures

All measures used in this study for the evaluation of the disease were adopted from the tools and measures recommended by the IMACS group [1, 2] (see below and in online Supplemental Table 1 for more detail).

Main outcomes of disease activity

The main set of activity measures comprised the following: (1) the total 7-domain Myositis Disease Activity Assessment visual analogue scale (VAS) (MYOACT total) index [1]; (2) the Manual Muscle Test in 8 muscle groups (MMT-8); (3) physician global activity (PhGA) on a 10-cm VAS; and (4) the 6-domain extramuscular activity of the MYOACT VAS [16].

Secondary measures of disease activity

Other measures of disease activity included the following: (1) the muscular disease activity (MYOACT muscular) VAS; (2) the patient/parent global activity (PGA) VAS; (3) the Health Assessment Questionnaire (HAQ); and (4) levels of the serum muscle enzyme creatine phosphokinase (CPK) [16].

Measures of damage

Evaluation of damage included the following: (1) the physician global damage (PhGD) VAS; (2) patient/parent global damage (PGD) VAS; and (3) the 11-domain global damage of the Myositis Damage Index (MDI) VAS [16].

Damage could only be evaluated if disease duration was ≥6 months.

Measure of quality of life

The quality-of-life measure was the physical/mental domain score of the 12-item Short-Form Health Survey (SF-12).

Autoantibodies

We recorded the presence of myositis-associated autoantibodies or myositis-specific autoantibodies, as confirmed in at least 2 determinations. The assays used included enzyme-linked immunosorbent assay, RNA and protein immunoprecipitation, line blotting (EUROLINE myositis profile), and chemiluminescence (anti-RNP or anti-RO).

The definitions of antisynthetase syndrome and IIM with ASAs were similar and included patients with ASAs and at least 1 of the following: constitutional symptoms (including fever), diffuse interstitial lung disease, arthritis, myositis, mechanic's hands, Raynaud's phenomenon, and skin lesions of dermatomyositis.

The remaining autoantibody subgroups were dermatomyositis-specific autoantibodies (anti-MDA5, anti-TIF1, anti-Mi2, anti-SAE), immune-mediated necrotizing myopathy-specific autoantibodies (anti-SRP and anti-HMGCR), myositis-associated antibodies, and seronegative (negative to any of these autoantibodies).

Other variables

We recorded whether patients met the 2017 European League against Rheumatism/American College of Rheumatology classification criteria for IIM and their major subgroups or the 2004 classification criteria for immune-mediated necrotizing myopathy [15, 16].

Demographic data, comorbidities, laboratory test results, and treatment were also recorded, as detailed in a previous study by our group [17].

Study size

The Myo-Spain registry is a cohort intended to collect multiple variables, with no prespecified hypothesis; therefore, sample size was not previously calculated for this work.

Statistical analysis

In the descriptive analysis, quantitative variables were expressed as mean ± standard deviation in the case of an approximately normal distribution and as median (interquartile range) in the case of a nonnormal distribution. Qualitative variables were expressed as absolute and relative frequencies (%).

Possible differences in the distribution of variables between incident and prevalent cases were evaluated

using the chi-square test for categorical variables, the *t* test for approximately normally distributed quantitative variables, and the Mann-Whitney test for nonnormally distributed quantitative variables.

Lastly, we analyzed the association between the main activity outcomes and other measures of activity, damage, and quality of life by fitting a multivariate generalized linear model (GLM). Pillai's Trace was used to analyze the relationship between the independent variables and the dependent variables. We applied a simple linear regression model to estimate the relationship between each predictor (independent variable) and each main activity outcome (dependent variable).

We used the statistical programs STATA v17.0 and SPSS v22.0. Statistical significance was set at $p < 0.05$.

Result

Overall characteristics of the sample

The study population comprised 136 incident cases (68.4% women) and 418 prevalent cases (74.4% women) with IIM from the 30 hospitals that participated in the Myo-Spain registry. Mean age at diagnosis was 55.4 ± 17.0 and 49.2 ± 16.7 years in the incident and prevalent groups, respectively. The most common diagnostic subgroups were antisynthetase syndrome (38.8%) and dermatomyositis (23.5%), with no differences between prevalent and incident cases for any diagnosis of IIM (Table 1).

Age at diagnosis and time from onset of symptoms to diagnosis were higher in the incident group. However, as expected, higher values were recorded in the prevalent group for meeting the classification criteria for IIM, the number of severe infections, the number of synthetic and biologic or targeted therapies since diagnosis (Table 1).

Taken as a whole, myositis-specific antibodies were the most frequent autoantibodies (370 [66.78%]) in our cohort followed by myositis-associated antibodies (245 [44.2%]). There were 107 (19.3%) seronegative cases. In turn, ASAs accounted for 39.0%. There were more patients with dermatomyositis-specific autoantibodies in the incident group and more patients with no autoantibodies in the prevalent group (Table 1).

Values for the disease activity measures were significantly higher in the incident group than in the prevalent group (Table 2). Analysis of the organ systems in MYOACT revealed that skin, constitutional, and muscle involvement were significantly more frequent in the incident group (online Supplemental Figure 1).

Damage was evaluated in 97 patients in the incident group (71.3%). Although the percentage of patients in whom damage was evaluated was higher in the prevalent group (92.8%), no differences were found between the groups for measures of damage (Table 2).

Values for the physical domain of SF-12 were better in the prevalent group than in the incident group. The difference was statistically significant (Table 2).

Characteristics of patients with antisynthetase autoantibodies

We analyzed the incident cases (27%) and prevalent cases (73%) among the 215 patients with ASAs (all diagnosed with antisynthetase syndrome) and found that 24 patients had skin lesions that were highly characteristic of dermatomyositis. Among the 215 patients with ASAs, 208 (96.74%) and 189 (87.91%) had ≥ 2 and ≥ 3 clinical manifestations of antisynthetase syndrome, respectively. Only 7 patients (3.26%) had a single manifestation distributed as follows: 3 myositis (1.40%), 3 diffuse interstitial lung disease (1.40%), and 1 arthritis (0.47%). No differences were found between incident and prevalent cases for the number of clinical manifestations (online Supplemental Table 2). The most common manifestations in these patients were constitutional symptoms (164 [76.2%]), myositis (176 [81.8%]), diffuse interstitial lung disease (159 [73.9%]), and arthritis (149 [69.3%]). No differences were found between the incident and prevalent groups for different manifestations in IIM patients with ASAs (Fig. 1).

All disease activity measures were statistically significantly higher in the incident group, except for muscular activity according to MYOACT, with a median of 0 in both groups, and CPK, for which no significant differences were recorded (Table 3). The most affected organ systems according to MYOACT were the pulmonary, cutaneous, and constitutional systems. We found that values for skin and constitutional involvement were significantly higher in the incident group (online Supplemental Figure 2)

Again, the percentage of patients in whom damage was evaluated was higher in the prevalent group, with no differences between the groups for any of the measures (Table 3).

Values for the physical domain of the SF-12 in patients from the prevalent group were statistically significantly better than in the incident group (Table 3).

Association between main outcomes of disease activity and other measures of activity, damage, and quality of life

The multivariate model initially yielded significant results overall. Statistically significant differences were observed between measures of activity, damage, and quality of life (independent variables) and at least 1 of the 4 main activity outcomes except for ASA positivity, interaction between ASA positivity and the prevalent group, PGD, and the SF-12 (online Supplemental Table 3). Subsequently, the univariate analysis of covariance for the main

Table 1 Clinical characteristics of IIM patients

Characteristic *N*=	Total 554	Incident group 136	Prevalent group 418
Sociodemographic			
Women	404 (72.92%)	93 (68.38%)	311 (74.40%)
Age at diagnosis (years)***	50.7 ± 17.0	**55.4 ± 17.0**	49.2 ± 16.7
Race			
Caucasian	470 (85.14%)	113 (83.09%)	357 (85.82%)
Hispanic	64 (11.59%)	19 (13.97%)	45 (10.82%)
African (Black and North African)	10 (1.81%)	1 (0.74%)	9 (2.16%)
Asian	7 (1.27%)	3 (2.21%)	4 (0.96%)
Other	1 (0.18%)	0 (0.00%)	1 (0.24%)
Months from symptom onset to diagnosis*	13.1 ± 23.7	**17.4 ± 30.9**	11.7 ± 20.6
Months of follow-up***	42.28 [12.39–91.82]	1.84 [0.33–5.88]	**61.0 [35.24–109.68]**
Meeting IIM classification criteria*	448 (80.87%)	101 (74.26%)	**347 (83.01%)**
Diagnostic subgroups of IIM			
Antisynthetase syndrome	215 (38.81%)	58 (42.65%)	157 (37.56%)
Dermatomyositis	130 (23.47%)	32 (23.53%)	98 (23.44%)
Overlap myositis syndrome	68 (12.27%)	9 (6.62%)	59 (14.11%)
Polymyositis	59 (10.65%)	14 (10.29%)	45 (10.77%)
Clinically amyopathic dermatomyositis	37 (6.68%)	8 (5.88%)	29 (6.94%)
Immune-mediated necrotizing myopathy	23 (4.15%)	9 (6.62%)	14 (3.35%)
Not classifiable	13 (2.35%)	4 (2.94%)	9 (2.15%)
Inclusion body myositis	9 (1.62%)	2 (1.47%)	7 (1.67%)
AAb subgroups			
Myositis-associated AAb	245 (44.22%)	56 (41.18%)	189 (45.22%)
Antisynthetase AAb[&]	215 (38.81%)	58 (42.65%)	157 (37.56%)
Dermatomyositis AAb*	128 (23.10%)	**42 (30.88%)**	86 (20.57%)
Seronegative*	107 (19.31%)	16 (11.76%)	**91 (21.77%)**
Immune-mediated necrotizing myopathy AAb	27 (4.87%)	10 (7.35%)	17 (4.07%)
Clinical manifestations and comorbidities			
Presentation			
Acute	105 (19.02%)	23 (16.91%)	82 (19.71%)
Subacute	237 (42.93%)	59 (43.38%)	178 (42.79%)
Chronic	210 (38.04%)	54 (39.71%)	156 (37.50%)
Characteristic skin lesions of dermatomyositis	237 (42.86%)	51 (37.50%)	186 (44.60%)
Dysphagia	180 (35.43%)	39 (31.97%)	141 (36.53%)
Calcinosis	33 (6.86%)	5 (4.55%)	28 (7.55%)
Diffuse interstitial lung disease	246 (49.2%)	55 (47.01%)	191 (49.87%)
Cancer	72 (17.82%)	20 (20.41%)	52 (16.99%)
Previous or current smoking	205 (37.21%)	51 (37.78%)	154 (37.02%)
Statins	131 (23.77%)	30 (22.22%)	101 (24.28%)
Severe infections*	61 (13.86%)	7 (6.73%)	**54 (16.07%)**
ICU admission since diagnosis	22 (4%)	9 (6.72%)	13 (3.13%)
Treatments since diagnosis			
sDMARDs***			
< 2	375 (67.69%)	**123 (90.44%)**	252 (60.29%)
≥ 2	179 (32.31%)	13 (9.56%)	**166 (39.71%)**
bDMARDs or targeted therapies**			
0	411 (74.19%)	**113 (83.09%)**	298 (71.29%)
≥ 1	143 (25.81%)	23 (16.91%)	**120 (28.71%)**
Immunoglobulins and/or plasmapheresis	153 (27.62%)	32 (23.53%)	121 (28.95%)

Data are shown as n (%) and mean ± standard deviation or median [interquartile range]

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

[&] Antisynthetase AAb: 215 patients including 24 with skin lesions that were highly characteristic of dermatomyositis

Chi-square test for categorical variables, *t* test for approximately normally distributed quantitative variables, and Mann-Whitney test for non-normally distributed quantitative variables

IIM Idiopathic inflammatory myopathy, *AAb* Autoantibodies, *ICU* Intensive care unit, *sDMARDs* Synthetic disease-modifying antirheumatic drugs (methotrexate, cyclophosphamide, mycophenolate mofetil, mycophenolic acid, cyclosporine A, azathioprine, leflunomide), *bDMARDs* Biologic disease-modifying antirheumatic drugs and targeted therapies (rituximab, anti-TNF, abatacept, apremilast, baricitinib, tofacitinib)

Table 2 Disease activity, damage and health-related quality of life in IIM patients

Characteristic *N*=	Total 554	Incident group 136	Prevalent group 418
MYOACT total (0–10) ***	1.0 [0.3–2.3]	**1.6 [0.7–2.9]**	0.9 [0.3–2.0]
MYOACT muscular (0–10) ***	0.0 [0.0–3.0]	**1.3 [0.0–4.4]**	0.0 [0.0–2.0]
Extramuscular activity in MYOACT (0–10) ***	2.0 [1.0–4.0]	**3.0 [2.0–5.5]**	2.0 [0.5–3.6]
Physician global activity (0–10) ***	3.0 ± 2.4	**4.3 ± 2.5**	2.6 ± 2.3
Patient global activity (0–10) ***	4.0 ± 2.7	**5 ± 2.4**	3.7 ± 2.7
MMT-8 (0–80) *	73.9 ± 11.1	**71.9 ± 12.3**	74.5 ± 10.6
Creatine phosphokinase (mg/dl)	98.0 [61.0–186.0]	**115.5 [61.5–317.0]**	95.0 [61.0–164.0]
Health Assessment Questionnaire (0–3) **	0.845 ± 0.781	**1.014 ± 0.839**	0.790 ± 0.754
Evaluable damage ***	485 (87.6)	97 (71.3)	**388 (92.8)**
Myositis Damage Index (0–10)	2.7 ± 2.4	2.5 ± 2.4	2.8 ± 2.4
Physician global damage (0–10)	2.9 ± 2.3	2.8 ± 2.4	2.9 ± 2.3
Patient global damage (0–10)	4.0 ± 2.8	3.9 ± 2.9	4.1 ± 2.8
SF-12 physical domain score (0–100) ***	36.9 ± 13.1	33 ± 12.3	**38.2 ± 13.1**
SF-12 mental domain score (0–100)	44.8 ± 13.4	43.5 ± 13.2	45.2 ± 13.5

Data are shown as median [interquartile range], mean ± standard deviation, and n (%)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Chi-square test for categorical variables, *t* test for approximately normally distributed quantitative variables, and Mann-Whitney test for non-normally distributed quantitative variables

The proportion of missing values was ≤ 11% for all the variables, with no significant differences between the incident group and the prevalent group

IIM Idiopathic inflammatory myopathy, *MYOACT* Myositis Disease Activity Assessment visual analog scale, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item short-form health survey

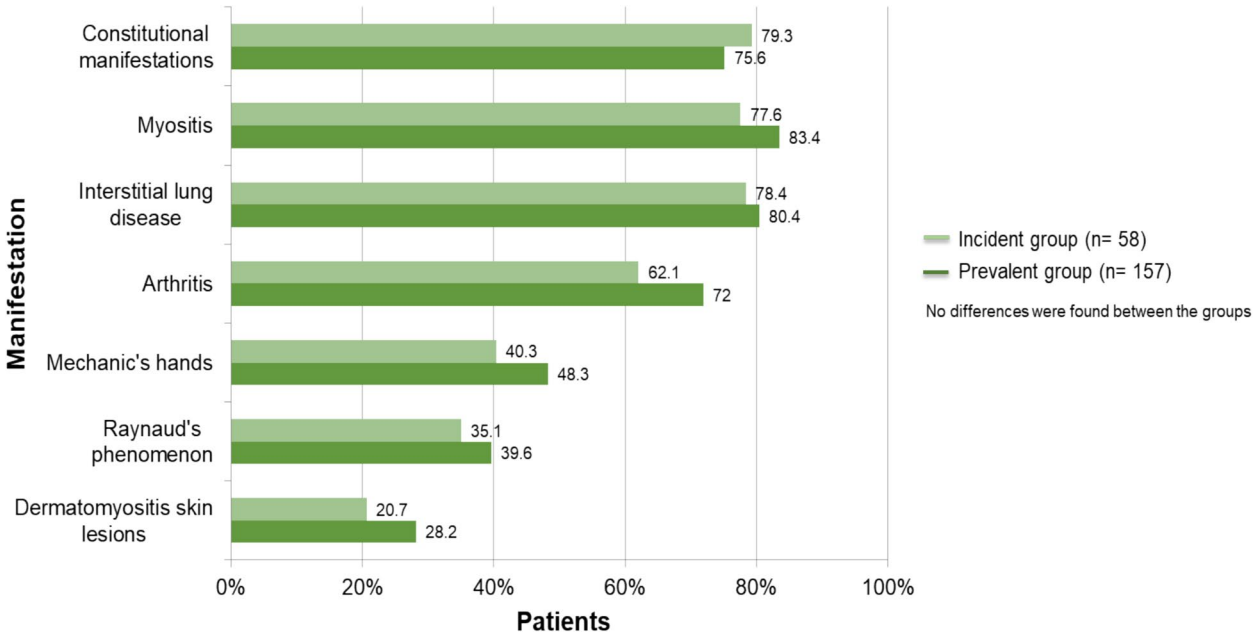

Fig. 1 Manifestations in IIM patients with antisynthetase autoantibodies

activity outcomes with respect to each of the independent variables revealed the following: 1) the MYOACT index was modified by PGA, MYOACT muscular, CPK, HAQ, and MDI; 2) extramuscular activity was modified by PGA, MYOACT muscular, CPK, HAQ, PhGD, PGD, MDI, the physical and mental domains of SF-12, ASA positivity, and the interaction between ASA positivity and the prevalent group; 3) PhGA was modified by PGA,

Table 3 Disease activity, damage and health-related quality of life in IIM patients with antisynthetase autoantibodies

Characteristic *N*=	Total 215	Incident group 58	Prevalent group 157
MYOACT total (0–10) ***	0.9 [0.4–1.7]	**1.5 [0.7–2.5]**	0.7 [0.3–1.6]
MYOACT muscular (0–10)	0 [0–2]	0 [0–3]	0 [0–1]
Extramuscular activity in MYOACT (0–10) ***	2 [1–4]	**4 [2–6]**	2 [1–3]
Physician global activity (0–10) ***	2.8 ± 2.3	**4.1 ± 2.3**	2.4 ± 2.1
Patient global activity (0–10) ***	3.9 ± 2.5	**4.9 ± 2.2**	3.5 ± 2.5
MMT-8 (0–80) **	76.0 ± 8.4	**74.7 ± 10.4**	76.5 ± 7.4
Creatine phosphokinase (mg/dl)	90.5 [55–153.5]	97.5 [56–182]	87.0 [55–140]
Health Assessment Questionnaire (0–3) *	0.753 ± 0.722	**0.941 ± 0.768**	0.681 ± 0.697
Evaluable damage ***	186 (86.1)	42 (72.4)	**143 (91.1)**
Myositis Damage Index (0–10)	2.7 ± 2.3	2.9 ± 2.4	2.6 ± 2.2
Physician global damage (0–10)	2.9 ± 2.3	2.9 ± 2.3	2.9 ± 2.2
Patient global damage (0–10)	3.9 ± 2.7	4 ± 2.7	3.9 ± 2.7
SF-12 physical domain score (0–100) ***	37.2 ± 12.7	32.8 ± 12.4	**38.9 ± 12.5**
SF-12 mental domain score (0–100)	45.5 ± 12.9	43.2 ± 13.5	46.4 ± 12.7

Data are shown as median [interquartile range], mean ± standard deviation, and n (%)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Chi-square test for categorical variables, *t* test for approximately normally distributed quantitative variables, and Mann-Whitney test for non-normally distributed quantitative variables

The proportion of missing values was ≤ 15% for all the variables, with no significant differences between the incident group and the prevalent group

IIM Idiopathic inflammatory myopathy; *MYOACT* Myositis Disease Activity Assessment visual analogue scale, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item Short-Form Health Survey

MYOACT muscular, CPK, PhGD, PGD, and being prevalent; and 4) the MMT-8 was modified by MYOACT muscular, HAQ, and PhGD (online Supplemental Table 4).

Finally, the simple linear regression models for each main activity outcome with the remaining independent variables activity, damage, and quality of life revealed a series of findings.

First, a negative association between the MYOACT index and MMT-8, prevalent cases, ASA positivity, and the physical and mental components of the SF-12, as well as a positive association with the remaining variables, although in the case of CPK, this association was very weakly positive (Table 4).

Second, no association was observed between extramuscular activity and CPK and ASA positivity. A negative association was observed for prevalent cases, MMT-8, and the physical and mental domains of SF-12, and a positive association was observed for the remaining variables (Table 5).

Third, no association was found between PhGA and ASA positivity. A negative association was found for prevalent cases, MMT-8, and the physical and mental components of SF-12. The association was positive for the remaining variables (Table 6).

Fourth, a negative association was found between MMT-8 and all the variables except ASA positivity, prevalent cases, and the physical and mental components of the SF-12, for which the association was positive (Table 7).

Table 4 Univariate analysis of the MYOACT total

MYOACT total	β	95% CI	*P*-value
Extramuscular activity in MYOACT	0.475	0.438–0.511	< 0.001
Physician global activity	0.469	0.432–0.5007	< 0.001
MMT-8	−0.045	−0.056 to −0.034	< 0.001
MYOACT muscular (0–10)	0.449	0.409–0.489	< 0.001
Patient global activity (0–10)	0.353	0.313–0.394	< 0.001
Creatine phosphokinase (U/L)	0.0002	4.51e-05–0.000314	0.009
Health Assessment Questionnaire (0–3)	0.845	0.688–1.002	< 0.001
Myositis Damage Index (0–10)	0.378	0.332–0.424	< 0.001
Physician global damage (0–10)	0.347	0.297–0.396	< 0.001
Patient global damage (0–10)	0.230	0.185–0.274	< 0.001
SF-12 physical domain score (0–100)	−0.046	−0.055 to −0.036	< 0.001
SF-12 mental domain score (0–100)	−0.018	−0.028 to −0.008	< 0.001
Prevalent group	−0.666	−0.966 to −0.365	< 0.001
Antisynthetase AAb group	−0.319	−0.588 to −0.050	0.020

Univariate analysis with simple linear regression models

MYOACT Myositis Disease Activity Assessment visual analogue scale, *β* Beta coefficient, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item Short-Form Health Survey, *AAb* Autoantibodies

Discussion

The present multicenter cross-sectional study included 554 patients diagnosed with IIM in the Myo-Spain

Table 5 Univariate analysis of the extramuscular activity in MYOACT

Extramuscular activity in MYOACT	β	95% CI	*P*-value
MYOACT total	1.167	1.078–1.257	< 0.001
Physician global activity	0.742	0.686–0.798	< 0.001
MMT-8	−0.047	−0.065 - −0.028	< 0.001
MYOACT muscular (0–10)	0.403	0.325–0.482	< 0.001
Patient global disease activity (0–10)	0.504	0.439–0.569	< 0.001
Creatine phosphokinase (U/L)	7.23e-05	−0.0001–0.0003	0.494
Health Assessment Questionnaire (0–3)	0.979	0.723–1.234	< 0.001
Myositis Damage Index (0–10)	0.499	0.424–0.575	< 0.001
Physician global damage (0–10)	0.507	0.431–0.582	< 0.001
Patient global damage (0–10)	0.320	0.251–0.389	< 0.001
SF-12 physical domain score (0–100)	−0.067	−0.082 to −0.053	< 0.001
SF-12 mental domain score (0–100)	−0.033	−0.049 to −0.018	< 0.001
Prevalent group	−1.534	−1.987 to −1.081	< 0.001
Antisynthetase AAb group	0.123	−0.294–0.540	0.563

Univariate analysis with simple linear regression models

MYOACT Myositis disease activity assessment visual analogue scale, *β* beta coefficient, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item Short-Form Health Survey, *AAb* autoantibodies

Table 6 Univariate analysis of the Physician global activity

Physician global activity	β	95% CI	*P*-value
MYOACT total	1.125	1.034–1.215	< 0.001
Extramuscular activity in MYOACT	0.761	0.704–0.818	< 0.001
MMT-8	−0.080	−0.097 to −0.063	< 0.001
MYOACT muscular (0–10)	0.620	0.552–0.688	< 0.001
Patient global activity (0–10)	0.600	0.541–0.659	< 0.001
Creatine phosphokinase (U/L)	0.0004	0.0002–0.0006	< 0.001
Health Assessment Questionnaire (0–3)	1.465	1.227–1.704	< 0.001
Myositis Damage Index (0–10)	0.545	0.470–0.620	< 0.001
Physician global damage (0–10)	0.616	0.546–0.685	< 0.001
Patient global damage (0–10)	0.386	0.319–0.453	< 0.001
SF-12 physical domain score (0–100)	−0.082	−0.097 to −0.068	< 0.001
SF-12 mental domain score (0–100)	−0.031	−0.046 to −0.015	< 0.001
Prevalent group	−1.743	−2.192 to −1.295	< 0.001
Antisynthetase AAb group	−0.219	−0.636–0.197	0.302

Univariate analysis with simple linear regression models

MYOACT Myositis Disease Activity Assessment visual analogue scale, *β* beta coefficient, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item Short-Form Health Survey, *AAb* Autoantibodies

Table 7 Univariate analysis of the MMT-8

MMT-8	β	95% CI	*P*-value
MYOACT total	−2.370	−2.960 to −1.780	< 0.001
Extramuscular activity in MYOACT	−0.978	−1.365 to −0.591	< 0.001
Physician global activity	−1.675	−2.036 to −1.314	< 0.001
MYOACT muscular (0–10)	−2.592	−2.930 to −2.254	< 0.001
Patient global activity (0–10)	−1.431	−1.765 to −1.096	< 0.001
Creatine phosphokinase (U/L)	−0.002	−0.003 to −0.001	0.009
Health Assessment Questionnaire (0–3)	−6.710	−7.806 to −5.613	< 0.001
Myositis Damage Index (0–10)	−1.162	−1.566 to −0.758	< 0.001
Physician global damage (0–10)	−1.463	−1.843 to −1.083	< 0.001
Patient global damage (0–10)	−1.097	−1.439 to −0.755	< 0.001
SF-12 physical domain score (0–100)	0.297	0.227–0.366	0.002
SF-12 mental domain score (0–100)	0.113	0.0414–0.185	< 0.001
Prevalent group	2.612	0.439–4.784	0.019
Antisynthetase AAb group	3.391	1.488–5.293	0.001

Univariate analysis with simple linear regression models

MYOACT Myositis disease activity assessment visual analogue scale, *β* beta coefficient, *MMT-8* Manual Muscle Test 8, *SF-12* 12-item Short-Form Health Survey, *AAb* autoantibodies

registry, that is, 136 incident cases and 418 prevalent cases. Differences in general characteristics and activity, damage, and quality of life were found between these groups. Furthermore, different measures of activity, damage, and quality of life were associated with the 4 main outcomes of activity validated in polymyositis/dermatomyositis. Positivity for ASAs in IIM did not affect disease activity evaluated according to extramuscular activity outcomes (MYOACT) and PhGA. Similarly, belonging to the group of patients with whose disease lasted >12 months (prevalent) was associated with reduced disease activity evaluated according to the main activity outcomes in this study.

In our cohort, disease was more active and quality of life poorer in the physical domain among recently diagnosed patients (incident group). In the case of patients with evaluable damage in this group, the severity of the damage was similar to that of the prevalent group. These findings were also recorded in the subgroup of patients with ASAs, except for muscle activity in MYOACT and CPK, where no differences between incident and prevalent cases were observed. The higher activity observed in incident patients could indicate that many patients are naïve to treatment or have recently started treatment, entailing more severe consequences with respect to the physical domain in quality of life. Moreover, in the present study, the presence of damage in recently diagnosed patients is noteworthy and has also been reported in patients with juvenile dermatomyositis in whom damage

was already evident at 6 and 12 months after diagnosis [7, 19]. This issue had not been previously addressed in adult IIM or in patients with ASAs. Our data favor early intensive treatment irrespective of age, since the presence of damage is associated with further damage during the course of the disease [10].

The main activity outcomes were chosen based on the fact that MYOACT is a validated tool for polymyositis/dermatomyositis in clinical trials and studies [1]. MMT-8, PhGA, and extramuscular activity (MYOACT) have proven to carry more weight, according to the conjoint analysis of the basic set of disease activity measures recommended in clinical studies on polymyositis/dermatomyositis [18]. We detected that measures for activity, damage, and disability were associated with all the activity outcomes, despite including several diagnoses in our cohort (38.81% antisynthetase syndrome, 23.47% dermatomyositis, 12.27% overlap myositis syndrome, 10.65% polymyositis, 6.68% clinically amyopathic dermatomyositis, 4.15% immune-mediated necrotizing myopathy), thus pointing to its validity in patients with IIM other than polymyositis and dermatomyositis [1, 18]. While some of these activity outcomes have been applied in recent studies in patients with antisynthetase syndrome [20], the associations we analyzed have not been previously assessed to determine the usefulness of activity outcomes for measuring disease activity in cohorts with different subtypes of IIM. The degree of association was greater with the MMT-8 outcome and lower with the MYOACT index. Therefore, this study confirms that, as in patients with polymyositis and dermatomyositis [18], MMT-8 is one of the measures that better evaluates disease activity. Given that the MYOACT index evaluates disease activity during the previous month, it would be less affected, at least in part, by measures associated with the time of consultation, such as PGA, CPK, MDI, PhGD, and PGD or those associated with the previous week, such as the HAQ.

Onset of antisynthetase syndrome may be with a single manifestation, although other manifestations may appear over time. Therefore, we chose a broad definition in our study. However, most of the patients had at least 3 clinical manifestations of antisynthetase syndrome, in addition to antibodies. Moreover, no differences were found between incident and prevalent cases for the number of clinical manifestations. Therefore, the sample of patients with antisynthetase antibodies seems to be quite homogeneous and with sufficient manifestations to evaluate extramuscular and muscular involvement in both incident and prevalent cases.

ASA positivity was associated with a higher MMT-8 value (muscle strength) and a lower MYOACT index. If we consider that in patients with ASAs, muscle involvement (MYOACT muscle, CPK, and MMT-8) was less severe than in the sample as a whole, then the association between the MYOACT index (which evaluates muscular and extramuscular involvement) and ASAs would be negative. PhGA and extramuscular activity are not modified by ASA positivity. Therefore, carrying ASAs would not affect these measures, with the result that they could be used in patients with antisynthetase syndrome, as in other types of myositis. To date, the criteria for response to treatment have only been validated in polymyositis/dermatomyositis, and, to apply them, PhGA and MMT-8 must be included. Our findings indicate that PhGA and extramuscular activity, which are not affected by ASA positivity, could be priority measures of activity in some therapeutic response criteria in patients with ASAs. This is particularly true of patients with no muscle involvement, a common finding in this type of myopathy, where extramuscular manifestations may be the only ones to appear during the course of the disease [21, 22]. Our findings for activity outcomes in patients with IIM and ASAs have not been reported previously.

The purpose of classifying cases as incident or prevalent was to understand the possible effect of time since diagnosis on the 4 main activity outcomes. We found that time since diagnosis is an independent factor associated with these outcomes. Follow-up time has been reported to be associated with disease activity evaluated according to MYOACT in juvenile dermatomyositis [7]. However, the association between time since diagnosis and disease activity evaluated according to the 4 outcomes was not addressed. Therefore, the outcomes could be useful tools for assessing disease activity, as they can be expected to reflect what is happening in clinical practice (that is, being prevalent is associated with lower disease activity).

With respect to the secondary activity measures, CPK was the only one showing a lower association with the main activity outcomes. In particular, the association with the MYOACT index was very mild and did not involve extramuscular disease activity. The association between serum CPK level and disease activity is variable, and while CPK level forms part of the core set of measures, it is considered a secondary measure (with less weight) [23] and therefore an optional variable in the treatment response criteria in dermatomyositis and polymositis [4].

Regarding damage, MDI and PhGD are the measures that are most associated with activity outcomes, particularly MMT-8 and PhGA. We also found that with less severe damage, muscle strength was greater, and disease activity reduced. The association between activity and damage is a closed circuit that first appears during the early stages of the disease. Our findings from the Myo-Spain cohort are consistent with those reported

for dermatomyositis. Early damage (6-12 months after diagnosis) evaluated according to the MDI predicts both damage and activity during the course of the disease [7, 19]. Early activity (first 6 months) also predicts damage evaluated according to the MDI during the course of the disease [19]. Based on our clinical practice, we believe that patients do not fully grasp the relevance of the damage caused by the disease and that this could affect their way of evaluating damage. Consequently, the PGD measure is associated less than the others with activity.

Physical function was associated with all the main activity outcomes. In particular, it affects muscle strength and PhGA. Quality of life was weakly associated with activity outcomes, showing that better quality of life was associated with reduced disease activity, including muscle weakness. Other studies, especially those analyzing dermatomyositis/polymyositis, revealed a correlation between disease activity, including muscle strength and extramuscular activity, and the physical domain of the SF-36 [7, 24, 25].

The strengths of our work include the lack of studies on adults with IIM that analyze the association between the main measures of disease activity and other measures of activity, damage, and quality of life, as we do here. No studies specifically determine whether the associations differ in patients who were recently diagnosed and those who were not. Furthermore, we specifically analyzed patients with ASAs as an example of a subgroup of IIM in which disease activity may be more determined by extramuscular manifestations than by muscular manifestations.

Our study is subject to a series of limitations. First, not all patients met the classification criteria for IIM (74.26% of incident cases and 83.01% of prevalent cases). Nevertheless, they were included based on the clinical diagnosis according to the judgement of a physician experienced in IIM. The definition used for patients with IIM and ASAs is a modification of the diagnostic criteria of Connors et al [26]. This definition includes skin lesions of dermatomyositis, which are common in affected patients [27], and constitutional symptoms other than fever. However, all patients with IIM and ASAs met the diagnostic criteria for antisynthetase syndrome according to Connors et al., as no patients had only constitutional symptoms, only skin lesions of dermatomyositis, or only both (Supplementary Table 2 and Table 5). Second, cases were differentiated according to recent diagnosis (≤ 12 months) and not according to early diagnosis, with little time between onset of symptoms and diagnosis. An analysis based on early diagnosis may have revealed other differences for this group. Third, we did not analyze measures of activity in subgroups without muscle weakness (eg, clinically amyopathic dermatomyositis) to determine whether the results were similar to those of the ASA group, where extramuscular manifestations carried more weight than muscular manifestations. However, this diagnosis was made for only 37 patients in our cohort. Therefore, the sample was insufficient to confirm associations. Fourth, in the prevalent cases, patients may have died before being included in the registry, with the result that the profile represented is one of less severe disease, thus explaining why the time from onset of symptoms to diagnosis was longer in the incident groups, when the opposite might be expected, and why there were no differences between the groups for any of the measures of damage. Fourth, our measure of quality of life was based on the SF-12 and not on the SF-36, as recommended by the IMACS group for the evaluation of quality of life in IIM [18]. Given the large number of participating centers, we believe that the SF-12 enables a more viable and applicable evaluation of quality of life. Furthermore, the SF-12 has proven to be well correlated with the SF-36 [28, 29]. Nevertheless, neither of the 2 are specific quality-of-life measures for IIM, and the Outcome Measures in Rheumatology organization (OMERACT) is now working to address this need [30]. Finally, another possible limitation is patient selection bias, namely, including patients who may have an easier follow-up or who have fewer comorbidities. To avoid this bias, the need to recruit all patients who meet the inclusion criteria per center was considered; this also becomes a necessity owing to the prevalence and incidence data of IIM. Recruitment of all patients who met the inclusion criteria was reinforced through periodic communication with the participating investigators and in meetings at the beginning of the study and during follow-up. Although this is a project of the Spanish Society of Rheumatology and the principal investigators at each center are rheumatologists, we opened participation to collaborating investigators from other specialties, such as internal medicine and neurology, to minimize possible recruitment bias. Inclusion of patients in the registry was supervised by the principal investigator at each center, who was always a rheumatologist.

Conclusion

Our study suggests that the main disease activity outcomes validated for polymyositis and dermatomyositis could also be used for other subtypes of IIM such as antisynthetase syndrome. Specifically, PhGA and extramuscular disease activity are not modified in IIM by the presence of ASAs, thus supporting their use for evaluation of the response to treatment in this subtype of IIM, in which extramuscular involvement is often the predominant or the only type of involvement. We also note that disease activity (both muscular and extramuscular) is more marked in patients with recently diagnosed disease (≤12 months).

Abbreviations

ASA	Antisynthetase autoantibody
ASAs	Antisynthetase autoantibodies
CPK	Creatine phosphokinase
HAQ	Health Assessment Questionnaire
IIM	Idiopathic inflammatory myopathy
IMACS	International Myositis Assessment and Clinical Studies
MMT-8	Manual Muscle Test 8
MDI	Myositis Damage Index
MYOACT	Myositis Disease Activity Assessment visual analogue scale
OMERACT	Outcome Measures in Rheumatology
PGA	Patient/parent global activity
PhGA	Physician global activity
PGD	Patient/parent global damage
PhGD	Physician global damage
SF-12	12-item Short-Form Health Survey
VAS	Visual analogue scale

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
TCI, MDA, and DSM contributed to conception and design of the study. TCI, IC, AP, LNN, JMB, VJ, FRB, ERL, ET, ETA, JN, JCF, ARR, JLM, SHP, VMFR, FS, CMA, AJM, IAG, MML, JMBO, CCC, MFG, IRF, NLR, JDSC, OM, ROC, PA, AGG, OSP, JLT, ICB, CPR, OIB, PVM, VOS, NGP, AR, EDF, JMLG, CB, JMPR, BEJI, JAVJ, EN, AITN and APL contributed to data collection. FJPG performed the statistical analysis. TC, IC, and MDA interpreted the data. TCI wrote the manuscript. All authors (TCI, IC, AP, MDA, LNN, JMB, VJ, FRB, ERL, ET, ETA, JN, JCF, ARR, JLM, SHP, VMFR, FS, CMA, AJM, IAG, MML, JMBO, CCC, MFG, IRF, NLR, JDSC, OM, ROC, PA, AGG, OSP, JLT, ICB, CPR, OIB, PVM, VOS, NGP, AR, EDF, JMLG, CB, JMPR, BEJI, JAVJ, EN, AITN, DSM, FJPG and APL) read and revised the manuscript and approved the submitted version. TCI is the author responsible for the overall content as guarantor.

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Data availability
No datasets were generated or analysed during the current study.

Declaration

Ethics approval and consent to participate
The study was approved by the reference Clinical Investigation Ethics Committee (Hospital La Paz, Madrid) and by the local ethics committees. All the patients gave their written informed consent before being included in the study.

Consent for publication
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Competing interests
The authors declare no competing interests.

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