

Factors Associated With Treatment Response in Patients With Idiopathic Inflammatory Myopathies: A Registry-Based Study

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Objective. To identify predictors of response to immunosuppressive therapy after 1 year, with a focus on autoantibodies, in patients newly diagnosed with idiopathic inflammatory myopathies (IIM) followed longitudinally in an electronic registry.

Methods. We assessed the association between autoantibody-defined groups and improvement according to American College of Rheumatology/European Alliance of Associations for Rheumatology 2016 response criteria.

Results. We identified 156 patients; of those, 111 (71%) were positive for any autoantibody tested, 90% received glucocorticoid treatment at baseline, and 78% received immunosuppressive drugs at some follow-up point. After 1 year from the index date, the overall median improvement score was 27.5 (interquartile range 10–51). No differences were observed in the total improvement score between the autoantibody-defined groups. Overall, 62% of patients ($n = 96$) showed a minimal response, 38% ($n = 60$) achieved a moderate response, and 19% ($n = 30$) achieved a major response. Regarding the different levels of response, dermatomyositis-specific autoantibodies were associated with a moderate response versus the seronegative group (reference), odds ratio 4.12 (95% confidence interval 1.2–16.5). In addition, dysphagia, time from symptom onset to diagnosis, and initial glucocorticoid dose were significant predictors of response after 1 year of follow-up.

Conclusion. Patients with DM-specific autoantibodies achieved better levels of response compared to other autoantibody-defined groups. Dysphagia, a shorter time span from symptom onset to diagnosis, and intensive initial immunosuppressive treatment were associated with a higher response rate after 1 year of pharmacologic treatment from the index date, regardless of autoantibody status.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of complex systemic disorders whose main symptoms are muscle weakness, low muscle endurance, and inflammatory infiltrates in muscle tissue biopsies (1). Extramuscular involvement, such as skin rash, arthritis, dysphagia, interstitial lung disease, cardiac disease, and malignancy, are common. Many of these diverse manifestations have been linked to the presence of specific autoantibodies, so-called myositis-specific autoantibodies (MSAs), which are mainly found in patients with IIM, and myositis-associated autoantibodies (MAAs), which are also present in other

autoimmune disorders (2,3). The autoantibody profile of each patient often corresponds to a specific clinical phenotype. The frequency of the various clinical manifestations and autoantibodies varies according to both ethnic and genetic background (4). Whether autoantibody status has an impact on treatment response and outcomes has not been studied in detail.

Glucocorticoids are regarded as a first-line therapy in combination with an additional immunosuppressive drug, such as methotrexate, azathioprine, mycophenolate, cyclosporine, or tacrolimus. New biologic drugs have emerged as an alternative for treating patients with refractory disease (5,6), and exercise is an important part of nonmedical treatment (7,8). Despite intense

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SIGNIFICANCE & INNOVATIONS

- Dermatomyositis-specific autoantibodies were associated with a moderate response after 1 year of pharmacologic treatment from the index date.
- The presence of dysphagia at the index date, a shorter time span from symptom onset to diagnosis, and more-intensive initial glucocorticoid treatment were predictors of response, regardless of autoantibody status.

treatment, many patients have persistent signs of systemic disease activity and do not regain muscle performance. To date, no biomarkers have been identified that predict response to treatment, other than those biomarkers for biologic drugs (9,10). One limitation in addressing this question has been the lack of international consensus as to how to assess improvement after treatment. In 2016 the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) proposed response criteria that define improvement in terms of both muscular and nonmuscular measurements, which have since been widely accepted (11). MSAs are an attractive option to test as potential biomarkers for treatment response and outcomes due to their association with distinct clinical phenotypes. Only a few studies have taken this approach so far, and they have been limited to patients with established, treatment-refractory disease (9,12,13). Thus, no information is available regarding MSAs as biomarkers for treatment response in patients newly diagnosed with IIM.

The present study aimed to test the potential of autoantibodies, as well as other clinical features, as predictors of treatment response, applying the new ACR/EULAR response criteria after 1 year of immunosuppressive therapy in a cohort with recent-onset IIM that had been followed longitudinally in an electronic health care registry.

MATERIALS AND METHODS

Study population. Since 2003, patients with IIM have been included and followed in a standardized way using the electronic Swedish Quality of Care Registry, which has a myositis-specific module, SweMyoNet. This registry prospectively collects demographic, clinical, serologic, and treatment data during inpatient and outpatient visits to the rheumatology clinic. Patients with a primary diagnosis of IIM are classified as having dermatomyositis (DM), polymyositis, amyopathic DM, inclusion body myositis, anti-synthetase syndrome (ASS), or juvenile DM. For this study, we retrospectively selected patients who fulfilled the EULAR/ACR 2017 classification criteria for definite or probable IIM in any of the above-mentioned subsets, as well as patients who met the criteria for ASS (14,15). All included patients were followed at Karolinska University Hospital and were registered in SweMyoNet within

12 months (range 0.2–11.3 months) of diagnosis between January 1, 2003, and December 31, 2015. Patients with inclusion body myositis and juvenile DM were excluded from this study (16,17). The date of inclusion to SweMyoNet was defined as the index date.

Treatment. Information on pharmacologic treatment was available from the SweMyoNet registry. Treatment of individual patients was based on the treating physician's decision and was in most cases started with high-dose glucocorticoids (0.75–1 mg/kg/day prednisolone, but not >80 mg) for 4–6 weeks, in combination with azathioprine (1.5–2 mg/kg/day), methotrexate (15–20 mg/day), or mycophenolate mofetil (2–2.5 grams/day). Glucocorticoids were tapered approximately every 3 to 4 weeks according to the treating physician's decision, based on the response to treatment (Vårdprogram myosit, Karolinska Universitetssjukhuset [in Swedish]). The use of glucocorticoids, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and any biologic agent, either abatacept or rituximab (during follow-up), was recorded as dichotomous variables. The glucocorticoid dose at the index date was recorded as a continuous variable.

Autoantibodies. Two assays were applied for autoantibody specificities: RNA- and protein-immunoprecipitation or line blot (Euroline Myositis Antigen Profile 4 [Euroimmun]) as described elsewhere (18). Seventy patients were tested by line blot and 86 patients by immunoprecipitation. 3-hydroxy-3-methylglutaryl-coenzyme A reductase autoantibodies were analyzed at the US National Institutes of Health using a combined protocol of immunoprecipitation followed by an enzyme-linked immunosorbent assay (19).

Autoantibody-defined subgroups. Patients were categorized by the presence of autoantibodies, as follows: 1) ASS (Jo1, PL7, PL12, EJ), 2) DM-associated autoantibodies (MDA5, anti-transcription intermediary factor 1 γ [anti-TIF1- γ], Mi2, SAE), 3) autoantibodies associated with immune-mediated necrotizing myopathy (IMNM: SRP and 3-hydroxy-3-methylglutaryl-coenzyme A reductase), 4) MAA without any MSA (PmScl, U1 RNP, Ro52, Ku), and 5) seronegative (negative to any of these autoantibodies).

Comorbidities. Any malignancy within ± 3 years of IIM diagnosis was defined as myositis-associated cancer and recorded as such. Interstitial lung disease, cardiac involvement, and dysphagia, as defined elsewhere, were recorded as dichotomous variables (20).

Definition of treatment response. We applied the 2016 ACR/EULAR criteria improvement score to assess clinical response to treatment (11). In short, the International Myositis Assessment and Clinical Studies group 6-item core set measures

of disease activity, all included in the SweMyoNet module, were used: patient global assessment (PtGA) of disease activity and physician global assessment (PhGA) of disease activity, both scored on a 10-cm visual analog scale (VAS); the Manual Muscle Test in 8 muscle groups (MMT8); the Health Assessment Questionnaire (HAQ); levels of the serum muscle enzyme creatine phosphokinase; and global extramuscular disease activity based on the physician's evaluation on a 10-cm VAS, including 6 organ systems (MYOACT tool) (21). Active disease was defined as a value of ≥ 1.5 on the PhGA (22). According to ACR/EULAR response criteria, the absolute percent change for each core set domain is calculated (final value – baseline value/range \times 100) (11). An improvement score is assigned to each measure based on this absolute change, and each individual core set measure is weighted such that those considered more important contribute more to the final score (11). Improvement scores for each of the 6 core set domains are summed to establish a total improvement score. The higher the change, the higher the improvement score. If the patient had $<5\%$ improvement or worsened on a particular domain, a score of 0 was assigned to that domain (11). The response thresholds were 20–39 for minimal, 40–59 for moderate, and 60–100 for a major response.

Statistical analysis. Descriptive statistical analyses were performed. The Kruskal-Wallis test was used for continuous variables with >2 independent samples, and Wilcoxon's rank test was used for comparisons of 2 independent samples. Chi-square test or Fisher's exact test were used for categorical variables, when appropriate. A linear regression model was used to test the association between the autoantibody status and the total improvement score adjusted by the baseline values for each core set measure. We also included an interaction parameter to identify whether the effect of the initial values for each core set measure varied among the autoantibody groups. A logistic regression model was used to test the association between autoantibody-defined groups and potential clinical predictors for each category of response, using the nonresponders as the reference category. To test for sensitivity, we excluded those patients who died during the observation period and checked for differences in the proportion of patients meeting the improvement criteria. A value of P less than 0.05 was defined as statistically significant. The statistical package employed was R, version 3.5.0 (23).

Ethics. Ethical approval was granted by the Regional Ethics Review Board of the Karolinska Institutet, Stockholm, Sweden. All patients signed an informed consent form before their data were included in the registry.

RESULTS

Patients. A total of 156 cases were identified (see Supplementary Figure 1, available on the *Arthritis Care & Research*

website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>). Sixty-two patients (40%) had DM, 8 (5%) had amyopathic DM, and 86 (55%) had polymyositis. Of all 156 cases, 39 (25%) met the criteria for ASS. The baseline demographic characteristics across each autoantibody group are summarized in Table 1. In all, 69% were female ($n = 107$) with a mean \pm SD age of 57 ± 14 years. The median duration of symptoms prior to diagnosis was 3 months (IQR 1.0, 8.5). All patients had active disease at the index date: one-third exhibited severe organ involvement (i.e., lung involvement or dysphagia), 6% had cardiac involvement, and 17% had a myositis-associated malignancy. Ninety percent of patients ($n = 140$) were given glucocorticoids at baseline. The median initial daily dose was 50 mg (IQR 25, 60 mg); 28 patients (18%) started on intravenous pulse steroids (>125 mg methylprednisolone). Besides glucocorticoids, 39% ($n = 61$) received methotrexate, 18% ($n = 29$) azathioprine, 22% ($n = 35$) mycophenolate mofetil, 20% ($n = 32$) cyclophosphamide, and 1% ($n = 2$) IVIg. Twelve percent ($n = 18$) received a biologic drug (abatacept or rituximab) within the first year. In total, 111 patients (71%) were positive to any autoantibody. The number of patients with ASS, DM-specific autoantibodies, IMNM-associated autoantibodies, and MAAs was 39 (25%), 28 (18%), 9 (6%), and 35 (22%), respectively. The number of patients negative for any autoantibody (seronegative) was 45 (29%). For information about each group, see Supplementary Table 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>.

Patients with ASS were more likely to have interstitial lung disease (67%) compared to the rest of the groups (overall $P < 0.001$). Cardiac involvement was more frequent in the IMNM group compared to other groups (overall $P = 0.04$), and the DM-specific autoantibody group had a higher erythrocyte sedimentation rate (ESR) at the index date ($P = 0.008$). A significantly higher number of patients with ASS were treated with mycophenolate mofetil, cyclophosphamide, and biologic drugs during the follow-up compared to the rest of the groups (overall $P < 0.005$, $P < 0.001$, and $P < 0.005$, respectively). Regarding treatment patterns over time, more patients included in SweMyoNet during the registry's first years were given glucocorticoids than those added to the registry in later years, while the latter were more likely to be given biologic drugs (see Supplementary Table 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>). No differences were observed between the autoantibody-defined groups in terms of dysphagia, cancer, or duration of symptoms prior to diagnosis.

Autoantibodies and treatment response. Table 2 summarizes the levels of response across the autoantibody-defined groups. After 1 year from the index date, the overall median improvement score was 27.5 (IQR 10, 51), with no significant differences among the autoantibody-defined groups. Table 3 and Figure 1 summarize the values for each core set

Table 1. Baseline demographic characteristics of 156 patients with idiopathic inflammatory myopathies by autoantibody group*

	Total	ASS (n = 39)	DM specific (n = 28)	IMNM (n = 9)	MAA (n = 35)	None (n = 45)	P†
Age at diagnosis, mean ± SD years	57 ± 14	54 ± 15	54 ± 16	58 ± 19	58 ± 12	61 ± 13	NS
Female, no. (%)	107 (69)	24 (62)	22 (78)	6 (67)	26 (74)	26 (58)	NS
Diagnosis, no. (%) or no.							
Amyopathic dermatomyositis	8 (5)	3	3	1	0	2	NS
Dermatomyositis	62 (40)	13	23	0	7	18	
Polymyositis	86 (55)	23	2	8	28	25	
Symptom duration before diagnosis, months	3.0 (1.0, 8.5)	3 (1, 9)	2.2 (0, 5.5)	3.2 (1, 12)	3.9 (0, 8.9)	3.5 (1, 8)	NS
Disease duration at index date from diagnosis, months	0.98 (0.2, 2.6)	0.7 (0.2, 2.2)	0.9 (0.1, 1.6)	2.6 (0.7, 7.0)	1.2 (0.5, 3.7)	1.2 (0.1, 3.5)	NS
ESR, mm/hour	20 (12, 31)	22 (16.5, 34)	29 (20, 47)	15 (9, 19)	15.5 (8, 28)	16 (10.5, 26)	0.008
Comorbidities, no. (%)							
ILD	52 (34)	26 (67)	10 (36)	1 (11)	11 (31)	4 (9)	<0.001
Dysphagia	57 (36)	8 (21)	11 (39)	3 (33)	18 (51)	17 (38)	NS
Cancer	26 (17)	5 (13)	8 (29)	2 (22)	3 (9)	8 (18)	NS
Cardiac involvement	9 (6)	1 (3)	1 (4)	3 (33)	2 (6)	2 (4)	0.04
Glucocorticoids, no. (%)	140 (90)	36 (92)	26 (93)	7 (78)	33 (94)	38 (84)	NS
Initial glucocorticoid dose, mg	50 (25, 60)	50 (25, 60)	52 (32, 50)	25 (12, 50)	45 (30, 60)	40 (30, 60)	NS
Methotrexate, no. (%)	61 (39)	11 (28)	8 (28)	4 (44)	19 (54)	19 (42)	NS
Azathioprine, no. (%)	29 (18)	8 (20)	4 (14)	2 (22)	6 (17)	9 (20)	NS
Mycophenolate mofetil, no. (%)	35 (22)	11 (28)	6 (21)	2 (22)	11 (31)	5 (11)	0.004
Cyclophosphamide, no. (%)	32 (20)	19 (48)	7 (25)	0 (0)	5 (14)	1 (0.2)	<0.001
Biologic drug, no. (%)‡	18 (12)	10 (26)	5 (18)	0 (0)	2 (6)	1 (2)	0.005

* Values are the median (interquartile range) unless indicated otherwise. ASS = antisynthetase syndrome group; DM specific = dermatomyositis-specific autoantibodies group; ESR = erythrocyte sedimentation rate; ILD = interstitial lung disease; IMNM = immune-mediated necrotizing myopathy autoantibodies group; MAA = myositis-associated autoantibodies group; NS = not significant.

† P value by chi-square test/Fisher's exact test for categorical data and by Kruskal-Wallis test for continuous data. $P < 0.05$ indicates a significant difference between the 5 groups.

‡ Use of a biologic drug (abatacept or rituximab) during the follow-up, i.e., 1 year after the index date.

measure and the absolute percent change at 1 year after the index date across the autoantibody-defined groups. We did not find significant differences in the absolute percent change in any core set measure among the autoantibody groups. At the index date, patients with ASS had a higher MMT8 score ($P = 0.01$), and patients with DM-specific autoantibodies had a higher extra-muscular score (overall $P = 0.002$). At 1 year of follow-up, patients with ASS continued to have higher MMT8 scores ($P = 0.038$), and patients with IMNM-associated antibodies had persistently higher creatine phosphokinase levels ($P = 0.001$).

Because initial values for each core set measure at baseline are associated with their values after a period of follow-up, and

subsequently with the total improvement score, we tested whether the various autoantibody groups had any effect on the total improvement score that was independent of the initial values for each core set measure and whether there was an effect from the autoantibody groups on the total improvement score depending on the initial values for each core set measure (interaction variable) (see Supplementary Table 3, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>). The unadjusted linear regression analysis showed that the DM-specific autoantibodies group was associated with a higher total improvement score compared with the seronegative group (reference group). After adjusting for the initial

Table 2. Total improvement score and number of patients achieving minimal, moderate, and major response after 1 year of treatment between autoantibody-defined groups*

	Total (n = 156)	ASS (n = 39)	DM specific (n = 28)	IMNM (n = 9)	MAA (n = 35)	None (n = 45)	P†
TIS, median (IQR)	27.5 (10, 51)	28 (13, 48)	48 (11, 63)	7.5 (2.5, 35)	35 (11, 58)	21 (7.5, 42)	0.07
Minimal	96 (62)	27 (69)	20 (71)	3 (33)	23 (66)	23 (51)	0.14
Moderate	60 (38)	13 (33)	17 (61)	2 (22)	16 (46)	12 (27)	0.03‡
Major	30 (19)	7 (18)	10 (36)	0 (0)	7 (20)	6 (13)	0.12

* Values are in the number (%) unless indicated otherwise. ASS = antisynthetase syndrome group; DM specific = dermatomyositis-specific autoantibodies group; IMNM = immune-mediated necrotizing myopathy autoantibodies group; IQR = interquartile range; MAA = myositis-associated autoantibodies group; None = patients negative to any antibody; TIS = total improvement score.

† P value by chi-square test/Fisher's exact test for categorical data and by Kruskal-Wallis test for continuous data. $P < 0.05$ indicates a significant difference between the 5 autoantibody-defined groups.

‡ Statistically significant.

Table 3. Individual core set measures at index date and follow-up, and absolute percentage change in 156 patients with idiopathic inflammatory myopathies and by autoantibody group*

	Total (n = 156)	ASS (n = 39)	DM specific (n = 28)	IMNM (n = 9)	MAA (n = 35)	Seronegative (n = 45)	P†
PhGA							
Index date	40 (20, 57)	40 (21, 59)	50 (35, 69)	20 (20, 39)	43 (29, 52)	31 (12, 60)	0.18
Follow-up	12 (3, 20)	10 (0, 20)	18 (10, 33)	20 (15, 20)	16 (5, 20)	10 (0, 20)	0.1
Absolute % change	-21(-40, 0)	-22 (-50, 3)	-30 (-45, -5)	0 (0, 0)	-28 (-40, -3)	-20 (-32, 0)	0.12
PtGA							
Index date	44 (25, 71)	47 (25, 61)	50 (32, 75)	35 (17, 46)	35 (24, 69)	46 (28, 71)	0.6
Follow-up	30 (10, 50)	22 (4, 44)	34 (8, 47)	24 (15, 41)	25 (12, 51)	42 (14, 65)	0.5
Absolute % change	-9 (-32, 3)	-12 (-39, 1.0)	-18 (-41, 0)	-3 (-19, 0.5)	-9.5 (-26.8, 4.5)	-2 (-24, 12)	0.29
MMT8							
Index date	73 (63, 78)	78 (69, 78)	69 (57, 78)	76 (68, 78)	71 (63, 76)	71 (63, 78)	0.01
Follow-up	78 (72, 80)	80 (78, 80)	79 (69, 80)	78 (74, 79)	76 (72, 79)	76 (69, 80)	0.038
Absolute % change	3 (0, 13)	1.3 (0, 8.5)	3.2 (0, 14)	2.5 (0.7, 8.2)	3.8 (0, 12.5)	1.3 (-1.6, 11.6)	0.64
HAQ							
Index date	0.8 (0.3, 0.4)	0.6 (0.2, 1.3)	1.0 (0.3, 1.5)	0.6 (0.3, 1.3)	0.8 (0.3, 1.3)	0.9 (0.3, 1.5)	0.7
Follow-up	0.5 (0, 1)	0.2 (0, 0.7)	0.2 (0, 1.7)	0.5 (0.1, 0.8)	0.5 (0.1, 1)	0.8 (0.1, 1.2)	0.19
Absolute % change	0 (-17, 0)	-4 (-21, 0)	-8 (-24, 0)	-4 (-10, -1)	-8 (-23, 3)	0 (-6, 4)	0.37
CK							
Index date	5.2 (1.5, 24)	5.9 (1.5, 5.2)	2.3 (1.2, 8.9)	12.5 (7.4, 9.5)	13.4 (1.6, 40)	4.1 (1.7, 26)	0.12
Follow-up	1.5 (1, 3.6)	1.6 (1.1, 2.1)	1.1 (0.8, 1.8)	7.6 (4.7, 10)	1.4 (0.8, 3.9)	1.7 (1.1, 5)	0.001
Absolute % change	-5 (-32, 0.2)	-5 (-31, 1)	-3 (-16, 0.1)	-8 (-28, -3)	-23 (-49, -1)	-2 (-22, 0.8)	0.27
EM							
Index date	28 (10, 43)	30 (10, 45)	43 (27, 55)	18 (4, 20)	25 (15, 40)	15 (0, 30)	0.002
Follow-up	10 (0, 18)	9.5 (0, 16)	12 (5, 27)	16 (10, 23)	10 (0, 16)	6 (0, 10)	0.08
Absolute % change	-11 (-32, 0)	-15 (-41, 0)	-21 (-37, 0)	0 (0, 0)	-9 (-32, -2)	-3 (-22, 0)	0.12

* Values are the median (interquartile range). ASS = antisynthetase syndrome group; CK = creatine kinase levels; DM specific = dermatomyositis-specific autoantibodies group; EM = extramuscular assessment; HAQ = Health Assessment Questionnaire; IMNM = immune-mediated necrotizing myopathy autoantibodies group; MAA = myositis-associated autoantibodies; MMT8 = Manual Muscle Test in 8 muscle groups; PhGA = physician global assessment; PtGA = patient global assessment.

† P value by Kruskal-Wallis test. $P < 0.05$ indicates a significant difference between the 5 autoantibody-defined groups.

values for each individual core set measure separately, the ASS group was associated with a higher total improvement score after adjusting for the initial MMT8 score, but it was associated with a lower improvement score after adjusting for the initial PtGA value ($P = 0.006$ and $P = 0.03$, respectively). The DM-specific autoantibodies group was associated with a lower total improvement score after adjusting for the initial value of PtGA ($P = 0.01$). With respect to this effect of each autoantibody group on the total improvement score depending on the initial values for each core set measure (interaction parameter), we found that besides the independent effect of the ASS group and initial value of the initial MMT8 score on the total improvement score, an even higher total improvement score is expected for the ASS antibody group compared with the reference group, i.e., the lower the initial MMT8 score, the higher the total improvement score, and even higher for the ASS antibody group than for the reference group ($P = 0.01$). Similarly, the effect of a low HAQ score on the total improvement score was higher in the MAA group compared with the reference group. No other significant interactions were observed (see Supplementary Table 3, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>).

Of the 156 patients initially identified, 96 (62%) met the criteria for minimal response, 60 (38%) met the criteria for moderate response, and 30 (19%) met the criteria for major response.

Regarding the effect of autoantibody status on the different levels of response, only patients with DM-specific autoantibodies were associated with the moderate response level ($\chi^2 = 10.4$, $df = 4$, $P = 0.034$). No significant associations between the autoantibody-defined groups and minimal or major responses were observed.

Characteristics of nonresponders and responders.

The characteristics of nonresponders (improvement score < 20) are summarized in Table 4. Nonresponder patients had a longer duration of symptoms prior to diagnosis and lower disease activity as measured both by PhGA and a lower ESR at the index date. They also received lower mean initial glucocorticoid doses, and significantly fewer patients received cyclophosphamide and biologic drugs than responding patients at each level of response. The nonresponders were less likely to have gastrointestinal involvement, represented by dysphagia, than patients who achieved moderate or major responses. When comparing the autoantibody-defined groups, no differences were found in the number of nonresponders and responding patients at any level of response.

Predictive factors for treatment response. As a next step, we performed a univariate logistic regression analysis to test the predictive value of the antibody-defined groups for each category of response. Table 5 summarizes the results of the

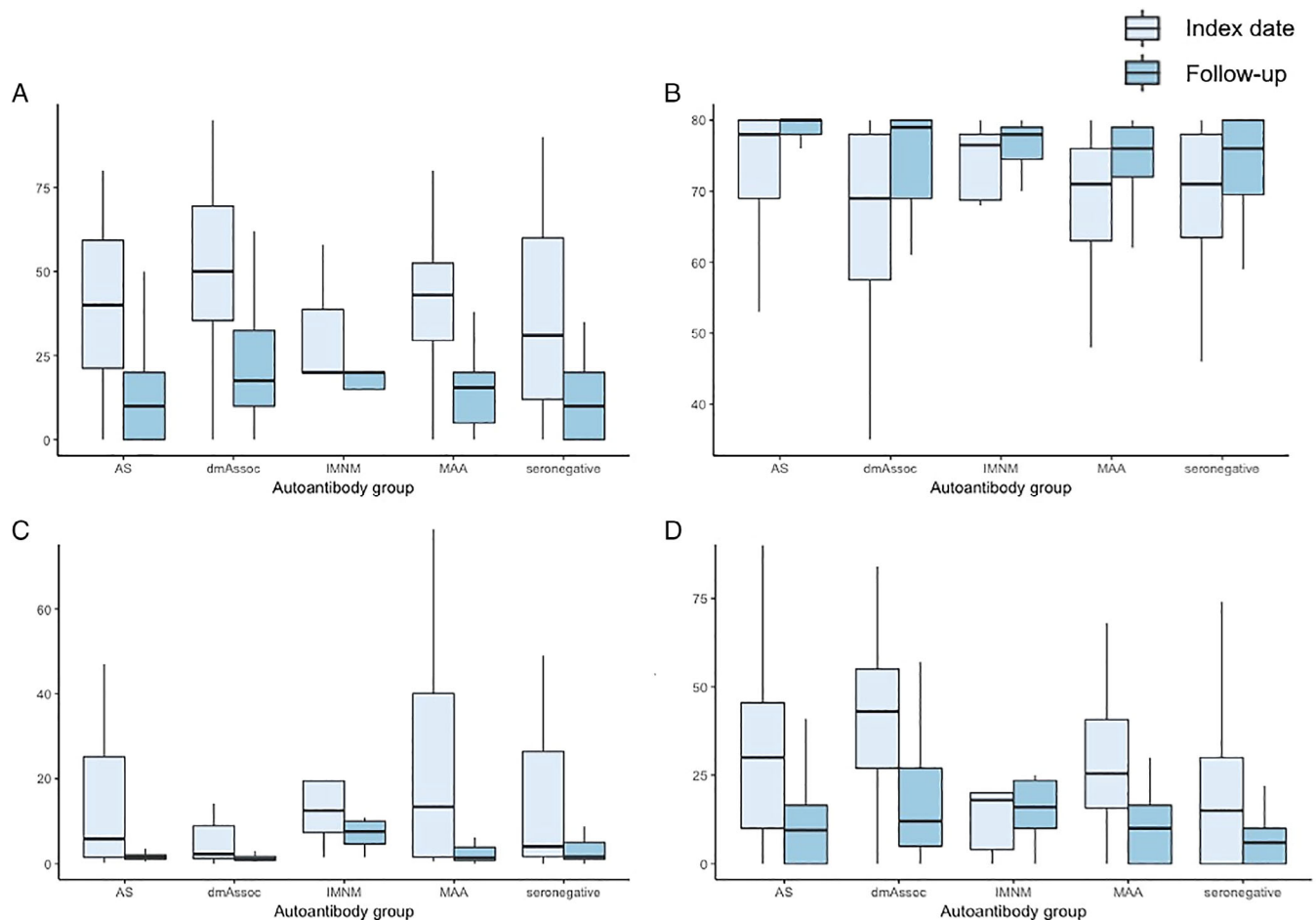


Figure 1. Values of core set measures at baseline and at 1 year after being treated. **A**, Physician global assessment; **B**, Manual Muscle Test in 8 muscle groups score; **C**, Creatine kinase levels, and **D**, Extramuscular visual analog scale. Boxes represent interquartile range. Horizontal lines represent median value. Whiskers show the range. AS = antisynthetase syndrome group; dmAssoc = dermatomyositis-specific autoantibodies group; IMNM = immune-mediated necrotizing myopathy autoantibodies group; MAA = myositis-associated autoantibodies group.

logistic regression models for each category of response. The multivariate logistic regression analysis demonstrated that the DM-specific autoantibody group was associated with moderate response (odds ratio [OR] 4.2 [95% confidence interval (95% CI) 1.2–16.5]). The DM-specific autoantibody group was also associated with minimal and major responses to a degree that did not reach significance. Two independent predictive factors were associated with response to treatment: time from first symptoms to diagnosis (OR 0.86 [95% CI 0.7–0.96] for major response) and dysphagia (OR 3.02 [95% CI 1.3–7.7] for minimal response and OR 3.2 [95% CI 1.2–9.5] for major response). Moreover, because these associations could reflect confounding by indication, we tested the dose of glucocorticoids per se with all 3 levels of response. An increase of 1 milligram of initial glucocorticoid dose was associated with up to a 4% increase in the odds of achieving a response. Finally, as a sensitivity analysis, 9 patients (6%) who died during the observation period were excluded: the associations between predictive factors and levels of response

remained similar (see Supplementary Table 4, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>).

DISCUSSION

In our single-center cohort of patients newly diagnosed with IIM, we found no significant differences in the total improvement score between the autoantibody-defined groups following the ACR/EULAR 2016 criteria. We did, however, observe that patients who were positive for DM-specific autoantibodies had a higher frequency of achieving a moderate response than the other groups. To our knowledge, this is the first study to analyze the usefulness of autoantibody status as a predictor for treatment response using the ACR/EULAR 2016 criteria.

Earlier studies have shown that DM-specific autoantibodies are markers of response in patients with established or refractory disease after treatment with rituximab, as well as markers of long-

Table 4. Comparison of characteristics between nonresponders and patients achieving minimal, moderate, and major response*

	Nonresponders (ref.) (n = 60)	Minimal (n = 96)	Moderate (n = 60)	Major (n = 30)
Age at diagnosis, mean \pm SD years	56 \pm 15	58 \pm 15	58 \pm 14	59 \pm 14
Female, no. (%)	38 (64)	66 (68)	46 (76)	21 (70)
Dermatomyositis phenotype, no. (%)	25 (42)	41 (42)	31 (51)	20 (66)
Duration of symptoms, months	5.2 (1.3, 13)	2.2 (0.4, 6.9)†	2.0 (0.0, 4.0)‡	1.0 (0.0, 2.8)§
Physician global assessment	20 (8, 40)	50 (37, 66)†	55 (40, 69) ‡	64 (50, 71)§
Interstitial lung disease, no. (%)	14 (23)	38 (39)	23 (38)	13 (43)
Dysphagia, no. (%)	15 (25)	41 (42)	28 (46)‡	16 (53)£
Cancer, no. (%)	8 (13)	18 (18)	14 (23)	9 (30)
ESR at baseline, mm/hour	14 (6, 26)	22 (15, 34)†	26.5 (20, 41)‡	29 (18, 42)§
ASS, no. (%)	12 (20)	27 (28)	13 (21)	7 (23)
DM specific, no. (%)	8 (13)	20 (20)	17 (28)	10 (33)
IMNM, no. (%)	6 (10)	3 (3)	2 (3)	0 (0)
MAA, no. (%)	12 (20)	23 (20)	16 (26)	7 (23)
Seronegative, no. (%)	21 (35)	23 (24)	12 (20)	6 (20)
Initial glucocorticoid dose, mg	30 (11, 44)	50 (39, 60)†	60 (50, 60)‡	60 (56, 70)§
Methotrexate, no. (%)	20 (33)	41 (43)	29 (43)	13 (43)
Azathioprine, no. (%)	10 (17)	19 (20)	9 (15)	3 (10)
Mycophenolate, no. (%)	14 (24)	21 (22)	14 (23)	9 (30)
Cyclophosphamide, no. (%)	6 (10)	26 (27)†	17 (28)‡	9 (30)§
Biologic drug, no. (%)	4 (7)	13 (13)	10 (16)	5 (16)

* Values are the median (interquartile range) unless indicated otherwise. ASS = antisynthetase syndrome group; DM specific = dermatomyositis-specific autoantibodies group; ESR = erythrocyte sedimentation rate; IMNM = immune-mediated necrotizing myopathy autoantibodies group; MAA = myositis-associated autoantibodies; ref. = reference.

† Comparisons between minimal responders and nonresponders by Wilcoxon's rank test with a *P* value <0.05.

‡ Comparisons between moderate responders and nonresponders by Wilcoxon's rank test with a *P* value <0.05.

§ Comparisons between major responders and nonresponders by Wilcoxon's rank test with a *P* value <0.05.

term remission (9,10,24,25). Similarly, our study suggests that DM-specific autoantibodies are markers of good response after conventional immunosuppressive treatment in patients within the early stages of the disease. There are several reasons that explain these findings. First, compared to the other autoantibody-defined groups, patients who harbored DM-specific autoantibodies had both higher levels of extramuscular involvement and the highest

levels of ESR, as measures of disease activity at baseline. Although we were not able to retrieve information regarding the specific extramuscular organs involved, cutaneous manifestations and lung disease in MDA5-positive cases are frequent in these patients. This fact is important, given that one aspect of the ACR/EULAR criteria is that the extramuscular activity, together with the physician's assessment, is the second most

Table 5. Factors associated with clinical response in patients with idiopathic inflammatory myopathies*

	Univariate model			Multivariate model		
	Minimal odds	Moderate odds	Major odds	Minimal odds	Moderate odds	Major odds
Seronegative (ref.)	1.0	1.0	1.0	1.0	1.0	1.0
ASS	2.05 (0.84–5.16)	1.33 (0.5–3.4)	1.38 (0.4–4.7)	2.3 (0.6–8.5)	0.95 (0.26–3.3)	1.6 (0.4–7.3)
DM specific	2.28 (0.85–6.5)	4.12 (1.5–11.6)†	3.5 (1.13–11.8)†	3.9 (0.99–18.3)	4.2 (1.2–16.5)†	3.01 (0.7–13)
IMNM	0.45 (0.1–1.96)	0.76 (0.1–3.7)	0.014 (0.01–2.2)	0.6 (0.1–3.6)	1.19 (0.1–7.4)	2.8 (0.8–5.3)
MAA	1.75 (0.7–4.45)	2.24 (0.9–5.9)	1.6 (0.4–5.4)	1.3 (0.4–3.9)	2.13 (0.7–6.6)	1.25 (0.3–5.2)
Initial GC dose	1.05 (1.03–1.07)†	1.04 (1.02–1.06)†	1.05 (1.03–1.08)†	1.04 (1.02–1.07)†	1.04 (1.02–1.07)†	1.04 (1.01–1.07)†
Time from 1st symptoms to diagnosis, months	0.98 (0.95–1.00)	0.98 (0.94–1.00)	0.86 (0.75–0.95)	0.97 (0.95–1.0)	0.99 (0.96–1.01)	0.86 (0.7–0.96)†
Dysphagia	2.22 (1.1–4.64)	2.1 (1.05–4.0)	2.4 (1.1–5.4)	3.02 (1.3–7.7)†	2.1 (0.9–5.1)	3.2 (1.2–9.5)†
Initial ESR	1.02 (1.0–1.04)	1.04 (1.01–1.06)	1.03 (1.01–1.05)	1.01 (0.98–1.03)	1.03 (1.0–1.05)	1.01 (0.99–1.04)
Use of CFM	3.3 (1.3–9.2)	2.05 (0.9–4.6)	1.9 (0.7–4.5)	1.1 (0.28–4.6)	1.23 (0.38–4.15)	6.0 (1.6–2.1)

* Values are the odds ratio (95% confidence interval). ASS = antisynthetase syndrome group; CFM = cyclophosphamide; DM specific = dermatomyositis specific autoantibodies group; ESR = erythrocyte sedimentation rate; GC = glucocorticoid; IMNM = immune-mediated necrotizing myopathy autoantibodies; MAA = myositis-associated autoantibodies group; ref. = reference.

† Statistically significant association.

important weighted contributor to the improvement score, after the MMT8 score.

Furthermore, patients with DM-specific autoantibodies had a trend toward higher absolute percentage change in PtGA than the other groups, which could be an effect of improvement in cutaneous signs, which usually correlates with better responses in subjective outcome measures (26). In addition, in patients with anti-TIF1- γ and anti-Mi2 autoantibodies, but not in patients without these specificities, some molecular pathways, such as the interferon signature, are predictors of response to treatment as measured by improvement in muscle strength and PhGA (27).

The autoantibody-defined groups exhibited notable differences in the core set measures at baseline and at follow-up, but not in the absolute percentage change. Patients with ASS usually exhibit a high level of extramuscular disease activity, represented by a high prevalence of interstitial lung disease, and a low level of muscle involvement (15). Indeed, in our study, patients with ASS autoantibodies presented the highest mean MMT8 scores, both at baseline and at follow-up, and a higher frequency of lung involvement (although they did not have a higher mean extramuscular score compared with the other autoantibody-defined groups). Interestingly, when we analyzed the interaction between the autoantibody groups and the initial value of each core set measure, we found that the ASS group and the DM-specific antibodies group were associated with higher total improvement scores than the reference group, an association that was independent of the baseline values for MMT8 and PtGA. Moreover, the total improvement score was higher when initial values for MMT8 were lower at baseline, and even higher in the ASS group compared with the reference group. Together, these findings indicate that the ACR/EULAR response criteria can capture the nature of response in the different autoantibody-defined groups.

In addition to DM-specific autoantibodies, we found other independent factors associated with different levels of response to treatment. The presence of dysphagia was strongly associated with minimal and major responses. In previous reports, dysphagia has been associated with a good response, probably due to more intensive treatment in patients with higher global disease activity and anti-TIF1- γ autoantibodies (28,29). Our findings, however, showed that dysphagia was a predictor independent of the initial dose of glucocorticoids. In this study, time from onset of symptoms to diagnosis and initial glucocorticoid dose were also independent factors associated with response to treatment.

Due to the long observation time of our cohort (>10 years), some concerns may arise about the differences in treatment patterns over the years. In fact, after performing an additional analysis, we found that the use of glucocorticoids was more frequent during the first years of the registry, whereas the use of biologic drugs was more frequent in later years (see

Supplementary Table 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24498/abstract>). However, neither of these differences was associated with any level of response. Nonetheless, our data support the importance of early initial treatment intervention to achieve improvement in patients with IIM according to the response criteria (30–33).

Our study has several limitations. First, autoantibodies were tested using 2 different assays. However, as previously reported, the overall concordance between these 2 assays was 78%, with a moderate agreement. Moreover, the agreement for the most prevalent specificities (e.g., Jo1) was good (18). Second, seronegative patients, particularly those without skin rash, may develop another myopathy beyond the observation period of this study. Third, the small cohort size prevented analyses of individual autoantibodies as predictors, and thus we grouped patients into clinically relevant autoantibody-defined subgroups. Still, the small sample size of autoantibody-defined groups might have limited the ability to detect differences in total improvement scores. Fourth, patients considered to be nonresponders might represent a group with mild disease, irrespective of autoantibody status (22). Fifth, the association of medications with treatment responses could be a potential confounder for indication influencing the degree of response to treatment. Lastly, we cannot rule out the possibility that occasional patients might have received aggressive treatment before the index date or experienced improvement before their inclusion in the SweMyoNet registry. A strength of the SweMyoNet registry is that it includes most patients treated at our clinic, both patients diagnosed in the inpatient ward and those diagnosed in the outpatient clinic, and thus represents various levels of disease severity.

In conclusion, in our retrospective study using prospectively collected data, we found that patients with DM-specific autoantibodies were more likely to have a moderate level of response compared to patients without these autoantibodies. Moreover, the presence of dysphagia, a shorter time from symptom onset to diagnosis, and more-intensive initial glucocorticoid treatment were independently associated with higher rates of clinical improvement after 1 year of pharmacologic treatment, for all subgroups. Our findings highlight the importance of identifying autoantibody-defined subgroups of patients with IIM early on, and of initiating intensive glucocorticoid treatment as soon as possible after diagnosis, as this identification and treatment predict higher rates of clinical response regardless of autoantibody status.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Espinosa-Ortega had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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