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Clinical science

Predictors of response to intravenous immunoglobulin in patients with dermatomyositis: the ProDERM study

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Abstract

Objectives: The phase 3 ProDERM study demonstrated intravenous immunoglobulin (IVIg) was safe and effective in patients with dermatomyositis (DM). This analysis assessed clinical and serological predictors of IVIg response in DM patients from ProDERM.

Methods: ProDERM was a prospective, randomized, placebo-controlled study of DM patients. For weeks 0–16, patients received 2.0 g/kg IVIg (Octagam, 10%) or placebo every 4 weeks. Eligible patients entered the open-label extension phase, where all received IVIg to week 40. Univariate and multivariate analyses examined associations between baseline variables and total improvement score (TIS), including myositis disease activity assessment tool (MDAAT; assessing different organ involvement), and myositis-specific and myositis-associated autoantibodies.

Results: Ninety-five patients were enrolled. Univariate analyses found no significant association between TIS at week 16 or 40 and age; sex; ethnicity; disease duration/activity; cutaneous, skeletal, gastrointestinal or muscle disease activity; or previous failed or concomitant medications. Multivariate analysis found patients with higher MDAAT cutaneous scores had a better chance of at least minimal TIS improvement. Higher MDAAT pulmonary scores were associated with a lower, but still considerable, chance of improvement. Patients with TIF1-γ antibodies had a better TIS response; however, after controlling for cutaneous disease activity, there was no significant association between antibody classification (including anti-TIF1-γ) and efficacy outcome.

Conclusion: IVIg was effective in treating DM patients regardless of demographic features and autoantibody status (for most autoantibodies). Patients with higher cutaneous disease activity and/or anti-TIF1-γ responded best to IVIg, while pulmonary disease activity predicted a lower, but still effective, IVIg response, warranting further investigation.

Trial registration: ClinicalTrials.gov, http://clinicaltrials.gov, NCT02728752.

Keywords: anti-TIF1-γ, autoantibody, autoimmune, cutaneous, dermatomyositis, intravenous immunoglobulin, myositis-associated antibodies, myositis-specific antibodies.

Rheumatology key messages

- Dermatomyositis patients responded to intravenous immunoglobulin regardless of age, gender, ethnicity and disease duration/activity.
- Intravenous immunoglobulin appeared effective regardless of patient antibody status for the majority of autoantibodies.
- Patients with high cutaneous disease activity and/or anti-TIF1-γ antibodies responded best to IVIg.

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Introduction

Dermatomyositis (DM) is a systemic autoimmune disease presenting primarily with proximal muscle weakness and skin symptoms [1]. Recent population-based studies have found that DM affects as many as 21–28 per 100 000 people, including children and adults [2, 3]. DM is heterogeneous and its pathophysiology is complex and poorly understood.

In recent years, research has focused on different autoantibodies identified in patients with DM and how these relate to varying presentations of the disease. Two distinct types of autoantibodies are implicated in DM [4]. Myositis-specific antibodies (MSA) are thought to be present in 50–70% of patients with DM [5], including anti-Mi-2, anti-NXP2, anti-MDA5, anti-TIF1-γ, anti-SAE, and anti-synthetase antibodies such as anti-Jo-1, anti-PL-7 and anti-PL-12. In addition, there are also a number of myositis-associated antibodies (MAA), including anti-PM/Scl, anti-U1 RNP, anti-Ro-60 and anti-Ku [6], which are not specific to patients with DM and idiopathic inflammatory myopathies (IIM).

Evidence suggests that different autoantibodies found in patients with DM are associated with distinct clinical phenotypes [1, 7–9]. Autoantibody testing is widely used to inform clinical decision making; a recent survey showed that over 80% of international myositis experts reported that the identification of a myositis autoantibody influenced their diagnostic confidence and treatment recommendation [10].

Treatment for DM historically included glucocorticoids and immunosuppressants. Recently, immunoglobulin therapy was shown to be safe and effective in patients with DM in a placebo-controlled, multicentre, phase 3 study (ProDERM) [11]. The efficacy of IVIg was demonstrated by significant improvement in the total improvement score (TIS), a weighted composite score reflecting the change in a core set of six measures of myositis activity over time, derived by consensus of the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) [11–13].

To optimize treatment regimens in different patients, it is important to understand which (if any) factors affect treatment response. The aims of this post hoc analysis were to determine clinical and serological predictors of response to IVIg, as well as overall clinical improvement assessed by TIS, in patients with DM from the ProDERM study [11].

Methods

ProDERM (NCT02728752) was a prospective, phase 3, double-blind, parallel-group, randomized, placebo-controlled study of patients with DM. Written informed consent was obtained from each patient. The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, and approved by applicable independent ethics committees or institutional review boards (listed in Supplementary Material, available at *Rheumatology* online).

Patients

ProDERM included patients aged ≥18 to <80 years with definite or probable DM according to Bohan and Peter criteria [14, 15]. Inclusion and exclusion criteria have been described [11]; patients with active and refractory disease on concomitant immunosuppression were enrolled [11]. The study excluded patients with cancer-associated myositis, or evidence of active malignant disease within the previous 5 years.

Study procedures

The study protocol has been described in detail [12]. In brief, ProDERM included a randomized, placebo-controlled phase from weeks 0–16, where patients were assigned 1:1 to receive 2.0 g/kg body weight IVIg (Octagam, 10%) or placebo (0.9% sodium chloride) every 4 weeks. All patients, except those who had confirmed deterioration while receiving IVIg, were permitted to continue into the open-label extension phase (weeks 16–40), in which all patients received 2.0 g/kg IVIg every 4 weeks for six further infusion cycles.

Study end points and assessments

The primary end point of the study was response to the study drug, defined as TIS at week 16 of ≥20, indicating at least minimal improvement, and with no confirmed deterioration up to week 16 (Supplementary Data S1, available at *Rheumatology* online) [11, 12, 16].

Clinical parameters

Myositis disease activity was assessed using measures and tools as follows (described in further detail in Supplementary Data S1, available at *Rheumatology* online): myositis disease activity assessment tool (MDAAT, which includes a 10-cm visual analogue scale [VAS], along with a myositis intention-to-treat activity index [MITAX]) [17]; modified cutaneous DM disease area and severity index (CDASI) [18]; manual muscle testing (MMT-8) tool; physician and patient global disease activity (both assessed on a 10-cm VAS); health assessment questionnaire (HAQ) disability index; and short form-36 (SF-36) health survey v2.

Serological parameters

Serum samples were taken at baseline and tested for antibodies by the Oklahoma Medical Research Foundation (Oklahoma City, OK, USA) (Supplementary Data S2, available at *Rheumatology* online). Samples were assessed for MSA (including anti-Jo-1, PL-12, SRP, Mi-2, SAE) and MAA (including anti-PM/Scl, Ku, U1 RNP, Ro-60) by protein immunoprecipitation with ^{35}S labelling and RNA immunoprecipitation. In addition, anti-TIF1-γ, MDA5 and NXP2 were assessed by immunoprecipitation blotting. A dichotomous yes/no result was obtained for each specific autoantibody.

Statistical methods

The ProDERM study was powered with respect to the primary end point, the proportion of TIS responders, as described previously [12]. The main population for analysis was the full analysis set, which included all randomized patients and was defined according to the intention-to-treat principle.

To determine which (if any) factors were associated with clinical improvement, clinical and serological factors, including demographics, baseline disease characteristics and the presence of MSA or MAA, were examined separately in a series of post hoc univariate analyses, followed by multivariate analysis (Supplementary Data S3, available at *Rheumatology* online).

To evaluate general autoantibody associations with the clinical and serological parameters, antibodies were grouped into four classifications. Classification 1 included antibody negative (i.e. no relevant autoantibodies detected), MSA only

and MAA only. Classification 2 included antibody negative, MSA, MAA and MSA+MAA (i.e. both MSA and MAA). Classification 3 included antibody negative, anti-synthetase (i.e. Jo-1 and PL-12), anti-TIF1-γ, other MSA (i.e. MSA autoantibodies other than anti-TIF1-γ, anti-Jo-1 and anti-PL-12) and MAA. Finally, classification 4 included antibody negative, anti-synthetase, anti-TIF1-γ, anti-Mi-2, other MSA (i.e. MSA autoantibodies other than anti-TIF1-γ, anti-Mi-2, anti-Jo-1 and anti-PL-12) and MAA.

Results

Demographics

In total, 126 patients were screened, of whom 95 were enrolled into the ProDERM study. In the first period, 47 patients were randomized to receive IVIg and 48 were randomized to receive placebo. In the IVIg group, 45 (95.7%) patients completed the first period, as did 46 (95.8%) in the placebo group. Five patients (10.4%) on placebo crossed over to IVIg during the first period and no patients on IVIg switched to placebo. In total, 69 (72.6%) patients completed the extension period.

Full details of patient disposition were described previously [11]. In summary, the median (range) age was 52.0 years (22.0–79.0) and 71 (74.7%) patients were female. Baseline characteristics of patients and demographics were generally balanced between the IVIg and placebo groups [11].

Occurrence of autoantibodies

In total, 49 (51.6%) patients were positive for MSA and 23 (24.2%) were positive for MAA. Of these, 10 patients were positive for both MSA and MAA, and for subsequent analyses these patients were included only in the MSA group, leaving 13 patients in the MAA group. No relevant antibodies were detected in 33 (34.7%) patients.

The frequency of each autoantibody is shown in Fig. 1. The most common antibody detected was anti-TIF1-γ, which occurred in 23 (24.2%) patients.

Demographics for patients in the three antibody groups are shown in Table 1. There were no statistically significant differences between the three groups, apart from MMT-8 score ($P = 0.01$), which was higher for patients who had MSA or MAA antibodies *vs* those with no relevant autoantibodies detected. Mean CDASI-A score was numerically higher for MSA-positive patients *vs* MAA-positive patients or those who had no relevant autoantibodies, but the difference did not reach significance ($P = 0.16$).

Several differences were seen in baseline characteristics between patients who were positive for anti-TIF1-γ *vs* those who were MSA positive and anti-TIF1-γ-negative. Patients who were positive for anti-TIF1-γ had a significantly higher mean cutaneous MDAAT score ($P = 0.02$), CDASI activity score ($P = 0.03$) and MMT-8 score ($P = 0.04$) than patients who were MSA positive and anti-TIF1-γ-negative (Supplementary Table S1, available at *Rheumatology* online). Also, the patients who were anti-TIF1-γ-positive had a lower mean pulmonary MDAAT score ($P = 0.008$) and there was a lower number of patients with active ILD ($P = 0.02$).

TIS response

The percentages of patients with a positive TIS outcome at weeks 16 and 40 are shown in Table 2 for each of the antibody groups. At week 16, 37 of 47 (79%) patients in the IVIg group *vs* 21 of 48 (44%) patients in the placebo group showed minimal or more improvement (TIS $\geq$20; $P < 0.001$), as shown previously [11]. In addition, 32 of 47 (68%) patients in the IVIg group *vs* 11 of 48 (23%) patients in the placebo group showed moderate/major improvement (TIS $\geq$40). At week 40, when all patients had received IVIg, ~70% of patients in each group showed at least minimal improvement and ~60% of patients in both groups showed moderate/major improvement.

At week 16, significantly more patients with MSA showed minimal or more improvement than patients with MAA ($P = 0.03$); however, a higher percentage of patients with MAA *vs* those with MSA were on placebo and had not

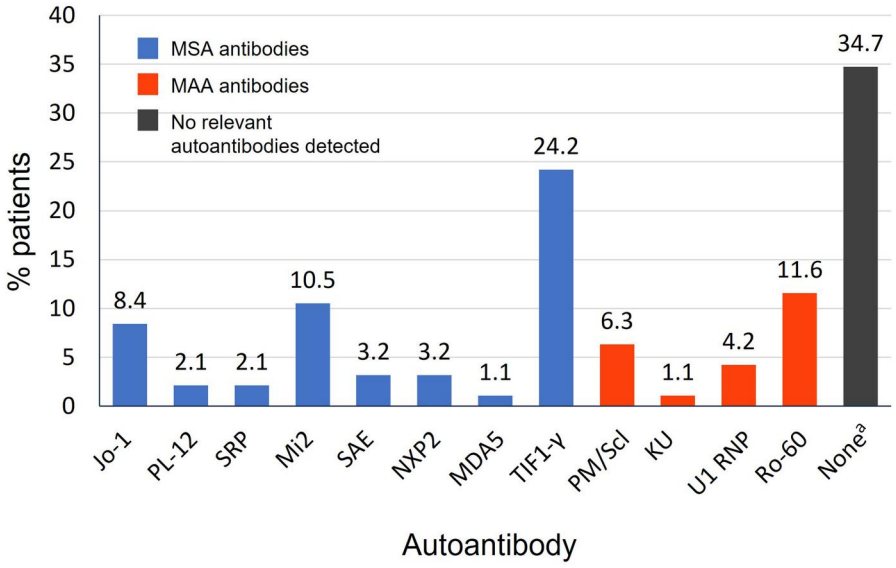

Figure 1. Numbers of dermatomyositis patients with myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) ($n = 95$). Patients may have been positive for more than one autoantibody type and therefore the percentage of patients totals more than 100%. All patients in the study were negative for the following autoantibodies: PL-7, OJ, EJ, U2 RNP, U3 RNP, RNA-Pol, KS, FER, MiTO, RIBO-P and U5 RNP. [a]No relevant autoantibodies detected. MAA: myositis-associated antibodies; MSA: myositis-specific antibodies

Table 1. Demographics

	MSA-positive[a] ($n = 49$)	MAA-positive[b] ($n = 13$)	No relevant autoantibodies detected ($n = 33$)	*P*-value
Age, mean (range), years	51.4 (22–79)	53.7 (33–70)	54.2 (28–77)	0.62[c]
Time since diagnosis, mean (range), years	3.66 (0.16–15.6)	5.04 (0.39–18.4)	5.8 (0.09–48.7)	0.62[d]
Sex, *n* (% female)	39 (79.6)	11 (84.6)	21 (63.6)	0.18[e]
Race, *n* (% White)	42 (85.7)	13 (100.0)	32 (97.0)	0.15[f]
BMI, mean (S.D.), kg/m^2	27.0 (5.0)	29.8 (6.0)	26.5 (4.1)	0.12[c]
Disease activity, *n* (%)				0.55[e]
Mild	10 (20.4)	4 (30.8)	12 (36.4)	
Moderate	31 (63.3)	8 (61.5)	17 (51.5)	
Severe	8 (16.3)	1 (7.7)	4 (12.1)	
Dysphagia, *n* (%)	20 (40.8)	8 (61.5)	10 (30.0)	0.15[e]
Arthritis, *n* (%)	15 (30.6)	7 (54.9)	13 (39.4)	0.28[e]
Mechanic's hand, *n* (%)	16 (32.7)	9 (69.2)	14 (42.4)	0.06[e]
Active ILD, *n* (%)	9 (20.9)	1 (10.0)	1 (3.5)	0.07[f]
Physician global disease activity, mean (S.D.)	5.2 (1.7)	4.3 (1.7)	4.9 (1.8)	0.22[c]
Patient global disease activity, mean (S.D.)	5.8 (2.1)	5.4 (1.5)	6.0 (1.3)	0.63[c]
MDAAT score, mean (S.D.)				
Cutaneous	4.3 (2.6)	3.4 (2.2)	4.6 (2.0)	0.21[d]
Skeletal	1.5 (1.9)	2.0 (2.0)	2.4 (2.1)	0.15[d]
GI	0.7 (1.4)	1.6 (2.2)	0.9 (1.7)	0.26[d]
Pulmonary	1.1 (1.6)	1.0 (1.7)	1.2 (2.1)	0.47[d]
Muscle	3.7 (1.5)	2.8 (2.9)	4.4 (2.4)	0.47[d]
CDASI activity score, mean (S.D.)	21.5 (14.8)	14.5 (8.4)	16.7 (13.2)	0.16[d]
CDASI damage score, mean (S.D.)	3.4 (4.2)	1.8 (2.1)	1.8 (2.3)	0.28[d]
MMT-8, mean (S.D.)	126 (16)	120 (16)	114 (22)	**0.01**[c]
HAQ score, mean (S.D.)	1.29 (0.65)	1.30 (0.55)	1.34 (0.75)	0.94[c]
SF-36 mental, mean (S.D.)				
Mental	44.4 (12.2)	42.6 (10.3)	44.2 (12.2)	0.89[c]
Physical	38.3 (9.3)	34.7 (6.0)	34.7 (8.1)	0.13[c]
Randomized treatment, *n* (%)				0.26[e]
IVIg	24 (49.0)	4 (30.8)	19 (57.6)	
Placebo	25 (51.0)	9 (69.2)	14 (42.4)	

[a] 10 patients positive for MSA were also positive for MAA.
[b] MAA-positive group contains only patients with MAA (no MSA).
[c] Analysis using analysis of variance (ANOVA).
[d] Analysis using Kruskal–Wallis test.
[e] Analysis using χ^2 test.
[f] Analysis using Fisher's exact test.

Bold text indicates statistical significance ($P < 0.05$). BMI: body mass index; CDASI: Cutaneous Disease Area and Severity Index; HAQ: health assessment questionnaire; GI: gastrointestinal; ILD: interstitial lung disease; IVIg: intravenous immunoglobulin; MAA: myositis-associated antibodies; MDAAT: myositis disease activity assessment tool; MMT-8: manual muscle-testing-8 (tool); MSA: myositis-specific antibodies; SF-36: short form-36 (questionnaire).

received IVIg treatment (69% of the MAA group *vs* 51% of the MSA group). Moreover, there was no significant difference between the proportion of patients with MSA *vs* patients without autoantibodies who showed minimal or more improvement at week 16 ($P = 0.12$).

By week 40, when all patients had received IVIg, there was no significant difference between the proportions with minimal or more improvement among patients with MSA (33/47; 70%), MAA (6/13; 46%) and patients without myositis antibodies (25/31; 81%) ($P = 0.07$).

Univariate analysis

Univariate analyses examined the associations between baseline variables and at least minimal or moderate/major improvement in TIS, at weeks 16 and 40. There was no significant association between the following baseline variables and either level of improvement, at week 16 or week 40: age; sex; ethnicity; disease duration or activity; dermatomyositis diagnosis; MDAAT score for the skeletal, gastrointestinal or muscle domains; MMT-8 or HAQ score; CDASI activity or damage scores; previous medications; presence of dysphagia, mechanic's hand, ILD or Raynaud's syndrome; blood tests; and venous thromboembolism risk factors. Significant associations found in each analysis are described below.

Analysis 1: at least minimal improvement at week 16

In univariate analyses examining the associations between baseline variables and at least minimal improvement in TIS at week 16 (Table 3), a significant association was found with any improvement at week 16 for the study group, antibody classification 3 (i.e. antibody-negative, anti-synthetase, TIF1-γ, other MSA, and MAA), MDAAT cutaneous and pulmonary scores, and extra-muscular global disease activity.

At week 16, the odds of at least minimal TIS improvement were more than four times higher for patients in the IVIg group *vs* the placebo group (odds ratio, 4.76). Patients with anti-TIF1-γ antibodies had a higher occurrence of at least minimal improvement in TIS than any other antibody type or classification, with 83% demonstrating improvement.

Higher baseline MDAAT cutaneous scores were associated with a higher occurrence of improvement at week 16. A 1-cm greater MDAAT cutaneous score was associated with a 25% increase in the odds of improvement. Conversely, higher baseline MDAAT pulmonary scores were associated with a lower level of improvement; a 1-cm greater score was associated with

Table 2. Association between autoantibody group and TIS outcome

	TIS outcome occurred, *n*/*N* (%)				*P*-value		
	All patients	MSA+	MAA+	Antibodies not detected	Overall	MSA+ *vs* MAA+	MSA+ *vs* antibodies not detected
Minimal or more improvement[a] at week 16							
All patients	58/95 (61)	35/49 (71)	5/13 (38)	18/33 (55)	0.06	**0.03**	0.12
Placebo group	21/48 (44)	15/25 (60)	3/9 (33)	3/14 (21)	0.05	0.17	**0.02**
IVIg group	37/47 (79)	20/24 (83)	2/4 (50)	15/19 (79)	0.32	0.13	0.71
Moderate/major improvement[b] at week 16							
All patients	43/95 (45)	27/49 (55)	4/13 (31)	12/33 (36)	0.13	0.12	0.10
Placebo group	11/48 (23)	9/25 (36)	2/9 (22)	0/14 (0)	**0.04**	0.45	**0.01**
IVIg group	32/47 (68)	18/24 (75)	2/4 (50)	12/19 (63)	0.51	0.31	0.40
Minimal or more improvement[a] at week 40							
All patients	64/91 (70)	33/47 (70)	6/13 (46)	25/31 (81)	0.07	0.11	0.30
Placebo group[c]	32/46 (70)	18/24 (75)	5/9 (56)	9/13 (69)	0.56	0.28	0.71
IVIg group	32/45 (71)	15/23 (65)	1/4 (25)	16/18 (89)	**0.03**	0.13	0.08
Moderate/major improvement[b] at week 40							
All patients	54/91 (59)	31/47 (66)	6/13 (46)	17/31 (55)	0.36	0.19	0.32
Placebo group[c]	28/46 (61)	18/24 (75)	5/9 (56)	5/13 (38)	0.09	0.28	**0.03**
IVIg group	26/45 (58)	13/23 (57)	1/4 (25)	12/18 (67)	0.31	0.24	0.51

[a] 'Minimal or more improvement' defined as score of 20 or higher.
[b] 'Moderate/major improvement' defined as score of 40 or higher.
[c] Patients on placebo switched to IVIg from week 16.
Bold text indicates statistical significance ($P < 0.05$). IVIg: intravenous immunoglobulin; MAA: myositis-associated antibodies; MSA: myositis-specific antibodies; TIS: total improvement score.

the odds of improvement reducing by around a third. Higher baseline values for extra-muscular global disease activity were associated with a greater occurrence of at least minimal improvement in TIS; every 1-cm greater score was associated with a 27% increase in the odds of improvement.

Analysis 2: moderate/major improvement at week 16

Univariate analyses also examined the association between baseline variables and moderate/major improvement in TIS at week 16 (Supplementary Table S2, available at *Rheumatology* online). When examined individually, there was a significant association with moderate/major improvement at week 16 for the study group, MDAAT cutaneous and pulmonary scores, higher global disease activity by physician assessment and SF-36 mental score.

Analysis 3: at least minimal improvement at week 40

Univariate analyses examined the association between baseline variables with at least minimal improvement in TIS at week 40 (Supplementary Table S3, available at *Rheumatology* online). Antibody classifications 3 (antibody-negative, MSA, MAA and MSA+MAA) and 4 (antibody-negative, anti-synthetase [i.e. Jo-1 and PL-12], TIF1, Mi-2, other MSA [i.e. MSA autoantibodies other than anti-TIF1-γ, anti-Mi-2, anti-Jo-1 and anti-PL-12] and MAA), creatine kinase, arthritis and IgG level were all significantly associated with at least minimal improvement at week 40.

Analysis 4: moderate/major improvement at week 40

Univariate analyses also examined the association between baseline variables with moderate/major improvement in TIS at week 40 (Supplementary Table S4, available at *Rheumatology* online). When examined individually, there was a significant association with moderate/major improvement at week 40 for arthritis and IgG level (on a continuous scale).

Multivariate analysis

Analysis 1: at least minimal improvement at week 16

The association between baseline variables with at least minimal improvement in TIS at week 16 was examined in a multivariate analysis (Table 4). As in the univariate analyses, the final multivariable model demonstrated that patients in the IVIg group and those with higher MDAAT cutaneous scores had a higher chance of improvement, whilst a higher MDAAT pulmonary score was associated with a lower chance of improvement. Odds of improvement in the IVIg group were over five times higher than for the placebo group. A one-unit increase in cutaneous score was associated with an approximate 25% increase in the odds of improvement, whilst a one-unit increase in pulmonary score was associated with only 0.68 times the odds of improvement. Patients with MSA were most likely to improve at week 16 compared with those with MAA or no relevant autoantibodies. The odds of improvement were over three times higher in this cohort than the odds for patients in whom no relevant autoantibodies were detected.

Alternative multivariate models of the association between baseline variables with at least minimal improvement in TIS at week 16 showed that after adjusting for the significant factors, there was no strong evidence that antibody classification was associated with TIS improvement at week 16 (Supplementary Table S5, available at *Rheumatology* online).

Analysis 2: moderate/major improvement at week 16

Multivariate models described the association between baseline variables and moderate/major improvement in TIS at week 16 (Supplementary Table S6, available at *Rheumatology* online). Study group, MDAAT pulmonary score, physician's global assessment of disease activity and SF-36 mental score were associated with moderate/major improvement at week 16. After adjusting for these variables, there was no additional effect of MDAAT cutaneous score, which was significant in the univariable analyses. None of the four antibody classifications were significantly associated

Table 3. Association of variables with at least minimal improvement in TIS[a] at week 16

Variable	Improvement, *n*/*N* (%)	Odds ratio (95% CI)	*P*-value
Study group			
Placebo	21/48 (44)	1	**0.001**
IVIg	37/47 (79)	4.76 (1.93, 11.7)	
Age[b]	—	1.03 (0.76, 1.41)	0.83
Age at diagnosis[b]	—	1.03 (0.77, 1.37)	0.86
Sex			
Female	43/71 (61)	1	0.87
Male	15/24 (63)	1.09 (0.42, 2.82)	
Ethnicity			
Not Hispanic/Latino	55/90 (61)	1	0.96
Hispanic/Latino	3/5 (60)	0.95 (0.15, 6.00)	
Disease duration			
≤1 year	19/25 (76)	1	0.14
1–5 years	23/44 (52)	0.35 (0.12, 1.03)	
>5 years	16/26 (62)	0.51 (0.15, 1.70)	
Dermatomyositis diagnosis			
Probable	17/28 (61)	1	0.97
Definite	41/67 (61)	1.02 (0.41, 2.52)	
Antibodies (classification 1)			
Antibody negative	18/33 (55)	1	0.06
MSA	35/49 (71)	2.08 (0.83, 5.24)	
MAA	5/13 (38)	0.52 (0.14, 1.93)	
Antibodies (classification 2)			
Antibody negative	18/33 (55)	1	0.11
MSA	30/41 (73)	2.27 (0.86, 6.01)	
MAA	5/13 (38)	0.52 (0.14, 1.93)	
MSA + MAA	5/8 (63)	1.38 (0.28, 6.79)	
Antibodies (classification 3)			
Antibody negative	18/33 (55)	1	**0.04**
Anti-synthetase	4/9 (44)	0.67 (0.15, 2.94)	
TIF1-γ	19/23 (83)	3.96 (1.10, 14.2)	
Other MSA[c]	12/17 (71)	2.00 (0.57, 6.97)	
MAA	5/13 (38)	0.52 (0.14, 1.93)	
Antibodies (classification 4)			
Antibody negative	18/33 (55)	1	0.07
Anti-synthetase	4/9 (44)	0.67 (0.15, 2.94)	
TIF1-γ	19/23 (83)	3.96 (1.10, 14.2)	
Mi-2	6/8 (75)	2.50 (0.44, 14.3)	
Other MSA[d]	6/9 (67)	1.67 (0.36, 7.82)	
MAA	5/13 (38)	0.52 (0.14, 1.93)	
Disease activity			
Mild (0–3)	12/26 (46)	1	0.19
Moderate (4–6)	37/56 (66)	2.27 (0.80, 5.87)	
Severe (7–10)	9/13 (69)	2.63 (0.64, 10.7)	
MDAAT cutaneous	—	1.25 (1.04, 1.51)	**0.02**
MDAAT skeletal	—	0.98 (0.80, 1.21)	0.85
MDAAT GI	—	0.88 (0.68, 1.13)	0.31
MDAAT pulmonary	—	0.68 (0.53, 0.88)	**0.003**
MDAAT muscle[e]	—	0.81 (0.54, 1.22)	0.32
Activity—physician	—	1.23 (0.95, 1.58)	0.12
Activity—patient	—	1.08 (0.85, 1.37)	0.52
Extra-muscular disease	—	1.27 (1.01, 1.60)	**0.04**
MMT-8 score[b]	—	1.09 (0.87, 1.35)	0.46
HAQ score	—	0.82 (0.44, 1.52)	0.52
Creatine kinase[f]	—	0.65 (0.31, 1.37)	0.26
Creatine kinase (categorical)			
<ULN	36/53 (68)	1	0.13
≥ULN	22/42 (52)	0.52 (0.23, 1.20)	
No. DM medications taken at baseline	—	1.21 (0.61, 2.41)	0.58
No. failed immunosuppressives[g]	—	0.98 (0.69, 1.39)	0.91
Baseline glucocorticoid dose[b]	—	0.69 (0.38, 1.26)	0.23
Dysphagia			
No	35/57 (61)	1	0.93
Yes	23/38 (61)	0.96 (0.42, 2.24)	
Arthritis			
No	38/60 (63)	1	0.55
Yes	20/35 (57)	0.77 (0.33, 1.81)	

(continued)

Table 3. (continued)

Variable	Improvement, *n*/*N* (%)	Odds ratio (95% CI)	*P*-value
Mechanic's hand			
No	38/56 (68)	1	0.11
Yes	20/39 (51)	0.50 (0.21, 1.16)	
Active ILD[h]			
No	50/76 (66)	1	0.24
Yes	3/7 (43)	0.39 (0.08, 1.87)	
IgG[i]	—	1.01 (0.50, 2.06)	0.97
IgG (categorical)			
<LLN (7 g/l)	6/10 (60)	1	0.94
≥LLN (7 g/l)	52/85 (61)	1.05 (0.28, 4.00)	
Haemoglobin[b]	—	1.04 (0.76, 1.42)	0.80
Leukocytes[j,k]	—	0.84 (0.42, 1.65)	0.60
Platelets[k,l]	—	0.98 (0.72, 1.33)	0.90
Creatinine[b]	—	0.99 (0.76, 1.28)	0.92
Raynaud's syndrome			
No	58/93 (62)	—	—
Yes	0/2 (0)	—	—
CDASI activity[j]	—	1.14 (0.96, 1.34)	0.13
CDASI damage[j]	—	1.30 (0.69, 2.45)	0.41
SF-36 mental[b]	—	1.23 (0.87, 1.76)	0.24
SF-36 physical[b]	—	1.18 (0.73, 1.91)	0.51
Baseline VTE risk factors			
0	34/50 (68)	1	0.22
1	14/29 (48)	1.05 (0.17, 1.12)	
2 or 3	10/16 (63)	0.78 (0.24, 2.54)	

[a] At least minimal improvement defined as TIS ≥20.
[b] Odds ratio given for a 10-unit increase.
[c] 'Other MSA' includes patients with MSA autoantibodies but excludes those with anti-synthetase autoantibodies (i.e. anti-Jo-1 and anti-PL-12) and anti-TIF1-γ autoantibodies.
[d] 'Other MSA' includes patients with MSA autoantibodies but excludes those with anti-synthetase (i.e. anti-Jo-1 and anti-PL-12), anti-TIF1-γ, and anti-Mi-2 autoantibodies.
[e] Analysis performed on data from 26 patients only (due to missing data).
[f] Variable analysed on the log scale (to base 10).
[g] Immunosuppressive drugs taken previously and stopped plus immunosuppressive drugs taken at baseline.
[h] Analysis performed on data from 83 patients only (due to missing data).
[i] Odds ratio given for one multiple of Lower Limit of Normal (7 g/l).
[j] Odds ratio given for a 5-unit increase.
[k] Analysis performed on data from 94 patients only (due to missing data).
[l] Odds ratio given for a 50-unit increase.
CDASI: cutaneous dermatomyositis disease area and severity index; GI: gastrointestinal; HAQ: health assessment questionnaire; IgG: immunoglobulin G; ILD: interstitial lung disease; IVIg: intravenous immunoglobulin; LLN: lower limit of normal; MDAAT: myositis disease activity assessment tool; MMT-8: manual muscle-testing-8 (tool); *n*: number of patients showing improvement; *N*: number of patients in the group; SF-36: short form-36 (questionnaire); TIF1: transcriptional intermediary factor 1; TIS: total improvement score; VTE: venous thromboembolism.

Table 4. Final multivariate model for predicting at least minimal improvement in TIS[a] at week 16 (analysis 1)

Variable	Odds ratio (95% CI)	*P*-value
Study group		
Placebo	1	0.001
IVIg	5.54 (1.94, 15.8)	
MDAAT cutaneous	1.24 (1.00, 1.55)	0.05
MDAAT pulmonary	0.68 (0.51, 0.91)	0.009
Antibodies (classification 1)		
Antibody negative	1	0.06
MSA	3.28 (1.07, 10.1)	
MAA	0.85 (0.19, 3.80)	

[a] At least minimal improvement defined as TIS ≥20. IVIg: intravenous immunoglobulin; MAA: myositis-associated antibodies; MDAAT: myositis disease activity assessment tool; MSA: myositis-specific antibodies; TIS: total improvement score.

with moderate/major improvement at week 16 after adjusting for the other variables in the analysis.

Analysis 3: at least minimal improvement at week 40

Multivariate models described the association between baseline variables and at least minimal improvement in TIS at week 40 (Supplementary Table S7, available at *Rheumatology* online). Creatine kinase, arthritis, IgG and SF-36 mental score were all independently associated with any improvement at week 40.

Antibody classifications 3 and 4 were associated with at least minimal improvement at week 40, although the results were of borderline significance for classification 4 (Supplementary Table S7, available at *Rheumatology* online). For classification 3, the greatest improvement was in the anti-TIF1-γ group, with the lowest level of improvement in the anti-synthetase, other MSA and MAA groups. Similar results were observed for classification 4, with the anti-TIF1-γ group again having the highest occurrence of improvement.

Analysis 4: moderate/major improvement at week 40

Finally, multivariate models described the association between baseline variables with moderate/major improvement in TIS at week 40 (Supplementary Table S8, available at *Rheumatology* online). Age and IgG were significantly associated with moderate/major improvement in TIS at week 40. Age was not significant in the univariable analysis, but reached significance in the multivariable analysis. Arthritis, which was significant in the univariable analysis, was not significant in this analysis. After adjusting for the other factors in the models, there was no evidence that antibody

Table 5. Association between specific autoantibodies/autoantibody groups and TIS outcome

Timepoint and improvement	Outcome occurred, *n/N* (%)		*P*-value
	Antibody negative	Antibody positive	
Anti-synthetase[a]			
Week 16			
Minimal or more[b]	54/85 (64)	4/10 (40)	0.15
Moderate/major[c]	40/85 (47)	3/10 (30)	0.31
Week 40			
Minimal or more[b]	60/82 (73)	4/9 (44)	0.07
Moderate/major[c]	50/82 (61)	4/9 (44)	0.34
Anti-Mi-2			
Week 16			
Minimal or more[b]	50/85 (59)	8/10 (80)	0.19
Moderate/major[c]	37/85 (44)	6/10 (60)	0.32
Week 40			
Minimal or more[b]	60/82 (73)	4/9 (44)	0.07
Moderate/major[c]	50/82 (61)	4/9 (44)	0.34
Anti-TIF1-γ			
Week 16			
Minimal or more[b]	41/74 (55)	17/21 (81)	**0.03**
Moderate/major[c]	30/74 (41)	13/21 (62)	0.08
Week 40			
Minimal or more[b]	45/70 (64)	19/21 (90)	**0.02**
Moderate/major[c]	36/70 (51)	18/21 (86)	**0.005**

[a] Anti-synthetase antibodies included Jo-1 and PL-12.
[b] Minimal or more improvement defined as TIS ≥20.
[c] Moderate/major improvement defined as TIS ≥40.
MAA: myositis-associated antibodies; MSA: myositis-specific antibodies; TIF1: transcriptional intermediary factor 1; TIS: total improvement score.

classification was significantly associated with moderate/major improvement in TIS at week 40.

Association between specific antibodies and TIS outcome

The associations between the three antibody groups (MSA, MAA and no relevant antibodies), as well as specific antibodies, with TIS outcome are shown in Table 5. For this analysis, the two patients who were positive for both anti-Mi-2 and anti-TIF1-γ were considered as positive for anti-Mi-2 and negative for anti-TIF1-γ. There was no significant difference in TIS outcome between patients with/without anti-synthetase antibodies (i.e. anti-Jo-1 or anti-PL-12) or those with/without anti-Mi-2 antibodies, and improvement in TIS at week 16 or week 40. However, significantly more patients with anti-TIF1-γ antibodies (both IVIg and placebo groups included) demonstrated at least minimal improvement in TIS at week 16 and at least minimal or moderate/major improvement at week 40.

Prompted by the finding that patients with higher cutaneous disease activity and/or anti-TIF1-γ antibodies responded best to IVIg, we examined if patients who were positive for anti-TIF1-γ had higher cutaneous scores at baseline. The 23 patients who were anti-TIF1-γ-positive had a mean (S.D.) baseline CDASI-A score of 26.8 (15.8), whereas the 29 patients who were negative for anti-TIF1-γ had a mean score of 9.5 (6.6). Despite this difference, however, after controlling for cutaneous disease activity, there was no significant association between antibody classification, including TIF1-γ, and TIS in our study (Supplementary Table S4, available at *Rheumatology* online).

Discussion

Results from this analysis demonstrated that patients with DM responded to IVIg irrespective of age, gender, ethnicity, disease duration or activity, baseline glucocorticoid dose, drugs received at baseline, and the number of failed treatments. Although patients with anti-TIF1-γ antibodies or higher cutaneous disease activity responded best to IVIg treatment, and patients with higher pulmonary disease activity had a lower response to IVIg, patients in all categories, including those with MAA or no relevant autoantibodies, responded to IVIg treatment.

Of patients in the ProDERM study, 51.6% were positive for MSA and 24.2% were positive for MAA. In the literature there is high variability in reports of DM-associated autoantibody prevalence. For example, in a study of 222 patients with DM, MSA were detected in 34.4% of patients and MAA were detected in 41.4% of patients [19], while 80–90% of DM patients were found to have MSA using sensitive assays in a different cohort [20]. Further, MSA are associated with certain HLA haplotypes; for example, TIF1-γ is associated with DQB1*02:02 in Caucasian adults [21], and hence variability is expected among different ethnic populations.

For patients in this study, higher levels of cutaneous disease activity and muscle weakness, and lower levels of pulmonary involvement and ILD, were seen in DM patients with anti-TIF1-γ antibodies *vs* those who were positive for MSA and negative for anti-TIF1-γ. Our results align with those from a systematic review of 1065 DM patients with anti-TIF1-γ, which found that of patients without malignancy, cutaneous symptoms were common, especially Gottron's sign (56.3%), heliotrope rash (75%) and nailfold capillary changes (31.3%), as well as muscle weakness (58.3%) [22]. Similarly, a retrospective study that included 14 anti-TIF1-γ-positive DM patients (12 with malignancies) found that cutaneous manifestations and dysphagia were the most common symptoms in these patients, with no patients presenting with ILD [8].

Previously, a machine learning analysis evaluating treatment response of patients with IIM showed resolution of

cutaneous symptoms, including heliotrope rash and periungual erythema, with immunoglobulin therapy [23]. We found that patients with high cutaneous disease activity and those who had TIF1-γ antibodies had a better TIS response to IVIg treatment. However, after controlling for cutaneous disease activity, there was no significant association between antibody classification, including TIF1-γ, and efficacy outcome in this study.

Although the number of patients was small, we also report that patients with MAA responded less favourably at week 16 than those with MSA or no detectable autoantibodies. This may have been due to more patients with MAA being on placebo during the randomized phase.

In this study, patients with a higher baseline level of pulmonary disease activity had a less robust response to IVIg treatment, perhaps representing a more refractory subset. Of note, the majority of patients in ProDERM did not exhibit pulmonary symptoms at baseline, and the overall level of pulmonary disease in this cohort was low.

Limitations of this study included that a Bonferroni correction was not performed due to the hypothesis-generating nature of the analysis. Multiple antibody analyses were performed on different groups of patients, due to the focus of autoantibodies as the area for investigation, but with low numbers of patients for some analysis groups; for example, patients with MAA on IVIg. Also, the study assessed only a limited panel of autoantibodies, and types including anti-Ro-52 were not included. In addition, autoantibody tests were qualitative, with no quantitative assessments performed, and autoantibody status was not re-tested at the end of the study to determine whether clinical improvement was associated with longitudinal changes. Finally, differential effects of autoantibodies on muscle, skin and other organs were not evaluated.

Despite these limitations, this was a prospective, long-term study that comprehensively and systematically analysed the association of demographics, clinical and laboratory features, as well as autoantibody status, with treatment response to IVIg, which is of value to understanding which patients with DM respond best to IVIg.

Conclusions

IVIg was effective in treating patients with DM across many demographic features, including age, gender and ethnicity, as well as disease duration and activity, and regardless of tested autoantibody positivity or negativity. No significant difference was seen in the percentage of patients with MSA *vs* those with no relevant autoantibodies, who responded to IVIg. Patients with higher cutaneous disease activity and/or anti-TIF1-γ antibodies responded best to IVIg, while pulmonary disease activity predicted a lower, but still effective, IVIg response, which warrants further investigation.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Access to the data underlying this paper is tightly governed by various legislative and regulatory frameworks. De-identified clinical and laboratory data and response to treatment data for the study cohort included in this study can only be made available to legitimate researchers and clinicians from medical and academic institutions, for academic and clinical research on request to Octapharma Pharmazeutika Produktionsges.m.b.H. A proposal with a detailed description of study objectives and a statistical analysis plan will be requested. The proposal will be evaluated based on European and international data protection regulations and regulations about secondary use of patient data. After approval of a proposal, de-identified data will be shared through a secure online platform upon signing a data processing agreement. The study protocol, statistical analysis plan and main results are available at https://clinicaltrials.gov/ct2/show/NCT02728752.

Contribution statement

Christina Charles-Schoeman, Joachim Schessl and Rohit Aggarwal: Conceptualization, Methodology, Investigation, Resources, Writing—review & editing, Supervision. Elisabeth Clodi: Project administration, Funding acquisition, Writing—review & editing, Resources. Zsuzsanna Bata-Csörgő, Mazen M. Dimachkie, Zoltan Griger, Sergey Moiseev, Chester V. Oddis, Elena Schiopu, Jiri Vencovský, Todd Levine: Investigation, Resources, Writing—review & editing.

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