



ORIGINAL RESEARCH

# Efficacy of Intravenous Immunoglobulin for Systemic Manifestations of Dermatomyositis Beyond Muscular and Cutaneous: Sub-analysis of the ProDERM Study

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## ABSTRACT

**Introduction:** Muscle and skin involvement are well defined in dermatomyositis but other symptoms contribute significantly to the disease burden and their treatment is not well characterized. This post hoc analysis of ProDERM assessed the effect of intravenous immunoglobulin (IVIg)

Rohit Aggarwal and Joachim Schessl were dual first authors and contributed equally to this work.

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treatment on other manifestations of dermatomyositis beyond muscular and cutaneous involvement.

**Methods:** ProDERM was a randomized, placebo-controlled study. For weeks 0–16, patients with dermatomyositis received 2.0 g/kg IVIg (Octagam, 10%) or placebo every 4 weeks. Eligible patients entered the open-label extension, where all received IVIg to week 40. Pulmonary, skeletal, constitutional, gastrointestinal, and cardiovascular disease activity was assessed using the myositis disease activity assessment tool, comprising a visual analog scale (VAS; 0–10 cm) and myositis intention-to-treat activity index.

**Results:** Of 95 patients enrolled, 47 received IVIg and 48 received placebo to week 16. At baseline, 37.9% of patients experienced pulmonary, 64.2% experienced skeletal, 76.8% experienced constitutional, 33.7% experienced gastrointestinal, and 15.8% experienced cardiovascular involvement (VAS>0.5). Among these patients,

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for those on IVIg, the following mean VAS scores decreased from baseline to week 16: pulmonary (37.7%;  $P=0.001$ ), skeletal (52.6%;  $P<0.001$ ), constitutional (44.4%;  $P<0.001$ ), and gastrointestinal (49.2%;  $P=0.005$ ). No corresponding improvement was seen with placebo except for constitutional VAS. With IVIg, the proportions of patients with arthritis (36.2 to 17.8%;  $P=0.01$ ), arthralgia (68.1 to 0.0%;  $P<0.001$ ), and fatigue (68.1 to 3.3%;  $P=0.008$ ) decreased from baseline to week 16. In the combined cohort, the proportions of patients with dysphonia (20.0 to 8.1%;  $P=0.04$ ), arthralgia (66.3 to 39.8%;  $P<0.001$ ), weight loss (10.5 to 3.4%;  $P=0.04$ ), fatigue (75.8 to 50.0%;  $P<0.001$ ), and dysphagia (40.0 to 18.4%;  $P<0.001$ ) decreased from baseline to week 40.

**Conclusion:** IVIg was effective in treating pulmonary, skeletal, constitutional, and gastrointestinal manifestations of dermatomyositis. We advocate exploring IVIg as treatment for dermatomyositis, beyond muscle and skin manifestations.

**Trial Registration:** ClinicalTrials.gov identifier, NCT02728752.

**Keywords:** Arthritis; Arthralgia; Dermatomyositis; Constitutional; Gastrointestinal; Immunoglobulins; Intravenous; Pulmonary; Octagam; Skeletal

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## Key Summary Points

### *Why carry out this study?*

In dermatomyositis, muscle and skin involvement are well defined but other symptoms contribute significantly to the disease burden and their treatment is not well characterized.

This post hoc analysis of the ProDERM study assessed the effect of intravenous immunoglobulin (IVIg) treatment on other manifestations of dermatomyositis beyond muscular and cutaneous involvement.

### *What was learned from the study?*

Pulmonary, skeletal, constitutional, and gastrointestinal involvement decreased with IVIg treatment, as assessed on the myositis disease activity assessment tool visual analog scale, and the proportions of patients with arthritis, arthralgia, and fatigue decreased in patients on IVIg.

We advocate exploring IVIg as treatment for dermatomyositis, beyond muscle and skin manifestations.

## INTRODUCTION

Dermatomyositis (DM) is an inflammatory myopathy typically characterized by progressive muscle weakness and skin symptoms, which is estimated to affect between one and 21 people per 100,000 of the US population [1–3]. Muscle and skin involvement have been well characterized in patients with DM and numerous studies have examined the efficacy of therapies for treatment of these symptoms [4]. However, clinical involvement of other systems, including pulmonary, skeletal, gastrointestinal (GI), constitutional, and cardiovascular, plays a significant role in the disease burden of DM and, moreover, the effects of treatments on these systems are not well characterized.

Pulmonary manifestations are estimated to affect 21–80% of patients with DM [5, 6] and they are associated with increased morbidity

and mortality [7, 8]. In particular, interstitial lung disease (ILD) is a severe manifestation of DM estimated to affect 35–40% of patients with inflammatory myopathies and is linked to poor prognosis and early mortality [9]. Joint involvement, such as arthritis and arthralgia, is also reported in patients with DM. Arthralgia is thought to be an early symptom of DM and is estimated to affect around one-third of patients with DM [10]. Constitutional manifestations are also common; in a study of 564 individuals with myositis, 78% reported extreme fatigue or exhaustion [11]. Fatigue has a profound negative impact on quality of life; however, treatment of this aspect remains challenging and the effectiveness of various interventions has been reported as “very poor” [12].

GI involvement in patients with DM occurs as a result of loss of pharyngoesophageal muscle tone, leading to upper-third esophageal dysmotility. In patients with DM, the most common GI manifestation is early-phase swallowing dysphagia, affecting around two-thirds of patients with active disease [13]. Although the majority of GI involvement in DM is mild, GI symptoms can be life-threatening in severe cases [13]. Cardiovascular involvement is well established in patients with DM, with clinical symptoms caused by coronary artery disease and myocarditis [14]. Myocardial symptoms in patients with inflammatory myopathies are an unfavorable prognostic factor and a common cause of mortality in patients with DM [15, 16].

Treatment for the symptoms of DM has historically involved first-line therapy with glucocorticoids, followed by immunosuppressants. As a result of the rarity of DM, and wide range of its manifestations, there have been no large, randomized trials to investigate the efficacy of treatments for the majority of symptoms beyond those affecting muscle and skin.

Recently, intravenous immunoglobulin (IVIg) therapy was shown to be efficacious and have a favorable safety profile in a placebo-controlled, double-blind, multicenter, phase 3 study (ProDERM) in adult patients with DM [17, 18]. The primary endpoint of ProDERM was the efficacy of IVIg, as demonstrated by significant improvement in the Total Improvement Score (TIS), a weighted composite score reflecting the

change in six core measures of myositis activity over time [17–19]. ProDERM included use of the Myositis Disease Activity Assessment Tool (MDAAT), a validated clinical instrument designed to evaluate disease activity in patients with myositis. One of its key components is a visual analog scale (VAS), which quantifies overall myositis disease activity in various organ systems/domains, including pulmonary, skeletal, constitutional, GI, and cardiovascular (in addition to cutaneous) [20]. In addition, MDAAT specifically quantifies commonly occurring symptoms of DM beyond muscular and cutaneous, such as ILD, arthralgia, fatigue, and dysphagia.

We performed a post hoc analysis of data from the ProDERM study to assess the effect of IVIg specifically on pulmonary, skeletal, constitutional, GI, and cardiovascular symptoms of dermatomyositis.

## METHODS

ProDERM (NCT02728752) was a prospective, phase 3, double-blind, parallel-group, randomized, placebo-controlled study of IVIg treatment in patients with DM [17, 18].

### Ethical Approval

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. ProDERM was approved by the relevant independent ethics committees or institutional review boards, as listed in the Ethics Committees section of the Supplementary Material. Each patient provided written, informed consent before being exposed to any study-related procedure, including screening tests for eligibility [17, 18]. Specific consent for publication was not provided as all data in this international study (from 36 European and North American centers) is fully anonymized.

### Patients

The ProDERM study included patients aged  $\geq 18$  to  $< 80$  years with definite or probable DM according to Bohan and Peter criteria [21, 22],

with active disease, who were on concomitant immunosuppression [17]. The study excluded patients with cancer-associated myositis, or evidence of active malignant disease within the previous 5 years. Inclusion and exclusion criteria have been described in full previously [17].

## Study Design

The study protocol has been described in detail [18]. In summary, the ProDERM study involved two periods. In the first period, from weeks 0 to 16, participants were randomized 1:1 to receive 2.0 g/kg IVIg (Octagam 10%; Octapharma AG) or placebo (0.9% sodium chloride) every 4 weeks [18].

All patients, except those who had confirmed deterioration while receiving IVIg, could continue into the open-label extension phase from weeks 16 to 40, during which all eligible patients received 2.0 g/kg IVIg for six additional cycles.

## Study Endpoints and Assessments

The primary endpoint of the ProDERM study was response to IVIg, defined by the percentage of patients with least minimal improvement (i.e., a score of  $\geq 20$ ) in 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 and European Alliance of Associations for Rheumatology [17–19]. MDAAT was performed prospectively in the ProDERM study to assess the disease activity of various organ systems, including pulmonary, skeletal, constitutional, GI, cardiovascular, and cutaneous [20]. Each organ system was assessed using a myositis disease activity VAS over 10 cm (with 0 cm representing absence of disease activity and 10 cm representing maximum disease activity), plus a myositis intention-to-treat activity index (MITAX). The MITAX assessed individual health conditions pertaining to each organ system, with each rated 0–4, where a score of 0 was “not present in the last 4 weeks,” 1 was “improving,” 2 was “the same,” 3 was “worse,” and 4 was “new in the last 4 weeks.” For the pulmonary domain, the VAS assessed “active interstitial lung

disease or respiratory muscle weakness requiring ventilatory support,” and the MITAX assessed dyspnea from respiratory muscle weakness, active reversible ILD, and dysphonia. For the skeletal domain, “severe arthritis with extreme loss of function” was assessed on the VAS, while arthritis and arthralgia were assessed via the MITAX. For the constitutional domain, the VAS assessed “severe fatigue or malaise resulting in being bed-bound and an inability to perform self care,” and the MITAX assessed pyrexia, weight loss, and fatigue. For the GI domain, “major abdominal crisis requiring surgery or intensive care” was assessed via the VAS, while the MITAX assessed dysphagia and abdominal pain related to myositis. For the cardiovascular domain, the VAS assessed “myocarditis, pericarditis, or severe arrhythmia requiring intensive care unit” and the MITAX assessed pericarditis, myocarditis, arrhythmia, and sinus tachycardia.

## Statistical Analyses

For this analysis, a VAS score of  $\leq 0.5$  for any individual domain was considered as showing no disease activity/involvement of that domain. The percentage of patients with  $\text{VAS} \leq 0.5$  or  $> 0.5$  at baseline, week 16, and week 40 was compared for each domain using the McNemar test, owing to the binary nature of the outcome variable.

Change in mean MDAAT VAS scores from baseline to week 16 and week 40 was analyzed using paired *t* tests, as the data were found to have an approximately normal distribution.

The presence of different health conditions was assessed through the MDAAT MITAX at baseline and at weeks 16 and 40. Each condition was categorized binomially as being present (score of 1–4) or absent (score of zero). Changes in the occurrence of the different conditions from baseline to both week 16 and week 40 were analyzed using a paired exact test. A second analysis considered MITAX scores on their original 5-point scale rather than binomial categorization. Owing to the ordinal nature of the scores, the analysis was performed using the Wilcoxon matched-pairs test.

## RESULTS

### Study Population

A total of 95 patients were enrolled in the ProDERM study, of whom 47 were randomized to receive IVIg and 48 were randomized to receive placebo in the first period, up to week 16. Of these, 45 patients (95.7%) in the IVIg group and 46 (95.8%) in the placebo group completed the first period. During the first period, five patients (10.4%) on placebo crossed over to IVIg and no patients on IVIg switched to placebo. In total, 69 (72.6%) patients completed the extension period.

Patient disposition was described in full previously [17]. In summary, 71 (74.7%) patients were female and the median (range) age was 52.0 years (22.0–79.0). The demographics and baseline characteristics of patients were generally balanced between the IVIg and placebo groups and are described in full in the previous publication [17].

### Spread of MDAAT VAS Scores

For each of the five domains assessed using the MDAAT, the distribution of VAS scores at baseline was assessed. For the skeletal and constitutional domains, the majority of patients had symptoms at baseline (i.e.,  $VAS > 0.5$ ); of 95 patients, only 34 (35.8%) patients had  $VAS \leq 0.5$  for the skeletal domain, indicating no involvement, and 22 (23.2%) patients had  $VAS \leq 0.5$  for the constitutional domain (Fig. 1b, c; and Table S1 in the Supplementary Material). For the pulmonary and GI domains, more than half of the patients did not have involvement at baseline ( $n = 59$  [62.1%] and  $n = 63$  [66.3%], respectively) (Fig. 1a, d; and Table S1 in the Supplementary Material).

By week 40, the proportion of patients with no involvement (i.e.,  $VAS \leq 0.5$ ) had increased significantly for all four domains, to the following (of 88 patients with available scores): no skeletal involvement,  $n = 56$  (63.6%,  $P < 0.001$ ); no constitutional involvement,  $n = 57$  (64.8%;  $P < 0.001$ ); no pulmonary involvement,  $n = 68$

(77.3%,  $P = 0.007$ ); and no GI involvement,  $n = 74$  (84.1%;  $P < 0.001$ ).

For the cardiovascular domain of the MDAAT, the majority of patients (80/95; 84.2%) had no involvement at baseline; this did not change significantly by week 40 (78/88 patients; 88.6%;  $P = 0.18$ ) (Fig. S1a).

### Mean MDAAT VAS Scores Over Time

For patients with  $VAS \geq 0.5$  at baseline, a significant improvement in mean VAS score for the pulmonary, skeletal, constitutional, and GI domains was seen from baseline to week 16 for the IVIg group and from baseline to week 40 for the combined cohort (Fig. 2a–d and Table 1). From baseline to week 16 in the IVIg group, mean skeletal VAS decreased by 52.6% (1.62 cm;  $P < 0.001$ ), constitutional VAS decreased by 44.4% (1.30 cm;  $P < 0.001$ ), pulmonary VAS decreased by 37.7% (1.15 cm;  $P = 0.001$ ), and GI VAS decreased by 49.2% (1.22 cm;  $P = 0.005$ ). In contrast, no significant improvement for these domains was noted for the placebo group at week 16 except for constitutional VAS (Table 1). A significant difference was seen in the change in VAS scores through week 16 between the IVIg and placebo groups for the pulmonary and skeletal scores (both  $P = 0.02$ ), but not for constitutional, GI, or cardiovascular scores ( $P = 0.18$ ,  $P = 0.27$ , and  $P = 0.22$ , respectively). At week 40, following patients on placebo switching to IVIg, significant improvement was seen for the combined cohort as compared with baseline, as follows: mean pulmonary VAS decreased by 38.2% (1.08 cm), skeletal VAS decreased by 60.1% (1.75 cm), constitutional VAS decreased by 58.2% (1.70 cm), and GI VAS decreased by 51.0% (1.27 cm;  $P < 0.001$  for all domains).

For the cardiovascular domain (Fig. S1b), few patients had  $VAS \geq 0.5$  at baseline and data were not available for all patients at all timepoints, making it difficult to draw conclusions. However, from baseline to week 16 a decrease in VAS of 21.4% (0.43 cm) was observed for patients in the IVIg group, and from baseline to week 40 for the combined cohort of patients a decrease of 22.4% (0.52 cm) was seen; both decreases were

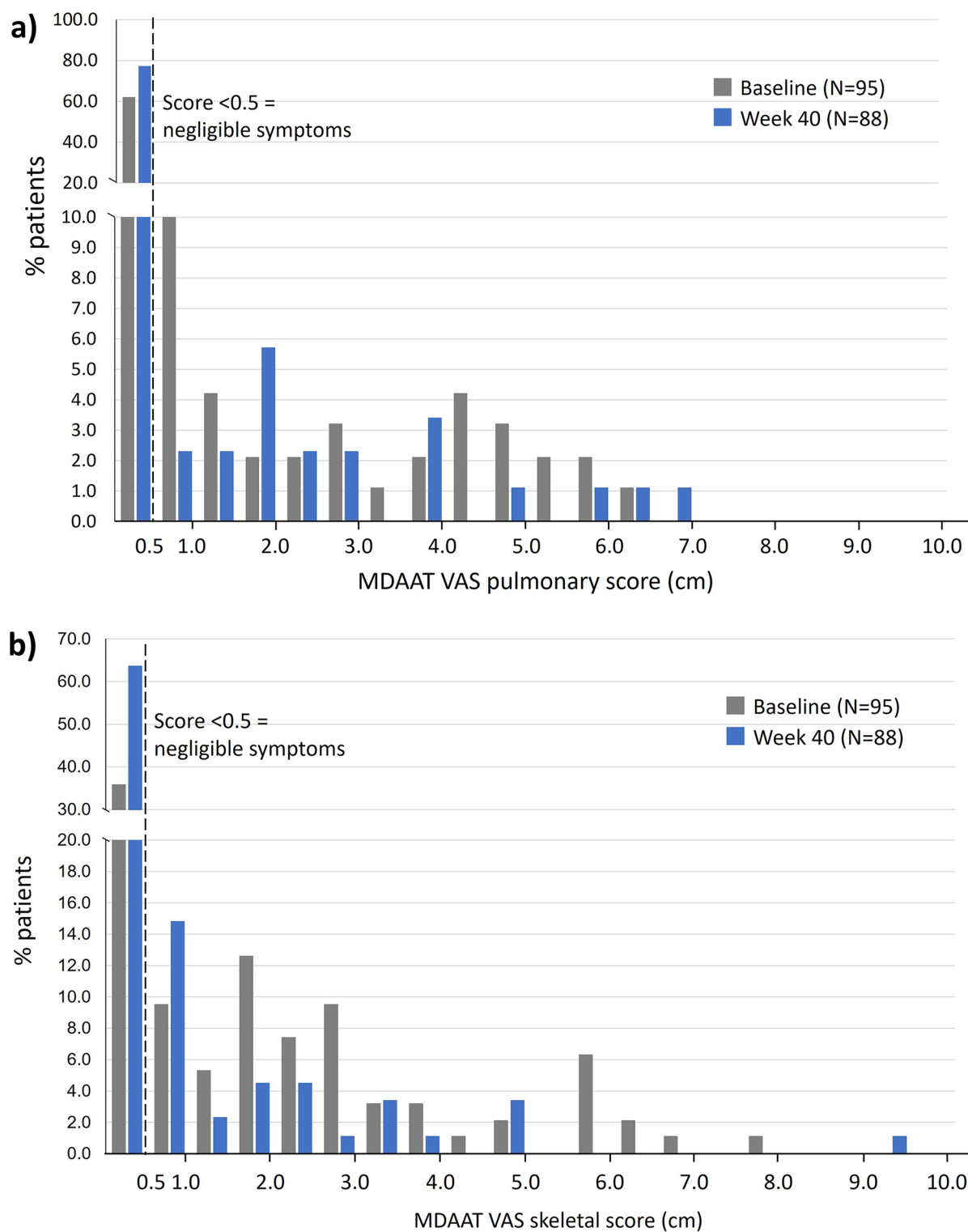


**Fig. 1** MDAAT VAS score at baseline and week 40 for **a** pulmonary, **b** skeletal, **c** constitutional, and **d** gastrointestinal symptoms. *MDAAT* Myositis Disease Activity Assessment Tool, *VAS* visual analog scale

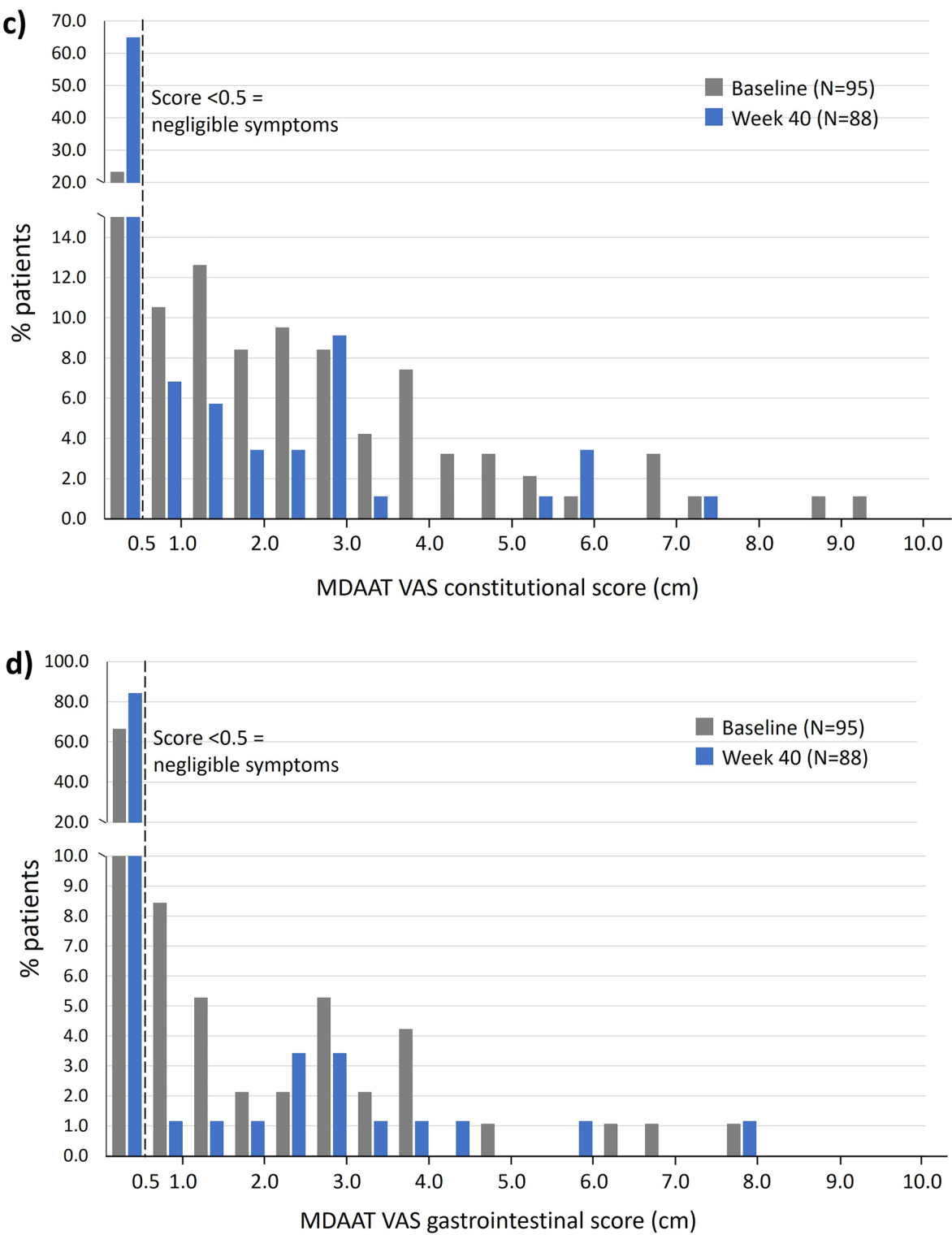


Fig. 1 continued

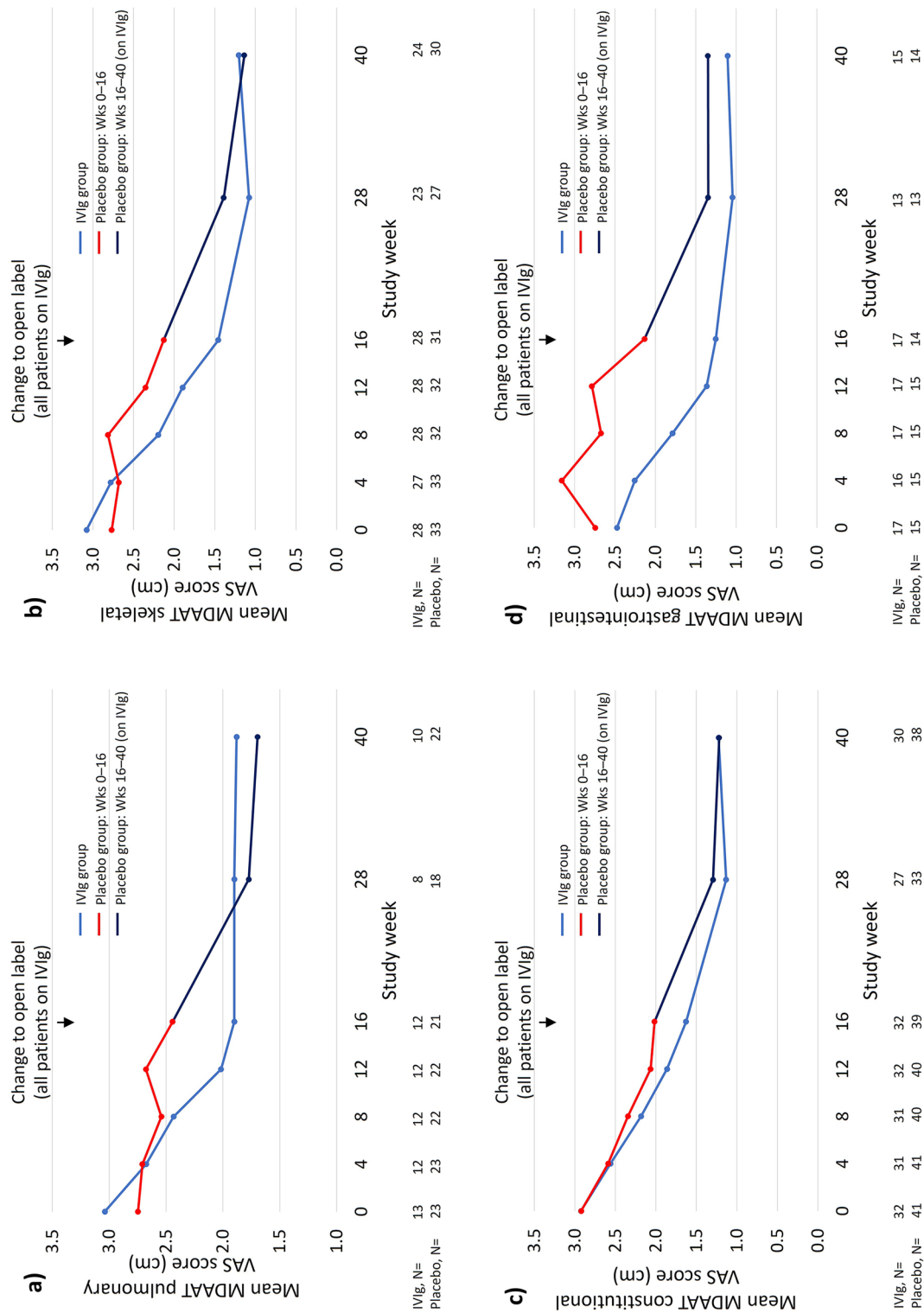


**Fig. 2** Changes in MDAAT VAS scores from baseline for a pulmonary, **b** skeletal, **c** constitutional, and **d** gastrointestinal symptoms, in patients with baseline MDAAT VAS scores of  $\geq 0.5$ . *IVIg* intravenous immunoglobulin, *MDAAT* Myositis Disease Activity Assessment Tool, *VAS* visual analog scale. Patients with MDAAT VAS score of  $< 0.5$  at baseline were excluded from analysis

**Table 1** Change in MDAAT VAS scores from baseline for patients with MDAAT VAS > 0.5, at week 16 and week 40

| Score                      | Study arm      | <i>n</i> | MDAAT VAS score, mean ± SD |                    | Change in MDAAT pulmonary VAS score, mean (95% CI) | <i>P</i> value, baseline to week 16/ week 40 | <i>P</i> value, placebo vs. IVIg at week 16 |
|----------------------------|----------------|----------|----------------------------|--------------------|----------------------------------------------------|----------------------------------------------|---------------------------------------------|
|                            |                |          | Baseline                   | Week 16 or week 40 |                                                    |                                              |                                             |
| MDAAT pulmonary score      | <i>Week 16</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 21       | 2.61 ± 1.93                | 2.44 ± 2.18        | − 0.17 (− 0.69, 0.35)                              | 0.50                                         | 0.02*                                       |
|                            | IVIg           | 12       | 3.05 ± 1.74                | 1.90 ± 2.01        | − 1.15 (− 1.75, − 0.55)                            | 0.001*                                       |                                             |
|                            | <i>Week 40</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 22       | 2.60 ± 1.94                | 1.70 ± 2.27        | − 0.90 (− 1.37, − 0.44)                            | < 0.001*                                     | –                                           |
|                            | IVIg           | 10       | 3.33 ± 1.60                | 1.88 ± 1.72        | − 1.45 (− 2.14, − 0.76)                            | 0.001*                                       |                                             |
|                            | All pts        | 32       | 2.83 ± 1.85                | 1.75 ± 2.09        | − 1.08 (− 1.45, − 0.70)                            | < 0.001*                                     |                                             |
| MDAAT skeletal score       | <i>Week 16</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 31       | 2.68 ± 1.89                | 2.13 ± 1.93        | − 0.54 (− 1.17, 0.08)                              | 0.08                                         | 0.02*                                       |
|                            | IVIg           | 28       | 3.08 ± 1.61                | 1.46 ± 1.84        | − 1.62 (− 2.33, − 0.92)                            | < 0.001*                                     |                                             |
|                            | <i>Week 40</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 30       | 2.70 ± 1.96                | 1.14 ± 1.39        | − 1.57 (− 2.22, − 0.92)                            | < 0.001*                                     | –                                           |
|                            | IVIg           | 24       | 3.18 ± 1.68                | 1.20 ± 2.14        | − 1.97 (− 2.93, − 1.01)                            | < 0.001*                                     |                                             |
|                            | All pts        | 54       | 2.91 ± 1.84                | 1.17 ± 1.74        | − 1.75 (− 2.29, − 1.20)                            | < 0.001*                                     |                                             |
| MDAAT constitutional score | <i>Week 16</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 39       | 2.75 ± 2.22                | 2.02 ± 2.07        | − 0.74 (− 1.34, − 0.13)                            | 0.02*                                        | 0.18                                        |
|                            | IVIg           | 32       | 2.93 ± 1.40                | 1.63 ± 1.43        | − 1.30 (− 1.88, − 0.71)                            | < 0.001*                                     |                                             |
|                            | <i>Week 40</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 38       | 2.89 ± 2.24                | 1.22 ± 1.83        | − 1.67 (− 2.36, − 0.97)                            | < 0.001*                                     | –                                           |
|                            | IVIg           | 30       | 2.96 ± 1.39                | 1.23 ± 1.59        | − 1.73 (− 2.36, − 1.10)                            | < 0.001*                                     |                                             |
|                            | All pts        | 68       | 2.92 ± 1.90                | 1.22 ± 1.72        | − 1.70 (− 2.16, − 1.23)                            | < 0.001*                                     |                                             |
| MDAAT GI score             | <i>Week 16</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 14       | 2.73 ± 1.15                | 2.14 ± 2.03        | − 0.59 (− 1.50, 0.31)                              | 0.18                                         | 0.27                                        |
|                            | IVIg           | 17       | 2.48 ± 2.21                | 1.25 ± 1.68        | − 1.22 (− 2.02, − 0.42)                            | 0.005*                                       |                                             |
|                            | <i>Week 40</i> |          |                            |                    |                                                    |                                              |                                             |
|                            | Placebo        | 14       | 2.48 ± 1.00                | 1.35 ± 1.84        | − 1.12 (− 2.07, − 0.18)                            | 0.02*                                        | –                                           |
|                            | IVIg           | 15       | 2.51 ± 2.34                | 1.11 ± 1.58        | − 1.40 (− 2.36, − 0.44)                            | 0.007*                                       |                                             |
|                            | All pts        | 29       | 2.49 ± 1.69                | 1.22 ± 1.69        | − 1.27 (− 1.90, − 0.64)                            | < 0.001*                                     |                                             |

Table 1 continued

| Score                       | Study arm      | <i>n</i> | MDAAT VAS score, mean ± SD |                    | Change in MDAAT pulmonary VAS score, mean (95% CI) | <i>P</i> value, baseline to week 16/ week 40 | <i>P</i> value, placebo vs. IVIg at week 16 |
|-----------------------------|----------------|----------|----------------------------|--------------------|----------------------------------------------------|----------------------------------------------|---------------------------------------------|
|                             |                |          | Baseline                   | Week 16 or week 40 |                                                    |                                              |                                             |
| MDAAT cardio-vascular score | <i>Week 16</i> |          |                            |                    |                                                    |                                              |                                             |
|                             | Placebo        | 6        | 2.15 ± 1.18                | 2.20 ± 1.79        | 0.05 (− 0.82, 0.92)                                | 0.88                                         | 0.22                                        |
|                             | IVIg           | 7        | 2.01 ± 1.52                | 1.59 ± 1.89        | − 0.43 (− 0.87, 0.02)                              | 0.06                                         |                                             |
|                             | <i>Week 40</i> |          |                            |                    |                                                    |                                              |                                             |
|                             | Placebo        | 7        | 2.43 ± 1.26                | 2.21 ± 1.81        | − 0.21 (− 1.09, 0.66)                              | 0.57                                         | –                                           |
|                             | IVIg           | 6        | 2.18 ± 1.59                | 1.30 ± 1.47        | − 0.88 (− 1.62, − 0.14)                            | 0.03*                                        |                                             |
|                             | All pts        | 13       | 2.32 ± 1.37                | 1.79 ± 1.66        | − 0.52 (− 1.06, 0.01)                              | 0.05                                         |                                             |

The respective analysis only included patients with VAS > 0.5

CI confidence interval, GI gastrointestinal, MDAAT Myositis Disease Activity Assessment Tool, VAS visual analog scale

\*Statistically significant difference ( $P < 0.05$ ) between the baseline score and that at week 16 or week 40

of borderline significance ( $P=0.06$  and  $P=0.05$ , respectively).

A similar pattern of improvement was seen when considering all patients, regardless of baseline VAS score, although the results were less pronounced for the GI and cardiovascular domains (Table S2 in the Supplementary Material).

To determine if response to IVIg was similar across all MDAAT domains in each patient or whether response varied between domains, improvement in VAS from baseline to week 40 was analyzed for the five domains described above (i.e., pulmonary, skeletal, constitutional, GI, and cardiovascular), as well as the cutaneous and extramuscular domains, which were described previously [18, 23]. For each patient, only domains in which they exhibited symptoms at baseline (i.e., had baseline VAS > 0.5) were considered, with response to IVIg classed as a decrease in VAS of > 0.5. For the 88 patients with scores available at both timepoints, overall, 52 (59.1%) showed improvement with IVIg in all domains in which they had symptoms at baseline. Five (5.7%) patients did not respond to IVIg in any affected domain that they exhibited symptoms at baseline. The remaining 32 (35.2%)

patients showed improvement in some, but not all, domains.

### Presence of Health Conditions Assessed by MDAAT MITAX

The presence or absence of individual health conditions associated with the pulmonary, skeletal, constitutional, GI, and cardiovascular domains was assessed by MDAAT MITAX, whereby a score of 1, 2, 3, or 4 indicated the presence of a health condition and 0 indicated its absence. At baseline, the most common health conditions present were fatigue ( $n=72$ ; 75.8%), arthralgia ( $n=63$ ; 66.3%), dysphagia ( $n=38$ ; 40.0%), arthritis ( $n=35$ ; 36.8%), dyspnea ( $n=24$ ; 25.5%), and dysphonia ( $n=19$ ; 20.0%), showing a marked systemic involvement of DM (Table S1 in the Supplementary Material).

For most health conditions, the number of patients experiencing each condition decreased numerically during the study in patients on IVIg, both to week 16 and week 40 (Fig. 3). At week 16, the proportion of patients with the following health conditions had decreased significantly from baseline in the IVIg group: arthritis (36.2 to 17.8%;  $P=0.01$ ), arthralgia (68.1 to 40.0%;

$P<0.001$ ), and fatigue (68.1 to 53.3%;  $P=0.008$ ). Also at week 16, there was a significant difference between the IVIg and placebo groups in the proportion of patients with arthritis ( $P=0.04$ ) and arthralgia ( $P=0.009$ ), and a numerical difference in the proportion of patients with fatigue, although this did not reach statistical significance ( $P=0.07$ ). By week 40, the proportion of patients with the following health conditions had decreased significantly from baseline in the combined cohort: dysphonia (20.0 to 8.1%;  $P=0.04$ ), arthralgia (66.3 to 39.8%;  $P<0.001$ ), weight loss (10.5 to 3.4%;  $P=0.04$ ), fatigue (75.8 to 50.0%;  $P<0.001$ ), and dysphagia (40.0 to 18.4%;  $P<0.001$ ). The percentage of patients with dyspnea from respiratory muscle weakness decreased numerically from baseline to week 16 in the IVIg group (25.5 to 17.8%;  $P=0.25$ ) and to week 40 in the combined cohort (25.5 to 20.9%;  $P=0.69$ ), although neither reached statistical significance.

#### Severity of Health Conditions Assessed by MDAAT MITAX

Considering the change in MITAX scores on their original 5-point scale from baseline, at week 16 an improvement was seen for the following health conditions for patients in the IVIg group: dyspnea ( $P=0.008$ ), arthritis ( $P=0.003$ ), arthralgia ( $P<0.001$ ), and fatigue ( $P<0.001$ ) (Table 2; full breakdown of scores shown in Table S3 in the Supplementary Material). Improvement was also seen for arthritis ( $P=0.02$ ) and fatigue ( $P=0.005$ ) using this scaling system for patients in the placebo group at week 16. A significant difference in improvement in arthralgia was seen between the IVIg and placebo groups at week 16 ( $P=0.002$ ); numerical differences in improvement of other symptoms between the IVIg and placebo groups were seen but these did not reach statistical significance.

By week 40, an improvement in the MITAX 5-point scale was seen for the following health conditions for patients in the combined cohort: dysphonia ( $P=0.02$ ), arthritis ( $P=0.004$ ), arthralgia ( $P<0.001$ ), weight loss ( $P=0.01$ ), fatigue ( $P<0.001$ ), and dysphagia ( $P<0.001$ ). For dyspnea, the changes in scores from baseline did not reach statistical significance ( $P=0.17$ ).

## DISCUSSION

Results from this post hoc analysis of data from the ProDERM study highlight the marked systemic involvement of symptoms of DM and demonstrate that IVIg was effective in treating the pulmonary, skeletal, constitutional, and GI symptoms. Significant improvement with IVIg was observed, particularly in the symptoms of arthritis, arthralgia, fatigue, weight loss, dysphonia, and dysphagia. Overall, patients in the ProDERM study displayed a wide range of active manifestations of DM at baseline, including fatigue, arthralgia, and arthritis. While these symptoms are not as widely recognized as those affecting skin and muscle, they are important for clinicians to consider as they affect the patient's overall disease status and quality of life and may indicate more active disease requiring aggressive therapy.

Glucocorticoids were historically accepted as the first-line treatment for DM; however, IVIg has become a favored treatment for severe or refractory DM [24]. In 2021, IVIg achieved US Food and Drug Administration approval in the USA for adult DM treatment based on the results of the ProDERM clinical trial [17]. To date, there remains only a limited number of studies reporting the effects of IVIg treatment on DM symptoms beyond the muscular and skin manifestations of the disease. In this analysis we assessed these lesser explored symptoms, with IVIg demonstrating significant symptom improvement across four out of the five evaluated systems.

Recently, the association of IVIg response and factors, including disease activity for each MDAAT domain and autoantibody status, including myositis-specific and myositis-associated antibodies, was investigated in patients from the ProDERM study [25]. The analysis found that patients with all categoric variables, including those with myositis-specific, myositis-associated, or no relevant autoantibodies, responded to IVIg treatment. Patients with higher cutaneous disease activity or anti-TIF1- $\gamma$  antibodies responded best to IVIg treatment, and patients with higher pulmonary disease activity had a lower, albeit still positive, response to IVIg.

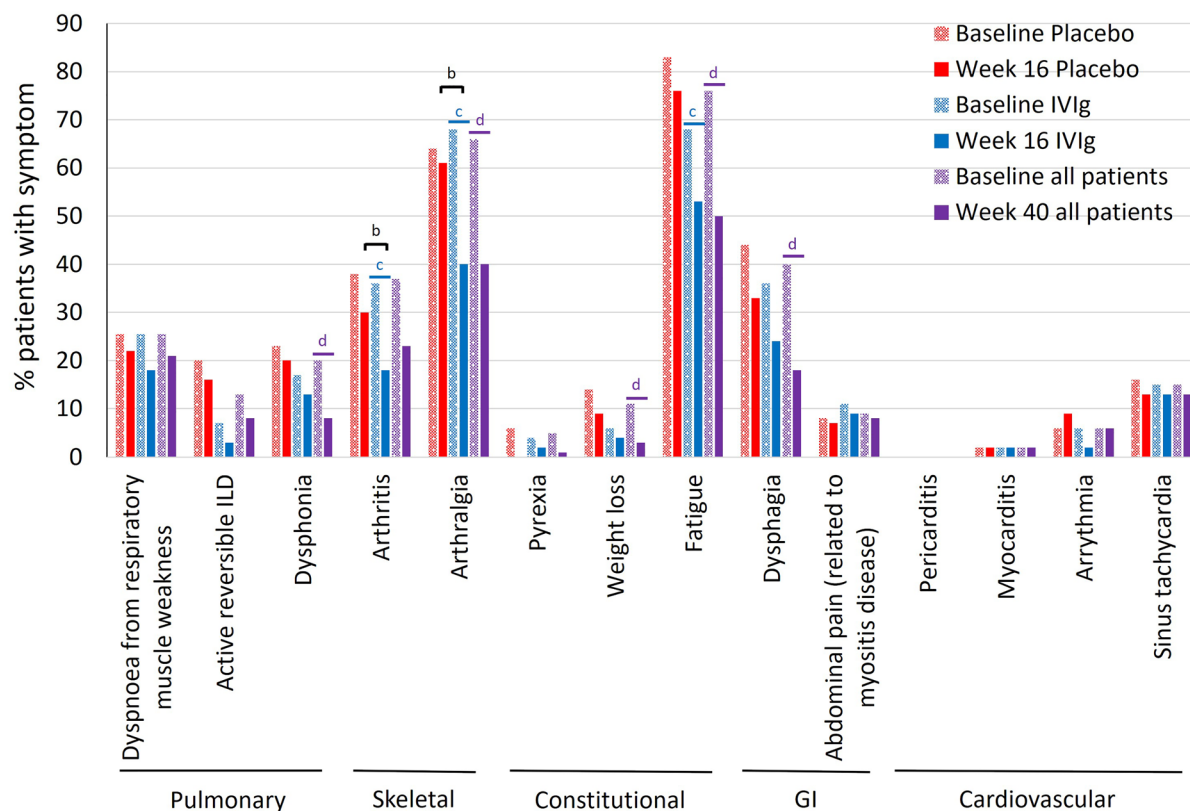


**Fig. 3** Percentage of patients with health conditions as recorded on the MDAAT MITAX score<sup>a</sup> at baseline, week 16, and week 40. *IVIg* intravenous immunoglobulin, *GI* gastrointestinal, *ILD* interstitial lung disease, *MDAAT* Myositis Disease Activity Assessment Tool, *MITAX* Myositis Intention-To-Treat Activity Index. <sup>a</sup>Patients with a

health condition described as 1—improving, 2—stable, 3—worsening, or 4—new, as per the MDAAT MITAX score. <sup>b</sup>Significant difference between IVIg and placebo groups at week 16 ( $P < 0.05$ ). <sup>c</sup>Significant difference from baseline to week 16 ( $P < 0.05$ ). <sup>d</sup>Significant difference from baseline to week 40 ( $P < 0.05$ )

The use of IVIg to treat ILD and other pulmonary manifestations, which are a major cause of mortality and morbidity in patients with DM, has been investigated in other studies. An observational study suggested that IVIg might be beneficial as salvage therapy in patients with active progressive anti-aminoacyl-tRNA synthetase antibody (AS)-associated ILD who are not responding to the combination of steroids and first-line immunosuppressant drugs. IVIg treatment demonstrated clinical improvement in the long-term management of AS-associated ILD, as well as reduction in steroid use [26]. In a study by Wang et al., the effect of IVIg therapy on rapidly progressive ILD was evaluated in patients with DM who were positive for anti-MDA5 autoantibodies. The study showed

that IVIg adjunct therapy was a very effective first-line treatment in these patients and may increase the survival and remission rate [27]. In the present analysis among all patients, the percentage of patients with dyspnea from respiratory muscle weakness, or patients with ILD, both decreased from baseline numerically at weeks 16 and 40, but neither reached statistical significance. Paired data were only available for one patient with active ILD at baseline/week 16 in the IVIg group, and for eight patients with active ILD at baseline/week 40 in the combined cohort. Two of the patients recovered to condition “absent,” although this result did not reach significance. The effect of IVIg on ILD in patients with DM warrants further investigation.

**Table 2** Severity of health conditions as recorded on the MDAAT MITAX score at baseline versus week 16 and week 40

| Factor                                       | Week 16: IVIg |                | Week 16: placebo |                | Week 40: all patients |                |
|----------------------------------------------|---------------|----------------|------------------|----------------|-----------------------|----------------|
|                                              | No. pts       | <i>P</i> value | No. pts          | <i>P</i> value | No. pts               | <i>P</i> value |
| <b>Pulmonary conditions</b>                  |               |                |                  |                |                       |                |
| Dyspnea from respiratory muscle weakness     | 45            | 0.008*         | 44               | 0.64           | 86                    | 0.17           |
| Active reversible ILD                        | 37            | 1.00           | 38               | 0.31           | 70                    | 0.31           |
| Dysphonia                                    | 45            | 0.27           | 45               | 0.29           | 86                    | 0.02*          |
| <b>Skeletal conditions</b>                   |               |                |                  |                |                       |                |
| Arthritis                                    | 45            | 0.003*         | 46               | 0.02*          | 88                    | 0.004*         |
| Arthralgia                                   | 45            | < 0.001*       | 46               | 0.33           | 88                    | < 0.001*       |
| <b>Constitutional conditions</b>             |               |                |                  |                |                       |                |
| Pyrexia                                      | 45            | 0.57           | 46               | 0.16           | 88                    | 0.18           |
| Weight loss                                  | 45            | 0.58           | 46               | 0.65           | 88                    | 0.01*          |
| Fatigue                                      | 45            | < 0.001*       | 46               | 0.005*         | 88                    | < 0.001*       |
| <b>Gastrointestinal conditions</b>           |               |                |                  |                |                       |                |
| Dysphagia                                    | 45            | 0.12           | 45               | 0.07           | 87                    | < 0.001*       |
| Abdominal pain (related to myositis disease) | 45            | 0.16           | 45               | 1.00           | 87                    | 0.56           |
| <b>Cardiovascular conditions</b>             |               |                |                  |                |                       |                |
| Pericarditis                                 | 44            | 1.00           | 42               | 1.00           | 83                    | 1.00           |
| Myocarditis                                  | 44            | 1.00           | 43               | 1.00           | 84                    | 1.00           |
| Arrhythmia                                   | 45            | 0.32           | 44               | 0.16           | 86                    | 0.41           |
| Sinus tachycardia                            | 45            | 0.16           | 45               | 0.98           | 87                    | 0.06           |

ILD interstitial lung disease, IVIg intravenous immunoglobulin, MDAAT Myositis Disease Activity Assessment Tool, MITAX Myositis Intention-To-Treat Activity Index

\*Statistically significant difference ( $P < 0.05$ ) between the IVIg and placebo groups

The most common GI manifestation in DM is dysphagia, which can strongly affect patients' quality of life and is often associated with severe complications such as weight loss or aspiration pneumonia [28]. There are several case studies reporting the positive therapeutic effects of immunomodulatory medication, including IVIg, on dysphagia symptoms and objective swallowing evaluations [28, 29], although larger randomized trials have not yet been performed. In

our study the number of patients with dysphagia at week 40 was significantly lower than at baseline, as was the number of patients with weight loss. However, it should be noted that dysphagia was mostly assessed by subjective patient report and was not an objective measure.

Treatment with IVIg also led to significant improvements in the symptoms of arthritis, arthralgia, and fatigue compared with placebo. While treatments such as methotrexate may

initially be given for inflammatory arthritis, the ability of an immunoglobulin therapy to improve the symptoms of joint disease makes it a powerful option for DM treatment.

For some of the evaluated symptoms, placebo effect may have been observed. This is as expected in DM and is also seen in larger trials with other autoimmune diseases, such as rheumatoid arthritis. The placebo effect is also often seen when assessing subjective symptoms such as fatigue [30].

Overall, the results from the ProDERM study suggest that IVIg could be an effective treatment option for patients with DM. Additionally, the study's robust design provides a comprehensive evaluation of the impact of IVIg on various domains beyond muscle and skin, with the analysis of MDAAT scores also revealing significant insights into disease activity in these patients.

### Limitations

A limitation of this analysis is that MDAAT lacks objective measurements, such as pulmonary function tests, electrocardiogram, high-resolution computed tomography, physical examination or activity levels to assess arthritis, or studies for dysphagia. Also, data capture for the MITAX component of the MDAAT was relatively complex and involved multiple different monitors and may therefore have been suboptimal. Nonetheless, MDAAT is a validated instrument that provides overall assessment by the physician of organ severity and specific clinical features, and in any trial a physician is likely to interpret the clinical data available to make an overall assessment of a particular organ or symptoms. Additionally, evaluation of ILD was very limited given the small number of patients with ILD, even though overall improvement was seen in the pulmonary domain. Few patients in the ProDERM study had cardiovascular symptoms as assessed via MDAAT, and for those who did, data were not available for all patients at all timepoints; therefore, it was not possible to comprehensively evaluate the effect of IVIg treatment on these symptoms. Also, patients who participate in clinical trials tend to modify their behavior and make lifestyle modifications

(such as better diet, exercise, and compliance habits), and it is possible that some of the organ system subjective improvements are the result of clinical trial participation.

Despite its limitations, this study represents one of the first prospective datasets describing the effects of IVIg specifically on pulmonary, skeletal, constitutional, GI, and cardiovascular symptoms of DM, improving our understanding of how patients with DM respond systemically to IVIg treatment.

## CONCLUSIONS

This analysis of results from the ProDERM study suggests that IVIg is an effective treatment option for symptoms of dermatomyositis beyond muscular and cutaneous symptoms, including pulmonary, skeletal, constitutional, and GI manifestations. In particular, IVIg was effective versus placebo in treating symptoms of arthritis, arthralgia, and fatigue. Considering these findings, we advocate further exploration into IVIg as a critical treatment modality for a wide range of aspects of dermatomyositis, beyond muscle and skin manifestations.

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**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>.

## Declarations

**Conflict of Interest.** Rohit Aggarwal has received research grants or contracts from Boehringer Ingelheim, Bristol Myers Squibb, EMD Serono, Janssen, Mallinckrodt, Pfizer, and Q32 Bio; and has acted as a consultant for Alexion, ANI Pharmaceuticals, Argenx, Artasome, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cabaletta Bio, Capella Bioscience, Corbus, CSL Behring, EMD Serono, Galapagos, Horizon Therapeutics, I-Cell, Immunovant, Janssen, Kezar, Kyverna, Lilly, Novartis, Nuvig Therapeutics, Octapharma, Pfizer, Roivant, Sanofi, Teva, Tourmaline Bio, and Verismo Therapeutics. Joachim Schessl has received support for the current manuscript and funding and consultancy

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**Ethical Approval.** The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. ProDERM was approved by the relevant independent ethics committees or institutional review boards, as listed in the Ethics Committees section of the Supplementary Material. Each patient provided written, informed consent before being exposed to any study-related procedure, including screening tests for eligibility [17, 18]. Specific consent for publication was not provided as all data in this international study (from 36 European and North American centers) is fully anonymized.

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