ORIGINAL ARTICLE

Trial of Intravenous Immune Globulin in Dermatomyositis

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ABSTRACT

BACKGROUND

Intravenous immune globulin (IVIG) for the treatment of dermatomyositis has not been extensively evaluated.

METHODS

We conducted a randomized, placebo-controlled trial involving patients with active dermatomyositis. The patients were assigned in a 1:1 ratio to receive IVIG at a dose of 2.0 g per kilogram of body weight or placebo every 4 weeks for 16 weeks. The patients who received placebo and those without confirmed clinical deterioration while receiving IVIG could enter an open-label extension phase for another 24 weeks. The primary end point was a response, defined as a Total Improvement Score (TIS) of at least 20 (indicating at least minimal improvement) at week 16 and no confirmed deterioration up to week 16. The TIS is a weighted composite score reflecting the change in a core set of six measures of myositis activity over time; scores range from 0 to 100, with higher scores indicating greater improvement. Key secondary end points included at least moderate improvement (TIS ≥40) and major improvement (TIS ≥60), and change in score on the Cutaneous Dermatomyositis Disease Area and Severity Index.

RESULTS

A total of 95 patients underwent randomization: 47 patients were assigned to the IVIG group, and 48 to the placebo group. At 16 weeks, 79% of the patients in the IVIG group (37 of 47) and 44% of those in the placebo group (21 of 48) had a TIS of at least 20 (difference, 35 percentage points; 95% confidence interval, 17 to 53; P<0.001). The results with respect to the secondary end points, including at least moderate improvement and major improvement, were generally in the same direction as the results of the primary end-point analysis, except for the change in creatine kinase level (an individual core measure of the TIS), which did not differ meaningfully between the two groups. Over 40 weeks, 282 treatment-related adverse events occurred in the IVIG group, including headache (in 42% of patients), pyrexia (in 19%), and nausea (in 16%). A total of 9 serious adverse events that were considered to be related to IVIG occurred, including 6 thromboembolic events.

CONCLUSIONS

In this 16-week trial involving adults with dermatomyositis, the percentage of patients with a response of at least minimal improvement based on a composite score of disease activity was significantly greater among those who received IVIG than among those who received placebo. IVIG was associated with adverse events, including thromboembolism. (Funded by Octapharma Pharmazeutika; ProDERM ClinicalTrials.gov number, NCT02728752.)

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‡A full list of the investigators and coinvestigators in the ProDERM Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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Dermatomyositis is an uncommon systemic autoimmune disorder of unknown pathogenesis.[1,2] The disorder in adults is characterized by chronic inflammation of the skin and muscles leading to rashes and progressive weakness, predominantly in proximal muscles.[1] Glucocorticoids are administered as first-line therapy, followed by various immunosuppressants. Intravenous immune globulin (IVIG), which is manufactured from purified liquid IgG concentrates from human plasma, has been used off-label as second- or third-line therapy for dermatomyositis, usually in combination with immunosuppressive drugs,[3,4] and has been recommended in European guidelines as a glucocorticoid-sparing agent in patients with this disorder.[5,6] A randomized, placebo-controlled trial involving 15 patients and several noncontrolled studies have suggested that IVIG may be effective in the treatment of dermatomyositis[3,7-10]; however, IVIG has been associated with thromboembolic events.[11-14]

One IVIG preparation[15] has been approved by the Food and Drug Administration, Health Canada, and the regulatory agencies in most European Union countries and the United Kingdom for the treatment of dermatomyositis. This approval was based on the results of the current Progress in Dermatomyositis (ProDERM) trial, which aimed to evaluate the efficacy and safety of this IVIG preparation in adults with dermatomyositis.

Methods

Trial Design and Oversight

The ProDERM trial was a prospective, phase 3, double-blind, parallel-group, randomized, placebo-controlled trial involving patients with dermatomyositis from 36 European and North American centers. Enrollment started in February 2017, and the last patient visit was in November 2019. Details of the trial design have been previously published,[16] and the protocol is available with the full text of this article at NEJM.org.

The trial was designed and conducted by the sponsor, Octapharma Pharmazeutika, in collaboration with the principal investigators. The sponsor collected the data, provided the IVIG and placebo, monitored the conduct of the trial, and performed the statistical analyses. The first author prepared the initial draft of the manuscript with the support of a medical writer (funded by the sponsor). The sponsor could not delay or interdict the submission of the manuscript for publication. The authors, working under confidentiality agreements with the sponsor, had access to the data, were fully responsible for all content and editorial decisions, and approved the final version of the manuscript for submission. The authors vouch for the accuracy and completeness of the data and the reporting of adverse events and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

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Written informed consent was obtained from each patient before any trial-related procedures were conducted. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation and was approved by the relevant independent ethics committees or institutional review boards, as applicable. The trial was monitored by an independent data monitoring committee.

Patients

Patients 18 to 80 years of age with definite or probable active dermatomyositis, determined according to the criteria of Bohan and Peter,[17,18] were eligible for the trial.[16] Patients were allowed to enter the trial if they had received previous treatment with a glucocorticoid or other immunosuppressive drug and had had either no response or an adverse event or if they were currently receiving concomitant treatment with a glucocorticoid, a maximum of two immunosuppressive drugs, or both. The maximum allowable glucocorticoid dose at trial entry was 20 mg per day of a prednisone equivalent, and the dose level at enrollment had to be maintained during the randomized, placebo-controlled phase of the trial. Concomitant treatment that was allowed in addition to glucocorticoids included a maximum of two immunosuppressive drugs (methotrexate, azathioprine, mycophenolate mofetil, sulfasalazine, leflunomide, tacrolimus, cyclosporine, or hydroxychloroquine). These drugs were permitted if treatment had been initiated at least 3 months before enrollment and at a stable dose not exceeding the maximal allowable dose for at least 4 weeks before enrollment. Biologic agents, cyclophosphamide, IVIG, and topical glucocorticoids were not allowed; no patients received Janus kinase inhibitors. During the open-label extension

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phase, concomitant medication for dermatomyositis could be tapered and stopped at the treating physician's discretion.

Myositis disease activity was assessed according to a core set of six measures that were designed for use in the evaluation of myositis.[19-21] The core set of measures that were used as the basis for the primary end point (described below) were the Manual Muscle Test–8 (MMT-8), a measure of strength in eight muscles tested bilaterally (total scores range from 0 to 150, with lower scores indicating weaker muscles); physician's global assessment (PhGA) of disease activity (assessed on a 10-cm visual-analogue scale, with 0 representing no evidence of disease activity and 10 extremely active or severe disease activity); patient's global assessment (PtGA) of disease activity (assessed on the same scale as used for the PhGA of disease activity); the Health Assessment Questionnaire (HAQ, in which total scores range in increments of 0.125 from 0 [no disability] to 3 [complete disability]); extramuscular disease activity (assessed on a 10-cm visual-analogue scale on which scores range from 0 to 10, with higher scores reflecting more disease activity in the extramuscular organs affected by myositis); and serum muscle-enzyme levels (creatine kinase, alanine and aspartate aminotransferase, lactate dehydrogenase, and aldolase). Patients were eligible for enrollment if they had muscle weakness, as determined by a score of less than 142 on the MMT-8, and at least two abnormal findings on the other five core measures (a score of ≥2 on the PhGA or PtGA of disease activity or the extramuscular disease-activity measure; an HAQ total score of ≥0.25; or a muscle-enzyme level >1.5 times the upper limit of the normal range). Further details of the six core-set measures are provided in the Supplementary Appendix, available at NEJM.org.

Any active rash that can be associated with dermatomyositis (heliotrope rash, Gottron's papules, or other typical dermatomyositis rashes) was not required for inclusion; however, all the patients had a rash. The presence of active dermatomyositis was determined by an independent adjudication committee of myositis experts (see the protocol). Muscle biopsies were not performed as part of the trial. Patients with cancer-associated myositis, overlap syndromes involving myositis (except Sjögren's syndrome), inclusion-body myositis, juvenile dermatomyositis, necrotizing myopathy, drug-induced myopathy, or polymyositis were excluded. Patients with a blood hyperviscosity or other hypercoagulable states or any history of thromboembolic events, such as deep-vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, transient ischemic attack, or peripheral artery disease (Fontaine stage IV — symptoms of necrosis, gangrene of the limb, or both) were excluded. A full list of eligibility criteria is provided in the protocol. Participating institutions were requested to maintain screening logs.

TRIAL PROCEDURES

The randomized, placebo-controlled phase of the trial was from week 0 to week 16. Randomization was performed in blocks of 4 and was stratified according to the PhGA disease-activity score before enrollment (with a score of 0 to 3 indicating mild disease activity, a score of 4 to 6 moderate disease activity, and a score of 7 to 10 severe disease activity).

The patients were assigned in a 1:1 ratio to receive IVIG (Octagam, 10%) at a dose of 2.0 g per kilogram of body weight or placebo (0.9% sodium chloride) every 4 weeks (weeks 0, 4, 8, and 12). At each of the four infusion cycles, the total dose of IVIG or placebo was given over 2 to 5 consecutive days. If given over 2 consecutive days (the typical timing of administration), the total dose was divided into two equal doses, each of which was administered as a continuous infusion for up to 5.5 hours. At the discretion of the investigator, the number of consecutive administration days for a given infusion cycle could be increased to up to 5 days, and the total dose was divided accordingly. Infusion bags were covered with pouches to maintain blinding.

In the randomized, placebo-controlled phase, if a patient met published criteria for clinical deterioration (i.e., confirmed deterioration) at or after week 8 at two consecutive visits,[16,22] the patient was crossed over to the other trial group. In such event, the hospital pharmacist, who was aware of the trial-group assignments but was not involved in the direct treatment or assessment of the patients, prepared the alternate IVIG or placebo, and the trial-group assignments remained concealed from the trial personnel and patients. The criteria for clinical deterioration are listed in the Supplementary Appendix.

All patients except those who had confirmed deterioration while receiving IVIG were allowed to continue into the open-label extension phase

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(weeks 16 to 40), in which patients received 2.0 g per kilogram of IVIG every 4 weeks for another six infusion cycles. Investigators could reduce the dose to 1.0 g per kilogram starting at week 28 if a patient's condition was stable, as assessed by the investigator. Patients with confirmed deterioration in the extension phase were withdrawn from the trial. Given the risk of thrombosis associated with IVIG infusion[11-14] and considering that active dermatomyositis may be an additional risk factor for thromboembolism, due in part to increased inflammatory processes and decreased mobility,[23-26] the Wells' probability scores for deep-vein thrombosis and pulmonary embolism were determined after each infusion in order to evaluate the risk of a thromboembolic event. If the Wells' probability score for deep-vein thrombosis (range, –2 to 9) was at least 2 (indicating moderate or high risk), a Doppler scan of the legs was obtained, and D-dimer levels were measured. Treatment of suspected thromboembolic events was initiated according to local clinical practice, and the assigned trial regimen was stopped.

END POINTS

The primary end point was a response, which was defined as a Total Improvement Score (TIS) of at least 20 (indicating at least minimum improvement) at week 16 and no confirmed deterioration up to week 16. The TIS is a weighted composite score reflecting the change in a core set of six measures of myositis activity over time; scores range from 0 to 100, with higher scores indicating greater improvement.[16] This score is calculated according to consensus 2016 American College of Rheumatology–European League against Rheumatism (ACR–EULAR) myositis response criteria for adult dermatomyositis and polymyositis.[27] At each time point, the percentage change from baseline in the absolute value for each core-set measure is calculated. On the basis of the magnitude of this percentage change, each core-set measure is allocated an "improvement score" in accordance with the ACR–EULAR response criteria, with differential weights assigned to the various core-set measures. The improvement scores for the six core-set measures are summed to provide the TIS. Because the TIS represents a change, it cannot be calculated at baseline (week 0). Further explanation of the TIS and its derivation is provided in the Supplementary Appendix.

There were 13 secondary efficacy end points: a response according to improvement category at week 16 (at least moderate improvement [TIS ≥40] or major improvement [TIS ≥60]); a response according to improvement category at week 40 (at least minimal improvement [TIS ≥20], at least moderate improvement, or major improvement); the mean change in scores on the modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) from baseline to week 16 (the CDASI total activity score [CDASI-A] ranges from 0 to 100, and the CDASI total damage score ranges from 0 to 32; higher scores on both indicate worse disease); the mean change in scores on the CDASI from week 16 to week 40; the mean change in quality of life, as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), from baseline to week 16; the mean change in quality of life from baseline to week 40; the mean change in individual core measures from baseline to week 16; the mean change in individual core measures from baseline to week 40; the mean TIS from baseline up to week 16; the mean TIS from baseline up to week 40; the time to at least minimal, at least moderate, and major improvement in TIS; the time to confirmed deterioration in the randomized, placebo-controlled phase and overall; and the percentage of patients in each trial group who met the criteria for clinical deterioration up to week 16.

Safety was assessed in all patients who received at least one dose of IVIG or placebo through 40 weeks. Adverse events, serious adverse events, and fatalities were documented throughout the trial at each visit (scheduled or unscheduled) and up to 4 weeks after the last administration of IVIG or placebo. Trial investigators assessed the causality of adverse events that occurred at their site. Adverse events were also regularly assessed by an independent data monitoring committee that also assessed all adverse events of special interest (thromboembolic events and hemolytic reactions). Trial personnel who documented adverse events were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

The trial was powered solely with respect to the primary end point. We estimated that 84 participants would be needed to provide the trial with 80% power to determine a significant difference, at an alpha level of 0.05, between the

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IVIG group and the placebo group in the percentage of patients who had a response, and we planned to enroll 95 patients to allow for potential dropout and to facilitate the stratified analysis. Further details of sample size and power calculations are provided in the Supplementary Appendix. Analyses of the primary efficacy end point were based on data from all the patients who underwent randomization. The last value before switching trial regimens was used in the analysis for patients who were switched to the alternate trial group. Values measured in the randomized, placebo-controlled phase after a patient had switched to the alternate trial group were excluded from the summary statistics.

The percentage of patients who had at least minimal improvement at week 16 (the primary end point) was compared between the trial groups with the use of the Cochran–Mantel–Haenszel test with a two-sided alpha level of 0.05 and an exact two-sided 95% confidence interval; the analysis included stratification according to the PhGA disease-activity score. A sensitivity analysis of the primary end point was performed with the use of a logistic-regression model that included the PhGA disease-activity score as a covariate. In a supportive analysis of the primary end point, differences between means were assessed with the use of the Wilcoxon–Mann–Whitney test. Changes from baseline to week 40 are presented descriptively, including unadjusted 95% confidence intervals, and no definite conclusions can be drawn from those data. Times to improvement in TIS were summarized with the use of Kaplan–Meier estimates; for the patients who crossed over to the alternate trial group, data were censored at the time of the switch. Analysis of covariance was used to analyze changes from baseline to week 16 for all continuous secondary end points, and the differences in least-squares means and the 95% confidence intervals were calculated. Because the widths of the 95% confidence intervals for secondary end points were not adjusted for multiplicity, no inferences can be drawn from these data.

In general, missing data were not imputed, with a few exceptions. In the analysis of covariance for the change from baseline to week 16, the last observed value was used in the main model in case of missing values (e.g., owing to early termination) and in case of a switch to the alternate trial group (because values obtained after the switch were not included in the analysis). For missing measurements of body weight, the last available body weight was used for all calculations related to dosing.

RESULTS

PATIENTS

Of 126 patients screened, 95 were enrolled: 47 were assigned to the IVIG group and 48 to the placebo group (Fig. 1). A total of 45 patients (96%) in the IVIG group and 46 patients (96%) in the placebo group completed the randomized, placebo-controlled phase of the trial and continued to the open-label extension phase (reasons for exclusions are given in Fig. 1). A total of 34 patients (72%) in the IVIG group and 35 patients (73%) in the placebo group completed the extension phase up to week 40. During the placebo-controlled phase, 5 patients in the placebo group crossed over to receive IVIG (2 patients were switched because of confirmed deterioration and 3 patients were switched in error); no patient in the IVIG group crossed over to receive placebo. Data on the primary and secondary end points were missing for 2 patients in each trial group. In total, 664 infusion cycles of IVIG were administered at a median dose of 2.0 g per kilogram over a median of 2.4 infusion days per cycle. The safety analysis during the placebo-controlled phase included 52 patients who received IVIG and 48 patients who received placebo, and the safety analysis during the open-label extension phase included 95 patients who received IVIG.

Demographics and other baseline characteristics were similar in the two groups (Table 1). Our cohort of patients at the participating centers was generally representative of the adult population of patients with dermatomyositis; therefore, only 5% of the patients were Black (Tables S1 through S3). All the patients had symmetric proximal muscle weakness and typical skin rash, with 71% having definite dermatomyositis according to the criteria of Bohan and Peter. On the basis of the clinical features present at enrollment, 98% of the patients met the probable or definite criteria for inflammatory myopathy according to the 2017 EULAR–ACR classification criteria for idiopathic inflammatory myopathies.[28] Patients had muscle weakness

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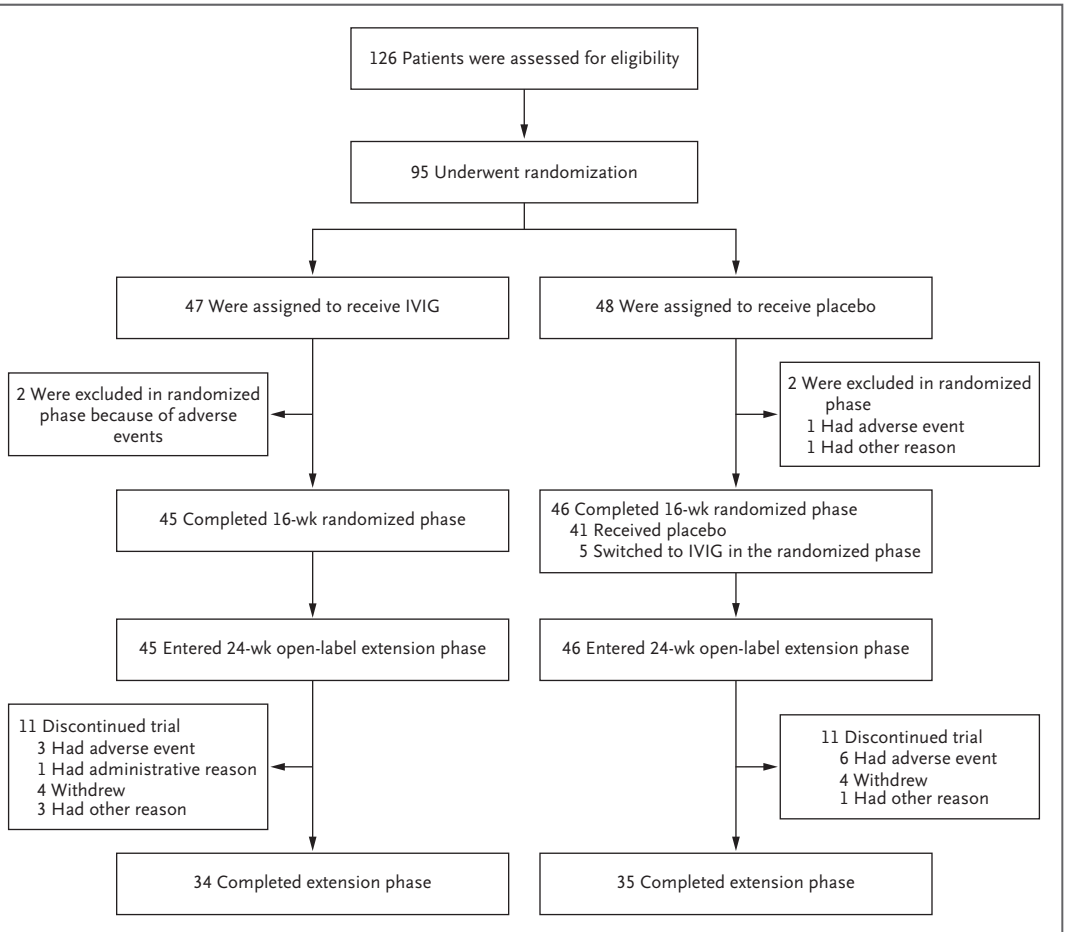

Figure 1. Screening, Randomization, and Follow-up.
IVIG denotes intravenous immune globulin.

and active disease, with a mean MMT-8 score of 120.9 and a mean PhGA disease-activity score of 5.0. Most patients (83%) had at least mild rash (CDASI-A >6), and 54% had moderate-to-severe dermatomyositis rashes (CDASI-A >14). The percentage of patients with a moderate-to-severe PhGA disease activity was 77% in the IVIG group and 69% in the placebo group. The mean MMT-8 and CDASI-A scores were 121.0 and 16.6, respectively, among the patients with moderate PhGA disease activity and 102.5 and 30.6, respectively, among those with severe PhGA disease activity.

The results for the other core components of the TIS were similar in the trial groups (Table 1). Among the 75 patients tested for myositis-related autoantibodies, 48% had myositis-specific autoantibodies and 27% had myositis-associated autoantibodies (Table S4).

Overall, 99% of the patients received concomitant therapy for dermatomyositis during the trial, with 88% receiving systemic glucocorticoids and 68% receiving nonglucocorticoid medications. The use of concomitant therapy was similar in the two trial groups (Table 1). Most patients had previous treatment failure with systemic glucocorticoids and at least one nonsteroidal immunosuppressive drug at or before enrollment (Table S5).

PRIMARY EFFICACY END POINT

At week 16, a response of at least minimal improvement (TIS of ≥20) was observed in 79% of the patients (37 of 47) in the IVIG group and in 44% (21 of 48) in the placebo group (adjusted difference, 35 percentage points; 95% confidence interval [CI], 16.7 to 53.2; P<0.001) (Table 2 and

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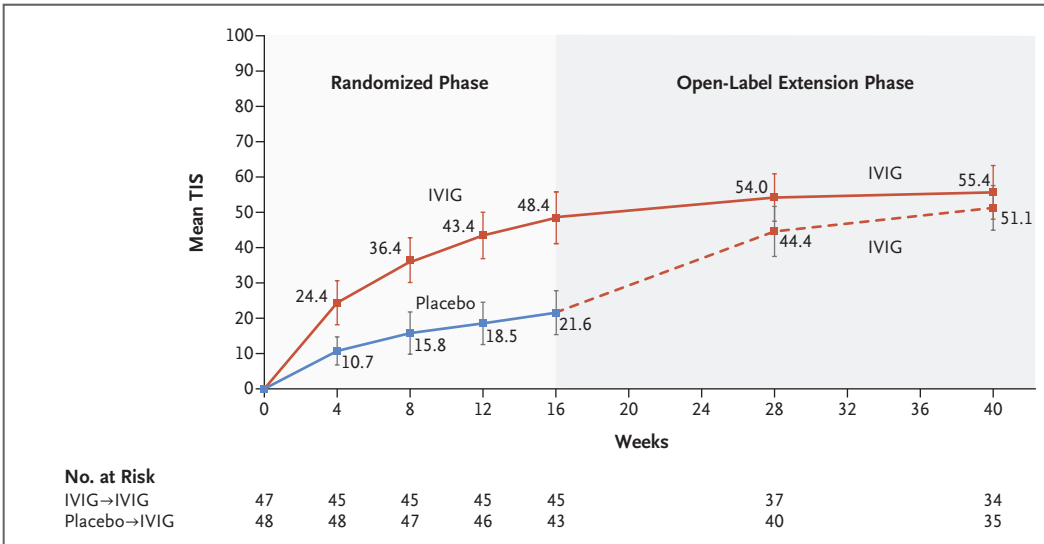

Figure 2. Total Improvement Score (TIS) at Week 16 and Week 40.

Shown is the mean TIS up to the end of the double-blind, randomized, placebo-controlled phase at week 16 and up to the end of the open-label extension phase at week 40. The TIS is a weighted composite score reflecting the change over time in a core set of six measures of myositis activity; scores range from 0 to 100, with higher scores indicating greater improvement (see the Supplementary Appendix). Conclusions cannot be drawn from the results from week 16 to week 40 (the open-label extension phase), because these results are descriptive only. I bars represent 95% confidence intervals.

Fig. S1A). In a supportive analysis of the primary end point, the mean (±SD) TIS at week 16 was 47.7±24.2 in the IVIG group and 21.3±20.8 in the placebo group (mean difference, 26.4 points; 95% CI, 17.2 to 35.6). In the subgroup analysis of the TIS at week 16, in which the patients were stratified according to the PhGA disease-activity score, the percentage of patients who had a response in the IVIG group, as compared with those in the placebo group, were as follows: mild disease activity (73% vs. 27%), moderate disease activity (79% vs. 52%), and severe disease activity (86% vs. 50%); however, the trial was not powered to determine a difference in this outcome, and the analysis was not adjusted for multiplicity.

SECONDARY EFFICACY END POINTS

At week 16, a response of at least moderate improvement (TIS of ≥40) was observed in 68% of the patients (32 of 47) in the IVIG group and in 23% of the patients (11 of 48) in the placebo group, and a response of major improvement (TIS of ≥60) was observed in 32% (15 of 47) and 8% (4 of 48), respectively (Table 2 and Fig. S1B). At the end of the open-label extension phase (week 40), the percentage of patients who had a response of at least minimum improvement was similar in the two groups (71% of the patients [32 of 45] in the IVIG group who continued to receive IVIG in the extension phase and 70% of the patients in the placebo group who received IVIG in the extension phase) (Table 2 and Fig. S1C). Approximately 60% of the patients in both groups had at least moderate improvement at week 40, with more than 30% of the patients in both groups having major improvement (Table 2). The results with respect to the secondary end points, including at least moderate improvement and major improvement and the mean change from baseline in the CDASI total activity score, were generally in the same direction as the results of the primary analysis (Table 2 and Fig. S2), with the exception of creatine kinase level, for which the 95% confidence interval included zero (Table 2). The widths of 95% confidence intervals for the between-group differences in the secondary end-point analyses were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data.

The mean TIS at week 16 was 48.4 points in the IVIG group, and it increased further on the

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basis of visual inspection of graphical results up to week 40 (Table 2 and Fig. 2). After the patients in the placebo group were switched to the IVIG regimen during the open-label extension phase, the mean TIS among them increased to a level approaching that seen in the IVIG group by week 40. The time to at least minimal improvement (TIS of ≥20) was a median 35 days in the IVIG group and 115 days in the placebo group (Fig. S3 and Table 2). The time to at least moderate improvement was 85 days in the IVIG group and 197 days in the placebo group, and time to major improvement was 283 days in both trial groups (Table 2). The time to confirmed deterioration in the randomized, placebo-controlled phase and the open-label extension phase could not be calculated owing to the low number of patients with confirmed deterioration (Table 2). During the placebo-controlled phase, clinical deterioration was confirmed in 3 patients (6%) in the placebo group and no patients in the IVIG group (Table 2).

A total of 84 patients were receiving concomitant glucocorticoids, among whom 15 (18%) were able to receive a reduced dose or discontinue the treatment during the open-label extension phase. Among the 91 patients who entered the extension phase, 8 (9%) had a reduction in the IVIG dose to 1.0 g per kilogram at or after 28 weeks.

SAFETY

In the randomized, placebo-controlled phase, 113 IVIG-related adverse events were recorded in 30 of 52 patients (58%) in the IVIG group, and 38 placebo-related adverse events were recorded in 11 of 48 patients (23%) in the placebo group (Table 3). During the entire trial, including the open-label extension phase, 282 treatment-related adverse events were documented with IVIG in 62 of 95 patients (65%); the most common were headache (in 42%), pyrexia (in 19%), and nausea (in 16%) (Table 3). Most treatment-related adverse events occurred during or within 72 hours after the end of an infusion cycle (in 92% [260 events]) and were mild (in 73.4% [207 events]), moderate (in 23.4% [66 events]), or severe (in 3.2% [9 events]). During the randomized, placebo-controlled phase, 5 serious adverse events occurred after an IVIG infusion in 3 patients (6%) (sepsis and pulmonary embolism in 1 patient, muscle spasm and dyspnea in 1 patient, and ventricular extrasystoles in 1 patient), and 4 serious adverse events occurred after a placebo infusion in 2 patients (4%) (tropical spastic paresis in 1 patient and hypertension and two episodes of sinus tachycardia in 1 patient). Overall, 9 serious treatment-related adverse events occurred among 7 patients during both phases of the trial (Table 3). No deaths and no hemolytic transfusion reactions were reported during the trial.

Because dermatomyositis (which is associated with decreased mobility and increased inflammatory processes)[23-26] and treatment with IVIG[11-14] are both considered to be risk factors for thromboembolic events, emphasis was placed on monitoring for these events. During the entire trial, 8 thromboembolic events were documented among 6 patients who received treatment with IVIG. A total of 6 thromboembolic events that were considered to be related to the trial regimen occurred among 5 patients, which led to an amendment to the trial protocol in July 2018 in which the maximum allowable infusion rate was reduced from 0.12 to 0.04 ml per kilogram per minute. A total of 59 patients were enrolled before and 36 patients were enrolled after amendment. The incidence of thromboembolic events was 1.54 per 100 patient-months before and 0.54 per 100 patient-months after amendment.

DISCUSSION

In the 16-week randomized, placebo-controlled phase of the trial, the percentage of patients who had a response of at least minimal improvement at week 16 was significantly higher among the patients who received IVIG than among those who received placebo. The percentage of patients who had a response of at least moderate improvement or a response of major improvement was greater with IVIG than with placebo, but the 95% confidence intervals for the between-group differences in these end points were not adjusted for multiple comparisons. The median time to at least minimal improvement was 35 days with IVIG and 115 days with placebo. The results of the other secondary end-point analyses were also generally in the same direction as the results of the primary efficacy analysis, including muscle strength and skin rash. Creatine kinase levels varied among the patients in the trial groups; however, there was no appreciable between-group difference in the change from

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristics	IVIG (N=47)	Placebo (N=48)	Total (N=95)
Median age (range) — yr	55.0 (22.0–77.0)	51.5 (22.0–79.0)	52.0 (22.0–79.0)
Female sex — no. (%)	36 (77)	35 (73)	71 (75)
Race — no. (%)†			
White	44 (94)	43 (90)	87 (92)
Asian	1 (2)	1 (2)	2 (2)
Black	2 (4)	3 (6)	5 (5)
Other	0	1 (2)	1 (1)
Ethnic group — no. (%)†			
Hispanic or Latino	0	5 (10)	5 (5)
Not Hispanic or Latino	47 (100)	43 (90)	90 (95)
Median time since diagnosis (range) — yr	2.4 (0.1–48.7)	2.9 (0.1–18.4)	2.6 (0.1–48.7)
Criteria of Bohan and Peter — no. (%)‡			
Symmetric proximal muscle weakness	47 (100)	48 (100)	95 (100)
Evidence of myositis on muscle biopsy	23 (49)	23 (48)	46 (48)
Elevation of serum skeletal muscle enzymes	43 (91)	44 (92)	87 (92)
Electromyographic finding consistent with myositis	31 (66)	26 (54)	57 (60)
Typical skin rash of dermatomyositis	47 (100)	48 (100)	95 (100)
Classification of dermatomyositis according to criteria of Bohan and Peter — no. (%)‡			
Definite	34 (72)	33 (69)	67 (71)
Probable	13 (28)	15 (31)	28 (29)
Dermatomyositis activity — no. (%)§			
Mild	11 (23)	15 (31)	26 (27)
Moderate	29 (62)	27 (56)	56 (59)
Severe	7 (15)	6 (12)	13 (14)
Concomitant medication for dermatomyositis — no. (%)¶			
Systemic glucocorticoid	40 (85)	44 (92)	84 (88)
Nonglucocorticoid medication	31 (66)	34 (71)	65 (68)
TIS core-set measures‖			
Mean MMT-8 score	119.5	122.2	120.9
Mean PhGA disease-activity score	5.13	4.82	4.97
Mean PtGA disease-activity score	5.86	5.79	5.82
Mean HAQ total score	1.35	1.26	1.31
Mean extramuscular disease-activity score	4.23	4.17	4.20
Median muscle enzyme level: creatine kinase — U/liter	141.0	113.0	127.0

* IVIG denotes intravenous immune globulin.
† Race and ethnic group were reported by the patient.
‡ To meet the criteria of Bohan and Peter,[17,18] a patient must have a typical skin rash of dermatomyositis in addition to two (for probable dermatomyositis) or at least three (for definite dermatomyositis) of the following four symptoms: symmetric proximal muscle weakness, evidence of myositis on muscle biopsy, elevation of serum skeletal muscle enzyme levels, and electromyographic finding consistent with myositis.
§ The classification of dermatomyositis activity was based on the physician's global assessment (PhGA) of disease activity, with a score of 0 to 3 indicating mild disease activity, 4 to 6 moderate disease activity, and 7 to 10 severe disease activity.

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Table 1. (Continued.)

¶ Concomitant therapy was allowed provided that the treatment was initiated at least 3 months before enrollment and was continued at a stable dose not exceeding the maximal allowable dose for at least 4 weeks before enrollment.
‖ Scores on the Manual Muscle Test–8 (MMT-8), a measure of strength in eight muscles tested bilaterally, range from 0 to 150, with lower scores indicating weaker muscles. Scores on the PhGA and the patient's global assessment (PtGA) of disease activity range from 0 (no evidence of disease activity) to 10 (extremely active or severe disease activity). Total scores on the Health Assessment Questionnaire (HAQ) range in increments of 0.125 from 0 (no disability) to 3 (complete disability). Extramuscular disease-activity scores range from 0 to 10, with higher scores reflecting more disease activity in terms of extramuscular organs affected by myositis.

baseline in creatine kinase level at week 16. The efficacy of IVIG with respect to the primary end point was observed among the patients across mild, moderate, and severe disease-activity categories.

Two previous double-blind, placebo-controlled trials investigating the efficacy of IVIG among patients with dermatomyositis were small but provided preliminary evidence of efficacy and safety.[10,29] One of the trials showed that IVIG, as compared with placebo, improved muscle strength and reduced neuromuscular symptoms.[10] In contrast, in the other trial involving patients with glucocorticoid-resistant polymyositis and dermatomyositis, muscle strength improved similarly in the IVIG group and placebo group.[29] In addition, a number of noncontrolled studies have shown that IVIG reduces symptoms of dermatomyositis.[3,7-9]

The current trial permitted concomitant therapy in parallel with the trial treatment, and 88% of patients were receiving concomitant glucocorticoids; one patient was not receiving concomitant medication for dermatomyositis at trial entry but had had previous treatment failure with a glucocorticoid and other immunosuppressive drugs. Approximately 20% of the patients who were receiving concomitant glucocorticoids were able to receive a reduced dose or discontinue the treatment during the open-label extension phase of the trial, but no conclusions can be made regarding a potential glucocorticoid-sparing effect of IVIG. Dose reduction was initiated at the physician's discretion and was not stipulated by the protocol; it is plausible that the percentage of patients who had a dose reduction may have been different if the decision had been patient-driven.

Most adverse events were reported during or within 72 hours after the IVIG infusion and were mild. Headache was common but was rated as mild in 75% of instances because the events were transient or did not interfere with routine activities; no premedications were used to mitigate these side effects of IVIG infusion unless they occurred in two consecutive cycles. Dermatomyositis and IVIG administration are risk factors for thromboembolic events,[11-14,23-26] and we emphasized monitoring for these events. Eight patients in the IVIG group discontinued IVIG because of adverse events, including six thromboembolic events in five patients, that were considered to be related to the trial regimen. After the first thromboembolic events of the trial were adjudicated, the protocol was modified to reduce the maximum infusion rate of IVIG, which led to a reduction in the incidence of thromboembolic events. No events of IVIG-related hemolytic anemia were reported during the trial.

The mechanism of action of IVIG in patients with dermatomyositis is not understood but may involve inhibition of complement consumption and interference with formation of the membrane attack complex.[30,31] These actions have been implicated in dermatomyositis and are considered to be pertinent because there is C3 activation in this condition, leading to formation and deposition of membrane attack complex on endomysial capillaries and subsequent capillary destruction resulting in microangiopathy; however, the relation between these actions and clinical changes in patients with dermatomyositis remains to be determined.[32-35] In addition, IVIG may lead to down-regulation of cytokines and chemokines[30] and modification of gene expression[31] in patients with dermatomyositis.

Our trial has several limitations. The duration of the randomized, placebo-controlled phase of the trial was brief at 16 weeks, and patients with juvenile, cancer-associated, or amyopathic dermatomyositis were excluded. The primary end point of the trial was based on the TIS, a composite response score approved by the ACR–EULAR

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Table 2. Results of Primary and Secondary Efficacy End-Point Analyses.*

End Point	IVIG (N=47)	Placebo (N=48)	Difference (95% CI)
Primary end point			
Response at week 16 — % of patients†	79	44	35 (17 to 53)‡§
Secondary end point¶			
Response according to TIS improvement category at week 16 — % of patients			
TIS ≥40: at least moderate improvement	68	23	45 (27 to 63)§
TIS ≥60: major improvement	32	8	24 (8 to 39)§
Response according to TIS improvement category at week 40 — % of patients‖			
TIS ≥20: at least minimal improvement	71	70	NA
TIS ≥40: at least moderate improvement	58	61	NA
TIS ≥60: major improvement	38	30	NA
Modified CDASI**			
Mean change in total activity score (95% CI)			
Baseline to week 16	−9.4 (−12.5 to −6.2)	−1.2 (−3.3 to 1.0)	−8.0 (−11.5 to −4.6)††
Week 16 to week 40	−1.8 (−3.3 to −0.3)	−8.5 (−12.5 to −4.5)	
Mean change in total damage score (95% CI)			
Baseline to week 16	−0.7 (−1.2 to −0.1)	−0.02 (−0.26 to 0.21)	−0.6 (−1.1 to −0.1)††
Week 16 to week 40	0.3 (−0.5 to 1.0)	−0.2 (−0.6 to 0.1)	
SF-36‡‡			
Mean change in physical component summary score (95% CI)			
Baseline to week 16	6.3 (3.6 to 9.0)	2.4 (0.6 to 4.2)	2.1 (−0.5 to 4.7)††
Baseline to week 40	8.4 (4.3 to 12.6)	6.3 (3.4 to 9.3)	
Mean change in mental component summary score (95% CI)			
Baseline to week 16	3.4 (1.1 to 5.6)	2.0 (−0.4 to 4.3)	1.4 (−1.2 to 4.1)††
Baseline to week 40	4.8 (1.5 to 8.2)	7.4 (3.9 to 10.9)	
Individual core measures of the TIS			
Mean change in MMT-8 score (95% CI)			
Baseline to week 16	14.4 (10.0 to 18.8)	3.2 (0.3 to 6.1)	8.6 (4.4 to 12.8)††
Baseline to week 40	20.1 (15.0 to 25.2)	12.0 (9.4 to 14.6)	
Mean change in disease-activity score (95% CI)			
PhGA			
Baseline to week 16	−2.4 (−3.0 to −1.8)	−0.60 (−1.15 to −0.04)	−1.4 (−2.1 to −0.8)††
Baseline to week 40	−3.1 (−3.7 to −2.4)	−2.9 (−3.6 to −2.3)	
PtGA			
Baseline to week 16	−2.2 (−2.9 to −1.5)	−1.1 (−1.8 to −0.5)	−1.0 (−1.8 to −0.1)††
Baseline to week 40	−2.7 (−3.7 to −1.8)	−2.8 (−3.5 to −2.0)	
Mean change (95% CI) in HAQ total score			
Baseline to week 16	−0.6 (−0.7 to −0.4)	−0.2 (−0.3 to −0.1)	−0.4 (−0.5 to −0.2)††
Baseline to week 40	−0.7 (−0.9 to −0.4)	−0.5 (−0.7 to −0.4)	
Mean change in extramuscular disease-activity score (95% CI)			
Baseline to week 16	−2.2 (−2.8 to −1.5)	−0.9 (−1.7 to −0.2)	−1.2 (−1.9 to −0.5)††
Baseline to week 40	−2.7 (−3.4 to −2.0)	−2.6 (−3.4 to −1.9)	

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Table 2. (Continued.)

End Point	IVIG (N=47)	Placebo (N=48)	Difference (95% CI)
Mean change in creatine kinase level (95% CI) — U/liter§§			
Baseline to week 16	−169.2 (−301.2 to −37.2)	−352.8 (−1011.9 to 306.3)	−80.3 (−213.4 to 52.9)††
Baseline to week 40	−169.4 (−326.1 to −12.7)	−56.5 (−247.9 to 134.8)	
TIS¶¶			
Week 4	24.4±20.8	10.7±13.7	NA
Week 8	36.4±21.1	15.8±20.4	NA
Week 12	43.4±21.9	18.5±20.2	NA
Week 16	48.4±24.4	21.6±20.2	NA
Week 28	54.0±20.0	44.4±22.0	NA
Week 40	55.4±21.7	51.1±18.3	NA
Median time to improvement in TIS (95% CI) — days			
At least minimal improvement			
Baseline to week 16	35 (29 to 58)	115 (84 to NC)‖‖	NA
Baseline to week 40	35 (29 to 58)	114 (84 to 195)	NA
At least moderate improvement			
Baseline to week 16	85 (58 to 113)	NC (NC to NC)‖‖	NA
Baseline to week 40	85 (58 to 113)	197 (195 to 282)	NA
Major improvement			
Baseline to week 16	NC (115 to NC)‖‖	NC (NC to NC)‖‖	NA
Baseline to week 40	283 (197 to 290)	283 (203 to NC)‖‖	NA
Median time to confirmed clinical deterioration in placebo-controlled phase and overall period (95% CI) — days	NC***	NC***	NA
Patients meeting criteria for clinical deterioration up to week 16 — no. (%)	0	3 (6)	NA

* Plus–minus values are means ±SD. Week 16 was the end of the double-blind, randomized, placebo-controlled phase of the trial, and week 40 was the end of the open-label extension phase. All patients received IVIG during the open-label extension phase. NA denotes not applicable, and NC not calculated.

† A response was defined as a Total Improvement Score (TIS) of at least 20, indicating at least minimal improvement, at week 16. The TIS is a weighted composite score reflecting the change in a core set of six measures of myositis activity over time; scores range from 0 to 100, with higher scores indicating greater improvement from baseline (a TIS of ≥40 indicates at least moderate improvement, and a TIS of ≥60 indicates major improvement).

‡ P<0.001 by the Cochran–Mantel–Haenszel test.

§ The between-group difference is expressed in percentage points.

¶ The widths of the 95% confidence intervals for the secondary end points have not been adjusted for multiple comparisons, and no inferences can be drawn from these data.

‖ Improvement at week 40 was assessed among 45 patients in the IVIG group and among 46 patients in the placebo group. Conclusions cannot be drawn from the results from week 16 to week 40 (the open-label extension phase), because these results are descriptive only.

** The modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) total activity score ranges from 0 to 100, and the CDASI total damage score ranges from 0 to 32; higher scores indicate worse disease.

†† Data are the least-squares mean difference (95% confidence interval) between IVIG and placebo at week 16.

‡‡ Physical and Mental Component Summary scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better health status.

§§ No notable changes were observed in the levels of other muscle enzymes (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and aldolase).

¶¶ Data on the TIS were available for 45 patients in the IVIG group and for 48 patients in the placebo group at week 4. The corresponding values for the subsequent assessment weeks were 45 and 47 at week 8; 45 and 46 at week 12; 45 and 43 at week 16; 37 and 40 at week 28; and 34 and 35 at week 40.

‖‖ NC in this cell indicates that the median time to improvement or the lower or upper limit of the 95% confidence interval was not calculated with the use of the LIFETEST procedure in the SAS statistical package (SAS Institute) because the percentage of patients with the event was too low.

*** NC in this cell indicates that the median time to confirmed clinical deterioration was not calculated with the use of the LIFETEST procedure because the percentage of patients with the event was too low.

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Table 3. Incidence of Adverse Events That Were Considered to Be Related to the Trial Regimen during the Placebo-Controlled and Extension Phases.

Adverse Event	Randomized, Placebo-Controlled Phase		Randomized and Open-Label Extension Phases
	IVIG (N=52)	Placebo (N=48)	IVIG (N=95)
Any related adverse event — % of patients (no. of events)	58 (113)	23 (38)	65 (282)
Most frequent related adverse event occurring in ≥5% of patients — % of patients			
Headache	37	6	42
Pyrexia	19	6	19
Nausea	12	4	16
Vomiting	6	0	8
Chills	6	2	7
Myalgia	6	0	7
Hypertension	6	6	6
Positive Coombs' test	4	0	5
Serious related nonthromboembolic adverse event — no. of patients/no. of events	1/2	0	2/3
Muscle spasm	1/1*	0	1/1*
Dyspnea	1/1*	0	1/1*
Loss of consciousness	0	0	1/1
Serious related thromboembolic adverse event — no. of patients/no. of events	0	0	5/6
Deep-vein thrombosis	0	0	1/1†
Pulmonary embolism	0	0	1/1†
Cerebrovascular accident	0	0	1/1
Cerebral infarction	0	0	1/1
Hypoesthesia	0	0	1/1
Pulmonary embolism	0	0	1/1
Related adverse events leading to discontinuation — % of patients (no. of events)	2 (6)	0	8 (19)
Fatal adverse events — no. of events	0	0	0

* Muscle spasm and dyspnea were two concurrent events in 1 patient.
† Deep-vein thrombosis and pulmonary embolism were two concurrent events in 1 patient and thus were counted as one thromboembolic adverse event.

that was developed and validated in accordance with a data-driven approach that was followed by consensus among rheumatologists, neurologists, and dermatologists.[19,27,36,37] The TIS has been used as the primary end point in smaller studies.[38,39] Training and experience are needed to acquire the scores for the core-set measures and to interpret the results. Because myositis autoantibodies were not systematically collected, we could not assess the effect of IVIG according to autoantibody subsets. The response rate in the placebo group was high, which may have been caused by the low threshold set for the achievement of minimal improvement, background immunosuppression, and the subjective nature of some end-point measures, such as the PhGA and PtGA of disease activity. A further limitation is that three patients in the placebo group were switched to the IVIG group on account of procedural errors; however, a sensitivity

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analysis showed that these errors did not affect the primary results of the trial.

In this 16-week, randomized, controlled trial of four infusion cycles of IVIG, the percentage of patients with dermatomyositis who had at least minimal improvement according to a composite score of disease activity was significantly greater with IVIG than with placebo; however, IVIG was associated with adverse infusion events and thromboembolism. Larger and longer trials to determine the long-term effects and risks of IVIG in patients with dermatomyositis are warranted.

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APPENDIX

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REFERENCES

1. Dalakas MC. Inflammatory muscle diseases. N Engl J Med 2015;372:1734-47.
2. Oddis CV, Aggarwal R. Treatment in myositis. Nat Rev Rheumatol 2018;14:279-89.
3. Danieli MG, Calcabrini L, Calabrese V, Marchetti A, Logullo F, Gabrielli A. Intravenous immunoglobulin as add on treatment with mycophenolate mofetil in severe myositis. Autoimmun Rev 2009;9:124-7.
4. Ho C, Visintini S. Off-label use of intravenous immunoglobulin for dermatological conditions: a review of clinical effectiveness. Ottawa: Canadian Agency for Drugs and Technologies in Health, April 20, 2018 (https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0965%20-%20Off-label%20IVIG%20Final.pdf).
5. Elovaara I, Apostolski S, van Doorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol 2008;15:893-908.
6. Enk A. Guidelines on the use of high-dose intravenous immunoglobulin in dermatology. Eur J Dermatol 2009;19:90-8.
7. Cherin P, Herson S, Wechsler B, et al. Efficacy of intravenous gammaglobulin therapy in chronic refractory polymyositis and dermatomyositis: an open study with 20 adult patients. Am J Med 1991;91:162-8.
8. Mastaglia FL, Phillips BA, Zilko PJ. Immunoglobulin therapy in inflammatory myopathies. J Neurol Neurosurg Psychiatry 1998;65:107-10.
9. Saito E, Koike T, Hashimoto H, et al. Efficacy of high-dose intravenous immunoglobulin therapy in Japanese patients with steroid-resistant polymyositis and dermatomyositis. Mod Rheumatol 2008;18:34-44.
10. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med 1993;329:1993-2000.
11. Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagul Fibrinolysis 2005;16:313-8.

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12. Marie I, Maurey G, Hervé F, Hellot M-F, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis: report of a series and review of the literature. Br J Dermatol 2006;155:714-21.
13. Caress JB, Kennedy BL, Eickman KD. Safety of intravenous immunoglobulin treatment. Expert Opin Drug Saf 2010;9:971-9.
14. Kapoor M, Hunt I, Spillane J, et al. IVIg-exposure and thromboembolic event risk: findings from the UK Biobank. J Neurol Neurosurg Psychiatry 2022;93:876-85.
15. Chandra T, Aggarwal R. Clinical trials and novel therapeutics in dermatomyositis. Expert Opin Emerg Drugs 2020;25:213-28.
16. Aggarwal R, Charles-Schoeman C, Schessl J, Dimachkie MM, Beckmann I, Levine T. Prospective, double-blind, randomized, placebo-controlled phase III study evaluating efficacy and safety of octagam 10% in patients with dermatomyositis ("ProDERM Study"). Medicine (Baltimore) 2021;100(1):e23677.
17. Bohan A, Peter JB. Polymyositis and dermatomyositis — (second of two parts). N Engl J Med 1975;292:403-7.
18. Bohan A, Peter JB. Polymyositis and dermatomyositis — (first of two parts). N Engl J Med 1975;292:344-7.
19. Rider LG, Giannini EH, Brunner HI, et al. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum 2004;50:2281-90.
20. Rider LG, Aggarwal R, Machado PM, et al. Update on outcome assessment in myositis. Nat Rev Rheumatol 2018;14:303-18.
21. Miller FW, Rider LG, Chung YL, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford) 2001;40:1262-73.
22. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013;65:314-24.
23. Selva-O'Callaghan A, Fernández-Luque A, Martínez-Gómez X, Labirua-Iturburu A, Vilardell-Tarrés M. Venous thromboembolism in patients with dermatomyositis and polymyositis. Clin Exp Rheumatol 2011;29:846-9.
24. Antovic A, Notarnicola A, Svensson J, Lundberg IE, Holmqvist M. Venous thromboembolic events in idiopathic inflammatory myopathy: occurrence and relation to disease onset. Arthritis Care Res (Hoboken) 2018;70:1849-55.
25. Carruthers EC, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study. Ann Rheum Dis 2016;75:110-6.
26. Chung W-S, Lin C-L, Sung F-C, Lu C-C, Kao C-H. Increased risk of venous thromboembolism in patients with dermatomyositis/polymyositis: a nationwide cohort study. Thromb Res 2014;134:622-6.
27. Aggarwal R, Rider LG, Ruperto N, et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: an international myositis assessment and clinical studies group/paediatric rheumatology international trials organisation collaborative initiative. Arthritis Rheumatol 2017;69:898-910.
28. Lundberg IE, Tjärnlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Arthritis Rheumatol 2017;69:2271-82.
29. Miyasaka N, Hara M, Koike T, Saito E, Yamada M, Tanaka Y. Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial. Mod Rheumatol 2012;22:382-93.
30. Dalakas MC. Mechanistic effects of IVIg in neuroinflammatory diseases: conclusions based on clinicopathologic correlations. J Clin Immunol 2014;34:Suppl 1:S120-S126.
31. Quick A, Tandan R. Mechanisms of action of intravenous immunoglobulin in inflammatory muscle disease. Curr Rheumatol Rep 2011;13:192-8.
32. Basta M, Van Goor F, Luccioli S, et al. F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. Nat Med 2003;9:431-8.
33. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest 1994;94:1729-35.
34. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann Neurol 1990;27:343-56.
35. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med 1986;314:329-34.
36. Ruperto N, Pistorio A, Ravelli A, et al. The Paediatric Rheumatology International Trials Organisation provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. Arthritis Care Res (Hoboken) 2010;62:1533-41.
37. Rider LG, Giannini EH, Harris-Love M, et al. Defining clinical improvement in adult and juvenile myositis. J Rheumatol 2003;30:603-17.
38. Lim J, Eftimov F, Verhamme C, et al. Intravenous immunoglobulins as first-line treatment in idiopathic inflammatory myopathies: a pilot study. Rheumatology (Oxford) 2021;60:1784-92.
39. Paik JJ, Casciola-Rosen L, Shin JY, et al. Study of tofacitinib in refractory dermatomyositis: an open-label pilot study of ten patients. Arthritis Rheumatol 2021;73:858-65.

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