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Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis

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Abstract

Background and Objectives

Myasthenia gravis (MG) is an autoimmune disease characterized by dysfunction at the neuromuscular junction. Treatment frequently includes corticosteroids (CSs) and IV immunoglobulin (IVIG). This study was conducted to determine whether immune globulin (human), 10% caprylate/chromatography purified (IGIV-C) could facilitate CS dose reduction in CS-dependent patients with MG.

Methods

In this randomized double-blind placebo-controlled trial, CS-dependent patients with MG (Myasthenia Gravis Foundation of America Class II–Iva; AChR+) received a loading dose of 2 g/kg IGIV-C over 2 days (maximum 80 g/d) or placebo at week 0 (baseline). Maintenance doses (1 g/kg IGIV-C or placebo) were administered every 3 weeks through week 36. Tapering of CS was initiated at week 9 and continued through week 36 unless the patient worsened (quantitative MG score ≥4 points from baseline). CS doses were increased (based on the current CS dose) in patients who worsened. Patients were withdrawn if worsening failed to improve within 6 weeks or if a second CS increase was required. The primary efficacy end point (at week 39) was a ≥50% reduction in CS dose. Secondary and safety end points were assessed throughout the study and follow-up (weeks 42 and 45). The study results and full protocol are available at clinicaltrials.gov/ct2/show/NCT02473965.

Results

The primary end point (≥50% reduction in CS dose) showed no significant difference between the IGIV-C treatment (60.0% of patients) and placebo (63.3%). There were no significant differences for secondary end points. Safety data indicated that IGIV-C was well tolerated.

Discussion

In this study, IGIV-C was not more effective than placebo in reducing daily CS dose. These results suggest that the effects of IGIV-C and CS are not synergistic and may be mechanistically different.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

AE = adverse event; **CS** = corticosteroid; **IGIV-C** = immune globulin (human), 10% caprylate/chromatography purified; **IP** = investigational product; **IVIG** = IV immunoglobulin; **LOCF** = last observation carried forward; **MC** = myasthenic crisis; **MG** = myasthenia gravis; **MG-ADL** = MG-Activities of Daily Living; **MG-QOL** = MG-Quality of Life Instrument; **QMG** = quantitative MG; **SAE** = serious AE; **TEAE** = treatment-emergent AE; **WOCF** = worst observation carried forward.

Trial Registration Information

The trial was registered on clinicaltrialsregister.eu (EudraCT #: 2013-005099-17) and clinicaltrials.gov (identifier NCT02473965).

Classification of Evidence

This study provides Class II evidence that IVIG infusions in adult patients with MG do not increase the percentage of patients achieving a ≥50% reduction in corticosteroid dose compared with placebo.

Myasthenia gravis (MG) results from autoimmune-mediated dysfunction at the neuromuscular junction. This dysfunction manifests through autoantibodies to postsynaptic proteins—commonly the acetylcholine receptor (85%–90%) and less frequently lipoprotein-related protein 4 and muscle-specific kinase.[1,2]

For MG unresponsive to cholinesterase inhibitors, the primary treatment is immunosuppression. The drugs of first choice are frequently corticosteroids (CSs). Treatment of severe MG or exacerbations frequently includes plasma exchange or IV immunoglobulin (IVIG).[3-5] Plasma exchange was shown to improve muscle strength in patients with MG.[6,7] Treatment with IVIG was found to produce effects equivalent to PE with fewer adverse effects.[8-10] The clinical benefit of IVIG during exacerbations of MG warranted inclusion in clinical guidelines of many neurologic societies and consideration as a core component of treatment for acute MG.[11,12]

Despite CS being first-line immunosuppressive therapy, long-term CS use is associated with potentially serious side effects. Because of this downside, tapering of CS to the minimum effective dose is a goal of MG management.[13] However, decreasing the dose without worsening the underlying MG is often challenging. Moreover, there are no standard tapering guidelines. In this study, immune globulin (human), 10% caprylate/chromatography purified (IGIV-C) was tested in CS-dependent patients with MG to determine whether IGIV-C administration could increase the percentage of patients achieving a ≥50% CS dose reduction compared with placebo.

Methods

Study Design

This phase 2 study was a multicenter randomized double-blind placebo-controlled trial conducted in 8 countries at 24 centers that screened and/or enrolled CS-dependent patients with MG. Sites were in Canada, the Czech Republic, Estonia, Germany, Hungary, Lithuania, Poland, and the United States.

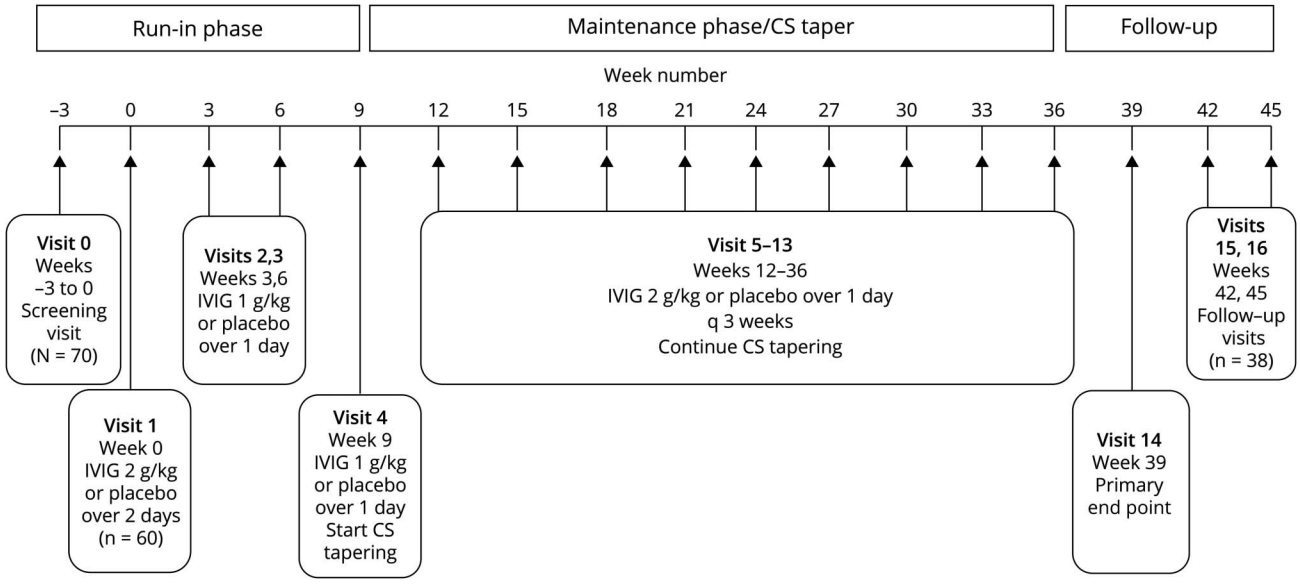
The primary objective was to evaluate the efficacy of IGIV-C compared with placebo (sterile 0.9% sodium chloride injection, United States Pharmacopeia [USP] or equivalent) in reducing the maintenance dosage of CSs in CS-dependent patients with MG. IGIV-C was given as an initial loading dose (2 g/kg)[5,10,14,15] followed by 12 maintenance doses (1 g/kg) every 3 weeks[15,16] (through week 36). The primary end point was the percentage of patients achieving a 50% or greater reduction in CS dose (prednisone equivalent) at week 39 from baseline/week 0.[17] The study had 4 phases: (1) screening, (2) investigational product (IP) run-in maintenance period, (3) CS tapering IP maintenance phase, and (4) safety/follow-up phase. Patients were randomized 1:1 to IGIV-C or placebo treatment. Randomization was stratified by baseline CS dose (15–40 mg/d of prednisone equivalent or 41–60 mg/d of prednisone equivalent).

Treatments

Patients randomized to IGIV-C treatment received a loading dose (2 g/kg) at the baseline visit (week 0) (Figure 1). The loading dose was divided over 2 days, with allowance for up to 4 days due to higher body weight (limit 80 g/d) or to increase tolerability. Maintenance doses of 1 g/kg over 1 day were given every 3 weeks through week 36. A longer dosing period (2 days) was allowed to allow for higher doses (maximum dose 80 g/d) or tolerability accommodations. Patients randomized to placebo received an equivalent volume of normal saline (0.9% sodium chloride, USP). IGIV-C and placebo were double blinded during loading dose and maintenance doses.

Tapering of CS doses was initiated after 3 doses of IGIV-C or placebo (week 9). If the patient's CS dose was >40 mg prednisone (or equivalent)/day, the dose was reduced by 10 mg (or equivalent)/day at each visit (every 3 weeks). If the patient's CS dose was ≤40 mg prednisone equivalent/day, the dose was reduced by 5 mg equivalent/day every 3 weeks. Patients on every-other-day CS dosing tapered by a commensurate amount, e.g., if >80 mg/every other day, the decrease every 3 weeks was 20 mg. The final CS taper to 0 mg prednisone equivalent/day was at the medical discretion of the investigator. Investigators attempted to maintain non-CS

Figure 1 Timeline for Evaluation of Potential Steroid-Sparing Effects of IV Immunoglobulin (IGIV-C) in Myasthenia Gravis



Additional information on patient disposition throughout the study is included in Figure 2. CS = corticosteroid.

MG medications consistently unless the patient experienced adverse effects from the treatment or worsening of MG. Worsening was defined as an increase of ≥4 points in the patient's quantitative MG (QMG) score from baseline.[17]

If MG worsening occurred during the CS tapering phase, the patient's CS dose was increased by 20 mg (prednisone equivalent if the current dose was ≥15 mg) or by 15 mg if <15 mg. In the case of every-other-day CS dosing, the patient's CS dose was increased by a commensurate amount, e.g., by 40 mg if the current dose was ≥30 mg. The increased dose was maintained for 6 weeks (next 2 consecutive visits). The patient was allowed to continue the study if the patient's MG stabilized, defined as an increase of ≤3 points in the patient's QMG score relative to baseline (week 0). If the worsening of MG was not improved within the 6-week period after the dose increase, the patient was withdrawn from the study.

If the increased CS dose successfully ameliorated the worsening of the QMG score (≤3-point increase over baseline) and the patient's clinical symptoms returned to baseline, a second CS tapering attempt was made. On the second attempt, the CS dose was not reduced below the dose at which symptom worsening was previously observed. Any patient whose symptoms required a second dose increase was withdrawn from the study.

Selection of Study Patients

Male and female patients aged 18–85 years, positive for anti-AChR antibody and with a confirmed diagnosis of generalized MG (Myasthenia Gravis Foundation of America [MGFA] Class II, III, IV, or V), were eligible for screening.[18] At screening, potential participants were required to have MG symptoms controlled by CS and historical MGFA Class II–IVa (MGFA Class IVb and V; only ocular MG excluded). Systemic CS for at least 3 months was required with a stable CS (prednisone equivalent) dose ≥15 and ≤60 mg/d for 1 month before screening. For potential particpants on an every-other-day dosing schedule, half their dose was required to meet the daily dose criteria. These criteria defined steroid-dependent MG for this study. In the opinion of the investigator, tapering of the patient's CS dose must have been clinically appropriate, and at least 1 previous taper attempt was required. Written informed consent was required.

Patients were excluded from the study if they had had any change in non-CS concomitant immunosuppressive therapy in the 6 months before screening or any change in CS dose or acetylcholinesterase inhibitor dose in the month before screening. A 3-point change in the QMG score (increase or decrease) between the screening and baseline (week 0) visits was disqualifying. A myasthenic crisis (MC) episode in the month before screening and any history of MC or hospitalization for an MG exacerbation associated with a CS taper were exclusionary. Other exclusions were malignancy in the past 5 years, thymoma requiring potential surgery, thymectomy in the prior 6 months, history of cardiovascular disease, renal impairment, elevated liver enzymes, or anemia.

Treatment within the last 12 months with an immunomodulating monoclonal antibody, plasma exchange within the past 3 months, or current anticoagulant therapy was disqualifying. A history of nonresponse to IVIG for MG, immunoglobulin therapy in the 3 months before screening, intolerance, or hypersensitivity to IVIG, thrombotic reactions to IVIG, or a known hyperviscosity or hypercoagulable state were also exclusionary. Patients with known IgA deficiency and anti-IgA antibodies were not eligible.

Table 1 Demographics of the Modified Intent-to-Treat Study Population

Characteristic	IGIV-C (n = 30)	Placebo (n = 30)	Total (N = 60)
Age, mean (SD)	47.6 (17.0)	48.5 (14.5)	48.1 (15.7)
Sex, n (%)			
Female	16 (53.3)	18 (60.0)	34 (56.7)
Male	14 (46.7)	12 (40.0)	26 (43.3)
Race, n (%)			
White (Caucasian)	27 (90.0)	27 (90.0)	54 (90.0)
Black (African American)	0	1 (3.3)	1 (1.7)
Asian	3 (10.0)	2 (6.7)	5 (8.3)
American Indian or Alaskan Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	0	2 (6.7)	2 (3.3)
Non-Hispanic or Latino	30 (100.0)	28 (93.3)	58 (96.7)
Geographic region, n (%)			
North America	11 (36.7)	13 (43.3)	24 (40.0)
Europe	19 (63.3)	17 (56.7)	36 (60.0)
Clinical history			
Prior thymectomy, n (%)	23 (76.7)	21 (70.0)	44 (73.3)
Time since MG diagnosis (yr), mean (SD)	8.96 ± 6.67	7.37 ± 7.16	8.17 ± 6.91

Abbreviations: IGIV-C = immune globulin (human), 10% caprylate/chromatography purified; MG = myasthenia gravis.

Investigational Product

The IGIV-C product used in this trial was Gamunex-C (immune globulin injection (human) 10% caprylate/chromatography purified, Grifols Therapeutics, LLC, Research Triangle Park, NC).[15] Normal saline (sterile 0.9% sodium chloride injection, USP) or equivalent served as the placebo in this study. The infusion was prepared by an unblinded pharmacist or designee such that the placebo infusion was indistinguishable from the IGIV-C infusion.

Study End Points

The primary efficacy end point for this study was the percent of patients achieving a 50% or greater reduction in CS dose at week 39 from baseline (week 0). Secondary efficacy end points measured from baseline (week 0) to week 39 were the percent reduction in CS daily dose and the time to the first episode of MG worsening (as defined above).

Exploratory end points related to CS therapy included the following: percent of patients achieving a ≥75% reduction in CS dose at week 39, percent of patients achieving a CS dose ≤7.5 mg (prednisone equivalent) at week 39, percent of patients CS-free at week 39, change in fasting serum glucose at week 39 vs baseline, percent of patients with fasting glucose ≤125 mg/dL at week 39 vs baseline, and a change in hemoglobin A1c at week 39 compared with baseline (week 0).

Exploratory end points related to MG were as follows: percent of patients experiencing an MC or worsening of MG requiring hospitalization through week 39 and week 39 through week 45, number of episodes of MG worsening from baseline (week 0) to week 39, changes in a 15-item MG-Quality of Life Instrument (MG-QOL 15) at weeks 39, 42, and 45 compared with baseline (week 0), changes in MG-Activities of Daily Living (MG-ADL) score at weeks 39, 42, and 45 from baseline (week 0), and changes from baseline (week 0) in the activity (binding, blocking, and modulating) of anti-acetylcholine receptor antibodies at week 39 (Covance Central Laboratory, Indianapolis, IN). In addition, the change in serum IgG levels from baseline (week 0) was measured at weeks 9, 24, and 39.

The guide for CS taper was the QMG score.[17] A 3-point improvement in the QMG score reflects a clinically significant improvement.[19] Study patients taking cholinesterase inhibitors were instructed not to take these medications for 12 hours before QMG testing. The MG-QOL 15 is a measure of mobility, symptoms, general contentment, and emotional well-being as assessed by the patient.[20-22] The MG-ADL score is designed to assess the effects of MG on usual daily activities. A 2-point improvement in MG-ADL was designated as clinically significant.[23] The MG Composite scale has been recommended by the MGFA as a quantitative measure for patients with generalized MG.[24,25] A 3-point improvement in the MG Composite was correlated with clinical improvement and meaningful improvement to patients.[26]

Safety Assessments

Safety assessment included reporting of all adverse events (AEs), serious AEs (SAEs), and discontinuations due to AEs. Patients were also monitored for thromboembolic events and hemolysis. Thromboembolic risk was assessed at screening, baseline (week 0; before infusion), after completion of the first loading dose infusion, after completion of the last loading dose infusion, and at weeks 3, 6, and 24 on completion of the maintenance infusion (hemolysis assessments were at these times plus 1 week postinfusion).

Statistical Analyses

The modified intent-to-treat population was the primary population for efficacy analysis, and patients were categorized according to their treatment. Primary and secondary analyses were also performed on the modified intent-to-treat population. The average daily CS dose was calculated for each patient based on the prescribed dose at the visit and the time interval between visits considering any dose changes in the interim between visits. The unstratified treatment comparison was made using the Fisher exact test. The stratified treatment comparison was made using the Cochran-Mantel-Haenszel

Table 2 Baseline or Screening Data on the Modified Intent-to-Treat Study Population

Characteristic mean (SD)	IGIV-C (n = 30)	Placebo (n = 30)	Total (N = 60)
Screening weight (kg)	78.6 (18.8)	79.7 (20.5)	79.1 (19.5)
Height (cm)	171.2 (9.6)	167.8 (8.9)	169.5 (9.4)
Screening BMI (kg/m^2)	26.7 (5.8)	28.1 (5.5)	27.4 (5.7)
Baseline QMG total score	12.1 (7.0)	11.2 (6.5)	11.6 (6.7)
Baseline MG composite total score	11.4 (9.7)	11.3 (9.4)	11.3 (9.5)
Baseline MG-QOL 15 total score	27.2 (13.8)	21.8 (13.3)	24.5 (13.7)
Baseline MG-ADL total score	5.3 (3.8)	5.1 (4.2)	5.2 (4.0)
Baseline fasting serum glucose (mg/dL)	98.0 (27.7)	106.6 (47.7)	102.3 (38.9)
Baseline serum IgG trough (g/L)	8.702 (2.616)	8.685 (1.962)	8.693 (2.292)
Baseline AChR-binding Ab (nmol/L)	68.02 (145.68)	71.56 (188.20)	69.79 (166.87)
Baseline AChR-blocking Ab (%)	28.6 (19.5)	22.0 (19.3)	25.3 (19.5)
Baseline AChR-modulating Ab (%)	47.9 (25.2)	51.5 (24.8)	49.7 (24.9)
Baseline HbA1c (%)	5.83 (0.71)	5.84 (0.89)	5.84 (0.80)
Daily prednisone dose prescribed[a] (mg)	24.5 (10.0)	26.9 (11.3)	25.7 (10.6)
Stratification based on prednisone dose,[a] n (%)			
15–40 mg/d	29 (96.7)	28 (93.3)	57 (95.0)
41–60 mg/d	1 (3.3)	3 (6.7)	3 (5.0)
Other nonsteroidal immunosuppressant therapy, n (%)[b]	14 (46.7)	21 (70.0)	35 (58.3)

Abbreviations: Ab = antibodies; AChR = acetylcholine receptor; ADL = activities of daily living; BMI = body mass index; HbA1c = hemoglobin A1c; IgG = immunoglobulin G; IGIV-C = IV immunoglobulin–caprylate/chromatography process; MG = myasthenia gravis; QMG = quantitative MG; QOL = quality of life.
[a] Prednisone or equivalent dose of another corticosteroid.
[b] Nonsteroidal immunosuppressants that were part of the background regimen included azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, and cyclophosphamide.

test adjusted for baseline CS dose (15–40 vs 41–60 mg/d). Analyses on secondary efficacy end points were performed using analysis of covariance. Missing data from patients who withdrew from the study were handled using the last observation carried forward (LOCF) method.

For the exploratory end points, the Fisher exact test was used for treatment comparisons without adjustment for stratified baseline prednisone equivalent dose due to small cell size. For patients who discontinued the study early with adverse outcomes related to MG, the missing CS dose at week 39 is imputed using the worst observation carried forward (WOCF) method. For participants who do not have CS dose at week 39 due to other reasons, the LOCF is used to impute the missing CS dose at week 39. Safety analyses were performed on data from the safety population and were analyzed descriptively.

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request. The study results and full protocol are available at clinicaltrials.gov/ct2/show/NCT02473965.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by Ethics Committees, Institutional Review Boards, or Research Ethics Boards at all participating institutions (complete list in the supplemental material), and authorization was granted by regulatory authorities in all participating countries. All participants provided written informed consent. The study was conducted in accordance with appropriate local laws and regulations, the international standards of Good Clinical Practice, and the Declaration of Helsinki. The trial was registered on clinicaltrialsregister.eu (EudraCT #: 2013-005099-17) and clinicaltrials.gov (identifier NCT02473965).

Results

Baseline Characteristics of Treatment Groups

Table 1 shows the demographic data for the IGIV-C treatment group and the placebo group. The treatment groups were very similar in terms of demographics, physical characteristics, and disease status (Table 2).

Patient Disposition

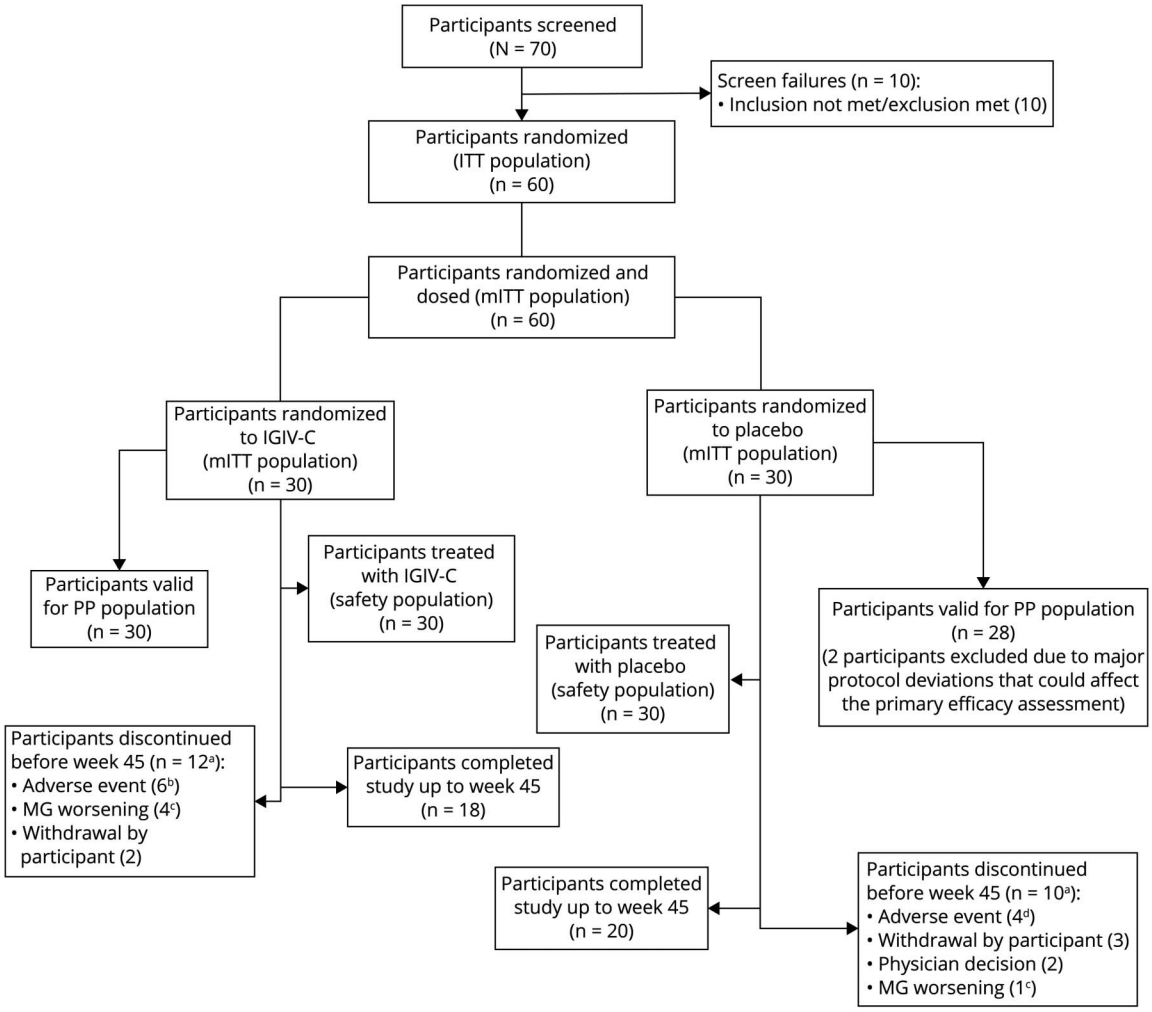
Seventy patients were screened for this study at 24 sites, and 60 were randomized (intent-to-treat population) (Figure 2). All 60 of these patients were included in the modified intent-to-treat population for efficacy analyses and the safety population for AE analyses. Thirty-eight patients (63.3%) completed all study visits. Similar numbers of completions were seen in both treatment groups: 18 (60.0%) IGIV-C and 20 (66.7%) placebo.

Of the 12 patients in the IGIV-C group that discontinued prematurely, 6 were due to AEs, 4 for MG worsening, and 2 withdrew consent (Table 3). Of the 10 premature withdrawals in the placebo group, 4 were due to AEs, 1 was due to MG worsening, 3 withdrew consent, and 2 were due to investigator decision (non-AE). MG worsening refers to protocol-directed discontinuation due to failure of the CS taper (see the Treatments section).

Efficacy End Points

The primary efficacy end point was the percentage of patients who achieved a 50% reduction in CS dose (week 39 vs baseline

Figure 2 Disposition of Participants



[a]All discontinuations effectively contributed to corticosteroid (CS) tapering efficacy end points except 3 participants who withdrew before week 9 (1 participant on IV immunoglobulin [IGIV-C] and 2 participants on placebo), as CS tapering was not to begin until at week 9 per the protocol. [b]Adverse events included worsening of myasthenia gravis (MG) (n = 4), hemolysis (n = 1), and dizziness (n = 1). [c]MG worsening in this figure refers to protocol-mandated discontinuation due to failed CS taper: CS unresponsive or second episode refers to MG worsening. [d]Adverse events included MG-related findings (n = 3) and sepsis (n = 1).

[week 0]). There was no significant difference between the treatment groups in this primary end point (p = 1.00). In the IGIV-C treatment group, 60.0% of the patients reached a 50% reduction in CS dose while 63.3% reached that level in the placebo group (Figure 3).

Analysis of the primary end point was also conducted with patients stratified by CS dose at baseline. However, because the number of patients in the higher CS dose stratum (41–60 mg prednisone equivalent per day) was very small and less than anticipated (n = 1 IGIV-C; n = 2 placebo), no valid statistical analysis could be conducted. Therefore, an additional analysis was conducted based on the median baseline CS dose prescribed at study entry.

Patients were divided by daily CS dose below and equal to or above the baseline median CS dose (20 mg/d prednisone or equivalent). For both treatment groups, patients on higher CS doses (>20 mg/d) were more likely to achieve a 50% reduction in their CS dose at week 39 than patients on lower CS doses (≤20 mg/d). This finding was seen in both arms: IGIV-C: 70.0% vs 55.0% and placebo: 66.7% vs 60.0% (Figure 3) with no meaningful between-arm difference in either subgroup (p = 1.00).

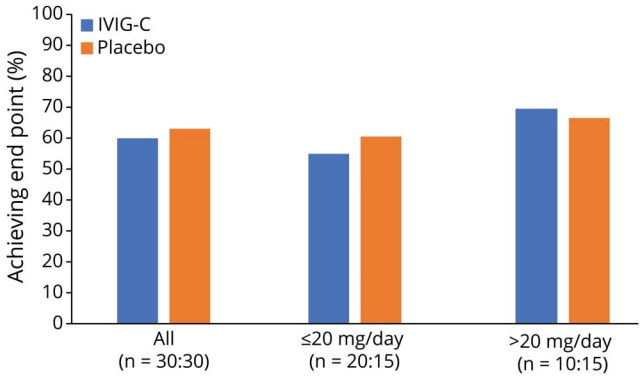
Secondary end points analyzed in this study were the percent reduction in CS dose and the time to first episode of worsening of MG symptoms. There were no statistically significant differences between the treatment groups in percent reduction in CS dose (52.04% ± 44.49% reduction [mean ± SD] in the IGIV-C arm; 54.69 ± 51.36% reduction in the placebo arm) or time to first episode of worsening (25th percentile of time to first worsening [≥+4 points QMG score] 33.10 weeks IGIV-C; 30.10 weeks placebo).

Table 3 Patient Disposition Over the Course of the Study

Patient disposition	IGIV-C, n (%)	Placebo, n (%)	Total, N (%)
Screened	—	—	70
Randomized (ITT population)	30 (100.0)	30 (100.0)	60 (100.0)
mITT population	30 (100.0)	30 (100.0)	60 (100.0)
Per-protocol population	30 (100.0)	28 (93.3)	58 (96.7)
Safety population	30 (100.0)	30 (100.0)	60 (100.0)
Discontinued prematurely	12 (40.0)	10 (33.3)	22 (36.7)
Adverse event	6 (20.0)	4 (13.3)	10 (16.7)
MG worsening	4 (13.3)	1 (3.3)	5 (8.3)
Withdrawal	2 (6.7)	3 (10.0)	5 (8.3)
Physician decision	0	2 (6.7)	2 (3.3)

Abbreviations: IGIV-C = IV immunoglobulin–caprylate/chromatography process; ITT = intent to treat; mITT = modified intent to treat.

Figure 3 Percentage of Patients Achieving the Primary Efficacy End Point: 50% Reduction in Corticosteroid (CS) Dose



Patients were stratified according to whether entry CS dose was at or below the median (n = 20 IGIV-C; n = 15 placebo) or above the median baseline dose (20 mg prednisone equivalent) (n = 10 IGIV-C; n = 15 Placebo). There were no significant differences between the treatment groups overall. Subgroups illustrate that numerically in both arms, a higher percentage achieved primary end point if entering in the higher CS dose quantile. IGIV-C = immune globulin (human), 10% caprylate/chromatography purified; IVIG = IV immunoglobulin.

The probability of MG worsening over time during the study period was calculated using the Kaplan-Meier method (Figure 4). This analysis showed no difference in the probability of MG worsening between the treatment groups (p = 0.744).

There were no significant differences in the exploratory efficacy end points except for IgG trough levels. There was a significantly larger increase in IgG trough levels in the IGIV-C treatment group than in the placebo group. All discontinuations effectively contributed to efficacy CS tapering end points except 3 before week 9 (1 active; 2 placebo).

Safety End Points

The safety data showed that IGIV-C treatments were well tolerated. The mean number of doses administered, the mean duration of exposure, and the mean number of infusion days were similar for both treatment groups.

Ninety percent (90.0%) of the patients in the IGIV-C group experienced at least 1 treatment-emergent AE (TEAE) similar to the placebo group (93.3%). The most common TEAEs (>15%) in the IGIV-C treatment group were headache, MG worsening, upper respiratory tract infection, and nausea. In the placebo group, the most common TEAEs were arthralgia, back pain, and nasopharyngitis.

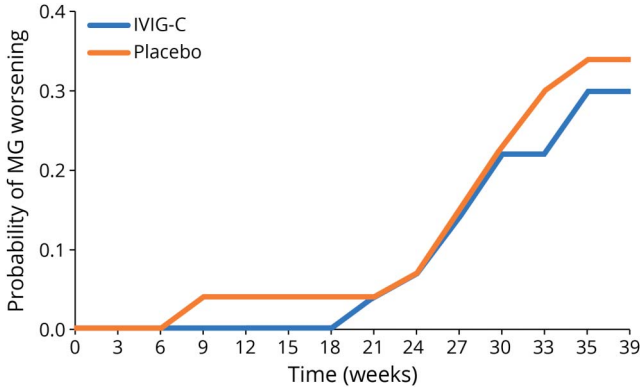
Most TEAEs were mild or moderate in both groups. Severe TEAEs were rare: IGIV-C: 4.5% and placebo: 13.4%.

SAEs were reported for 4/30 (13.3%) patients in the IGIV-C group and 6/30 (20.0%) patients in the placebo group. There was 1 death in the IGIV-C group and 2 deaths in the placebo group. One death was associated with MG in each arm. The deaths were attributed to an MG exacerbation, sepsis, and cardiac arrest in the setting of MG crisis, staphylococcal pneumonia, and acute respiratory failure. SAEs of MG exacerbations or MG crises were reported in 7 patients: 4 patients (13.3%) in the IGIV-C treatment group and 3 in the placebo group (10.0%).

Among 4 participants in the IGIV-C treatment group who had SAEs of MG exacerbation and/or MG crisis, all 4 had tapered completely off CS (CS-free), with MG being stable off CS before worsening precipitously. Among these 4 participants, 1 participant died despite increased CS dose and administration of commercial immunoglobulin, and 1 participant unresponsive to 8 plasma exchanges developed a permanent disability (tracheal narrowing) from prolonged intubation.

Among a total of 3 participants in the placebo treatment group with SAEs of MG exacerbation/MG crisis, 1 participant was

Figure 4 Kaplan-Meier Analysis of Probability of Myasthenia Gravis (MG) Worsening Over the Study Period



There was no significant difference between the treatment groups (p = 0.744) based on the log-rank test. MG worsening was defined as a ≥ 4-point increase in the quantitative MG (QMG) score.

completely tapered off to 0 mg CS at the time of MG exacerbation/crisis. Although hospitalized and treated with IVIG, CS was not reintroduced, and he died despite interventions. The other 2 placebo participants with SAEs of MG exacerbation/crisis requiring hospitalization had tapered to a nadir CS dose of 4 mg methylprednisolone or 10 mg prednisone daily.

Seven (23.3%) of 30 participants in the IGIV-C treatment group and 4/30 (13.3%) participants in the placebo treatment group had AEs leading to withdrawal. The AEs resulting in discontinuation were most commonly worsening of MG, MG exacerbations, and MG crisis. Other AEs leading to withdrawal included hemolysis, dizziness, sepsis, and cardiac arrest.

Classification of Evidence

This study provides Class II evidence that IVIG infusions in adult patients with MG do not increase the percentage of patients achieving a ≥50% reduction in corticosteroid dose compared with placebo.

Discussion

The primary objective of this study was to determine whether IGIV-C could facilitate the tapering of CS doses in CS-dependent patients with MG. No significant difference was seen in the primary end point of the number of patients achieving ≥50% reduction in CS dose at week 39 compared with baseline between IGIV-C treatment and placebo. It is important to note that this result may have been influenced by one of the selection criteria: eligible patients must have completed at least 1 prior attempt to taper CS. This assured that patients were on the lowest possible CS dose and that CS dose reduction was possible in these patients.

Analyses of secondary end points showed no significant effect of IGIV-C treatment on percent change in CS dose or time to the first episode of MG worsening. Similarly, exploratory efficacy measures showed no differences between the treatment groups. Overall, no benefit was observed for IGIV-C treatment over placebo in facilitating the reduction of CS dose in patients with MG in this 36-week treatment trial.

A key prospective element of the study design regarding patient disposition was that discontinued patients fully contributed to the efficacy end points regarding CS dose reduction. According to the protocol, patients were required to discontinue the study if they experienced MG worsening (QMG increase ≥ 4 points) that was unresponsive to a CS dose increase or worsening that recurred on a second CS taper. Predefined truncation of the CS taper assured that tapering failures were adequately reflected in the efficacy analyses, thereby minimizing the effect of premature discontinuations. Furthermore, in the efficacy analyses, LOCF was used, and for all CS-related end points, WOCF was used if discontinuations were due to treatment-emergent MG SAEs. In fact, all discontinued patients effectively contributed to the CS tapering efficacy end point except for 3 who discontinued before week 9 (1 IGIV-C and 2 placebo). Thereby, premature discontinuations did not affect the robustness of the efficacy results.

CSs are an important tool for treating MG not completely responsive to acetylcholinesterase inhibitors. A retrospective analysis showed that 74% of patients with MG responded to CS therapy.[16] The efficacy of CSs for treating MG may be due to their immunosuppressive effects.[27] Long-term use of CSs, however, can be associated with numerous serious adverse effects including weight gain, Cushing syndrome, impaired glucose tolerance, dyslipidemia, hypertension, osteoporosis, and, rarely, avascular necrosis of the femoral head.[13,28] The effect of these AEs can be reduced by dose reduction.[13] Therefore, the goal of CS therapy for MG is a minimum effective dose.

IVIG is also an effective treatment for MG[3,4] in certain settings and has anti-inflammatory and immunosuppressive effects.[29] The exact mechanisms are unclear but may include the inhibition of dendritic cell maturation, modulation of proinflammatory cytokine production,[30] reduced activation of complement pathways,[31] and blockade of Fc receptors on macrophages.[32] These mechanisms make IVIG useful in the treatment of other autoimmune neuromuscular diseases, e.g., chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.

Similar to the results seen with other immunosuppressive agents,[33-35] the current study showed that IVIG was not superior to placebo in allowing CS dose reduction. These results suggest that immunomodulation alone was insufficient to facilitate dose reduction. The anti-inflammatory effects of IVIG also did not allow dose reduction beyond that achieved with placebo. These results suggest that the effects of CS on MG are mechanistically different and cannot be compensated for by the immunomodulatory properties of IVIG.

The duration of this study (36-week treatment, primary end point assessment at 39 weeks and follow-up through 45 weeks) was designed to evaluate whether a 50% reduction in CS dosage could be realized as a tangible and meaningful benefit in a reasonable time frame. The duration of the CS taper portion of the study (starting at week 9 and ending at week 36) was 27 weeks or approximately 7 months. Therefore, the primary efficacy test for this study was whether stably administered IGIV-C could provide needed therapeutic support to allow a 50% reduction in CS dose over approximately 7 months—a practical time period to assess the clinically relevant effect of adding IVIG to an existing MG regimen.

A possible reason that IGIV-C did not produce a significant benefit above placebo might be that the placebo group itself achieved a ≥50% dose reduction 63% of the time. This improvement in the placebo group may make it difficult to demonstrate additional improvement from IVIG and has been seen in other MG trials.[5,12,36] This may reflect additional immunosuppressive effects of CS from relatively recent dosage changes, as the criteria for trial inclusion required at least 3 months of CS dosing before entry but only 1 month of stable CS dosing.

Longer durations of follow-up are sometimes feasible in retrospective studies, although these lack contemporaneous controls

and also may have significant variability in patient management and evaluation periods. For example, a recent uncontrolled, retrospective study[37] showed a significant reduction in CS dosing (<50%) with long-term IG dosing (subcutaneous or IV). The patients were treated for 15–78 months. This study found that CS dosing could also be reduced by other immunosuppressants.

The TEAEs seen in this study were similar to other studies of IVIG and CS in MG.[33-35,38,39] IVIG remains safe in patients with MG and may have a mechanism of action separate from and not synergistic or additive with that of CS. IGIV-C did not reduce the incidence of MG exacerbations/worsening during CS taper vs placebo. MG-related SAEs in both treatment groups during CS tapering emphasize that a CS taper should be conducted slowly with careful monitoring of patients for MG exacerbations.

In conclusion, the data from this study suggested no benefit of IGIV-C treatment over placebo in the reduction of daily CS dose. However, patients on higher baseline CS doses at baseline (≥20 mg/d prednisone equivalent) were more likely to achieve 50% reduction in dose than patients on lower baseline doses (<20 mg/d prednisone equivalent) in both treatment arms. The 50% reduction benchmark in the higher CS dose subgroup may have allowed for residual beneficial CS effects and was thereby easier to achieve.

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Disclosure

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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Disputes & Debates: Editors' Choice

Editors' Note: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

Dr. Michelle and investigators from the Johns Hopkins Myositis Center retrospectively analyzed clinical and pathologic data from 335 patients with inclusion body myositis (IBM) to identify unique phenotypes of the condition. The distinct clinical and pathologic characteristics of each demographic subgroup may be useful in clinical trial design and prognostication. Among the key findings, patients meeting criteria for IBM were diagnosed after a mean delay of 5 years, with fewer than half of patients (43%) with muscle biopsies demonstrating all 3 pathologic hallmarks (endomysial inflammation, rimmed vacuoles, and mononuclear invasion). Based on the limited sensitivity of muscle biopsy, Dr. Stenzel and colleagues agree with the authors that one should emphasize the clinical examination in making a diagnosis of IBM and supplement these observations with more advanced diagnostic testing and sequencing of mitochondrial DNA in muscle biopsy samples. Dr. Michelle et al. note that immunohistochemical testing and mitochondrial testing are not available in most US laboratories and their specificity in differentiating IBM from polymyositis may be limited. They stress the value of the 2011 European Neuromuscular Centre consensus diagnostic criteria, which combine clinical and pathologic features to establish the diagnosis. An update to these 2011 criteria is anticipated shortly.

James E. Siegler, MD, and Steven Galetta, MD
Neurology® 2023;101:499. doi:10.1212/WNL.0000000000207782

Reader Response: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

Werner Stenzel (Berlin), Hans-Hilmar Goebel (Berlin), and Felix Kleefeld (Berlin)
Neurology® 2023;101:499–500. doi:10.1212/WNL.0000000000207783

We read with interest the article by Michelle et al.[1] about clinical subgroups and factors associated with progression in patients with inclusion body myositis (IBM). The authors used Griggs criteria,[2] European Neuromuscular Centre 2011 criteria, and Lloyd Greenberg data-derived criteria,[3] including endomysial inflammation, invasion of non-necrotic fibers, and rimmed vacuoles.

This triad was only seen in 43% of biopsies and rimmed vacuoles were present in only 66%, which are low percentages. The authors argued that incomplete histopathologic patterns—apart from clinical misdiagnosis—may be a reason for misclassification as polymyositis (PM). They proposed less invasive diagnostic criteria and putting more value on clinical examination, such as quadriceps and finger-flexor weakness.

It has been shown that a diagnosis of PM has to be re-evaluated with modern approaches[4] and that many of the PM-mito cases are actually patients with early IBM, which cannot be identified on clinical grounds only because many patients have, in fact, mild nonspecific clinical signs.[5]

We recommend more precise and complete diagnostic procedures,[4] including major histocompatibility complex class I and II, p62, TAR DNA-binding protein 43, complement patterns,

Author disclosures are available upon request (journal@neurology.org).

T-cell characterization,[6] and mitochondrial abnormalities,[7] to determine whether a biopsy specimen corresponds to IBM.

1. Michelle EH, Pinal-Fernandez I, Casal-Dominguez M, et al. Clinical subgroups and factors associated with progression in patients with inclusion body myositis. *Neurology*. 2023;100(13):e1406-e1417. doi:10.1212/WNL.0000000000206777
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Author Response: Clinical Subgroups and Factors Associated With Progression in Patients With Inclusion Body Myositis

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We thank Stenzel et al. for their comment on our article[1] and agree that muscle biopsy analysis should ideally use more "modern" pathologic analysis to help distinguish polymyositis (PM) from inclusion body myositis (IBM). We have recently shown that transcriptomics[2,3] or reverse transcription PCR detection of mis-splicing events from muscle biopsies because of TAR DNA-binding protein 43 loss of function is sensitive and specific for a diagnosis of IBM.[4] This finding confirms a recent report that detection of mis-splicing predicts clinical development of IBM among patients diagnosed pathologically with "PM-Mito."[5]

In clinical practice, however, many clinical pathology laboratories in the United States do not routinely perform extensive immunohistochemical studies to help distinguish PM from IBM. Furthermore, the specificity of some pathologic features reported in IBM, for example, the presence of p62-positive aggregates,[5] have been questioned and require further validation. For these reasons, the 2011 European Neuromuscular Centre (ENMC) consensus diagnostic criteria use a combination of clinical and pathologic features to help establish the diagnosis.[6] Recent and ongoing international IBM clinical trials use the 2011 ENMC criteria, although an ENMC meeting is planned this year to update the diagnostic criteria.[7]

Hopefully, development of more precise pathologic criteria can be widely agreed upon and used to diagnose IBM more accurately in the future.

1. Michelle EH, Pinal-Fernandez I, Casal-Dominguez M, et al. Clinical subgroups and factors associated with progression in patients with inclusion body myositis. *Neurology*. 2023;100(13):e1406-e1417. doi:10.1212/WNL.0000000000206777
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CORRECTION

Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis

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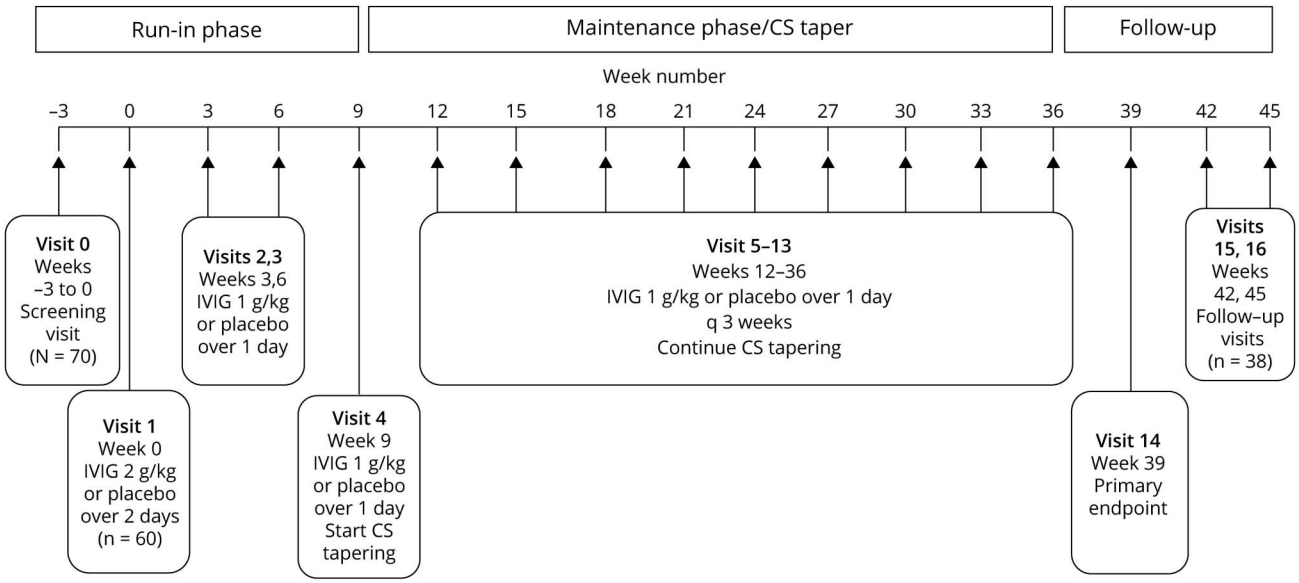
In the Research Article "Randomized Double-Blind Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis" by Bril et al.,[1] the maintenance dose in Figure 1 should be "1g/kg." Dosing is correctly reported in the abstract and body of the article. The corrected Figure 1 is below. The authors regret the error.

Reference

1. Bril V, Szczudlik A, Vaitkus A, et al. Randomized double-blind placebo-controlled trial of the corticosteroid-sparing effects of immunoglobulin in myasthenia gravis. *Neurology*. 2023;100(7)e671-e682.

Figure 1 Timeline for Evaluation of Potential Steroid-Sparing Effects of IV Immunoglobulin (IGIV-C) in Myasthenia Gravis



Additional information on patient disposition throughout the study is included in Figure 2. CS = corticosteroid.