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Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial

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Abstract

Introduction/Aims: Prospective, randomized, controlled trials of intravenous immunoglobulin (IVIG) maintenance therapy in myasthenia gravis (MG) are lacking. In this trial, we evaluated the safety and efficacy of caprylate/chromatography-purified IVIG; (IGIV-C) in patients with generalized MG undergoing standard care.

Methods: Sixty-two patients enrolled in this phase 2, multicenter, international, randomized trial (1:1 IGIV-C [2 g/kg loading dose; 1 g/kg every 3 weeks through week 21] or placebo). Efficacy was assessed by changes in Quantitative MG (QMG) score at week 24 versus baseline (primary endpoint) and percentage of patients with clinical improvement in QMG, MG Composite (MGC), and MG-Activities of Daily Living (MG-ADL) scores (secondary endpoints). Safety assessments reported all adverse events (AEs).

Abbreviations: AChR, acetylcholine receptor; AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; CS, corticosteroid; gMG, generalized myasthenia gravis; IVIG, intravenous immunoglobulin; IGIV-C, caprylate/chromatography-purified intravenous immunoglobulin; I/I, immunosuppressant/immunomodulator; ITT, intent to treat; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; MG-QOL, Myasthenia Gravis Quality of Life; mITT, modified intent to treat; NA, not applicable; ND, not determined; QMG, Quantitative Myasthenia Gravis; SAE, serious adverse event; TEAE, treatment-emergent adverse event; USP, US Pharmacopeia.

Previous presentation: The material in this manuscript has not been presented as a whole or in part at a national or international meeting.

For affiliations refer to page 52

Results: The change in QMG at 24 weeks was −5.1 for IGIV-C and −3.1 for placebo ($p = .187$). Seventy percent of patients in the IGIV-C group had improvement in MG-ADL (≥2-point decrease) versus 40.6% in the placebo group ($p = .025$). Patients showing clinical improvement in QMG and MGC (≥3-point decrease) were 70.0% for IGIV-C versus 59.4% for placebo ($p = .442$) and 60.0% for IGIV-C versus 53.1% for placebo ($p = .610$). IGIV-C was well tolerated; serious AEs were similar between arms. Three of four MG exacerbations requiring hospitalizations occurred in the IGIV-C arm with one death.

Discussion: Several efficacy parameters showed numerical results greater than those seen in the placebo group. This was a small study and may have been underpowered to see significant differences. Additional studies may be warranted to fully determine the efficacy of IVIG maintenance therapy in MG.

KEYWORDS
autoimmune disease, intravenous immunoglobulin, myasthenia gravis, neuromuscular disease

1 | INTRODUCTION

Intravenous immunoglobulin (IVIG) has been proven safe and effective for several conditions: primary immunodeficiency, idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy (CIDP),[1] and other indications in various countries. IVIG has also been shown to be efficacious for short-term treatment of acute exacerbations of myasthenia gravis (MG).[2–5] However, IVIG maintenance therapy for MG has not been extensively studied.[6,7]

IVIG can improve strength in patients with MG and is used as rescue therapy for MG exacerbation and crisis,[5,8,9] but data supporting the efficacy of IVIG as maintenance therapy for MG are lacking. Although there have been several studies assessing the efficacy of IVIG in MG in acute[2–4,10,11] and maintenance settings,[12–18] few have been controlled trials with none in the maintenance setting.[6,7] These controlled trials involved small numbers of patients ($n = 12$ and $n = 15$) and have limitations (e.g., premature termination due to lack of IVIG[7] or a crossover design with plasma exchange).[6] There is still a need for prospective, randomized, controlled trials of IVIG as acute and maintenance therapy in MG.

This is a prospective, randomized, double-blind, placebo-controlled trial of IVIG maintenance therapy in MG. In the current study, we assessed the safety and efficacy of immune globulin 10% caprylate/chromatography purified (IGIV-C) in symptomatic patients with generalized MG (gMG) being treated with standard-of-care therapy.

2 | METHODS

2.1 | Study design and objectives

The study consisted of screening (weeks −3–0), baseline and loading dose (week 0), and maintenance dosing (weeks 3–21) with the primary endpoint evaluated at week 24 (Figure S1). Patients were randomized 1:1 to IGIV-C or placebo treatment and received intravenous treatment every 3 weeks (double-blind). The method for assigning patients to treatment groups is described in the Data S1.

Randomization was stratified by the patient's MG therapy at randomization. The strata were as follows: (1) cholinesterase inhibitors only; (2) corticosteroid (CS) as the only immunosuppressant/immunomodulator (cholinesterase inhibitors allowed as concomitant medication); and (3) any non-CS immunosuppressant/immunomodulator alone or in combination with other MG medications (including CS and cholinesterase inhibitors).

The study protocol was approved by institutional review boards, ethics committees, or research ethics boards at all participating institutions. The study was authorized by regulatory authorities in all participating countries. Written informed consent was obtained from all subjects. All local regulations, international standards of Good Clinical Practice, and the Declaration of Helsinki were followed in this study. The full protocol and statistical plan can be accessed at https://clinicaltrials.gov/ct2/show/NCT02473952.

2.2 | Selection of study patients

Patients eligible for this study were recruited in 25 centers across Europe (Belgium, Czech Republic, Estonia, France, Germany, Hungary, Lithuania, and Poland) and North America (Canada and the United States). Patients were male or female, 18–85 years old, positive for anti-AChR antibodies, and with confirmed diagnosis of gMG—MG Foundation of America (MGFA) classification: Class II, III, or IVa.[19] At screening, potential participants were required to have a QMG score ≥10 while receiving standard care for MG. Standard of care was defined as follows: (1) cholinesterase inhibitor monotherapy (pyridostigmine/equivalent) with stable dosing ≥2 weeks and no immunosuppressants (in Germany, patients on cholinesterase monotherapy were not enrolled); (2) a cholinesterase inhibitor (stable dose ≥2 weeks)

and/or only one of the following (stable dosing for the indicated period): prednisone (≤60 mg/day/equivalent) ≥2 months, azathioprine ≥6 months, mycophenolate mofetil ≥6 months, methotrexate ≥6 months, and cyclosporine or tacrolimus ≥3 months; and (3) cholinesterase inhibitor (≥2 weeks) and/or prednisone (≤60 mg/day/equivalent, ≥1 month) and only one of the following: azathioprine, mycophenolate mofetil, methotrexate, or cyclosporine or tacrolimus (as described above).

Patients were excluded if they had received cyclophosphamide or any immunosuppressant not stated in the inclusion criteria in the last 6 months. Patients with a change in their MG treatment regimen or >2-point change in QMG score between screening (week −3) and baseline (week 0), a myasthenic crisis in the last month, or thymectomy in the last 6 months were excluded. Patients were also excluded for any malignancy in the last 5 years other than non-melanoma skin cancers or in situ cervical cancer. A thymoma potentially requiring treatment during the trial was also exclusionary. Other exclusionary treatments and conditions are listed in the Data S1.

2.3 | Investigational product

The investigational product (IGIV-C) used in this trial was Gamunex-C® (immune globulin injection (human) 10% caprylate/chromatography purified; Grifols Therapeutics LLC, Research Triangle Park, NC, USA).[1] The placebo treatment was an equal volume of normal saline (sterile 0.9% sodium chloride injection, USP) or equivalent.

2.4 | Treatments

The optimal dosing of IVIG for MG has not been determined. The dose chosen for this study, a loading dose of 2 g/kg over 2–4 days, was based on review articles showing that 2 g/kg was commonly used[20,21] and could be safely administered over a minimum of 2 days.[2–4] This dosing was also similar to that used for other neuroimmunological diseases, for example, Guillain–Barre syndrome and CIDP.[22,23] The dosing used in this study was that used in the phase 3 ICE study of IGIV-C in CIDP.[23]

Patients randomized to IGIV-C received a loading dose (2 g/kg) over 2 days at the baseline visit (week 0) (Figure S1). Maintenance doses (1 g/kg over 1 day) were administered every 3 weeks through week 21. Longer administration periods (up to 4 days for loading and 2 days for maintenance doses) were allowed for higher doses due to higher body weight (maximum dose 80 g/day) and to promote tolerability. Patients randomized to the placebo group were administered an equivalent volume of normal saline (0.9% sodium chloride, USP). Administration of IGIV-C and placebo was double-blinded. IGIV-C and placebo were prepared by an unblinded pharmacist and visually masked to prevent the unblinding of blinded site personnel and study participants during infusions.

The patient's concurrent MG medication regimen was held constant throughout the study unless there was an urgent medical need, the patient met the criteria for a treatment failure, or the patient had intolerable adverse effects.

The last dose of IGIV-C or placebo was administered at week 21 (visit 8), and the primary endpoint was assessed at week 24 (visit 9). The week 24 visit was also the end-of-study visit.

2.5 | Efficacy assessments

The mean change in Quantitative MG (QMG) score[24] from baseline to week 24 was the endpoint to evaluate the primary efficacy objective of this study. A decrease in QMG score was indicative of clinical improvement.

Three endpoints were set to evaluate the secondary efficacy objective: (1) percentage of patients who showed clinical improvement (defined as ≥3-point decrease[25]) in QMG score at week 24 compared to baseline; (2) percentage of patients who showed clinical improvement (defined as ≥3-point decrease) in MG Composite (MGC) score[26,27] at week 24 compared to baseline; (3) percentage of patients who showed clinical improvement (defined as ≥2 point decrease) in MG-Activities of Daily Living (MG-ADL) score[28] at week 24 compared to baseline.

In addition, a series of exploratory efficacy endpoints were set that included the following: the percentage of patients who experienced clinical improvement in QMG or MGC scores during the maintenance phase of the study (weeks 6, 9, 12, 15, 18, and 21); the time to clinical improvement in QMG score; the time to treatment failure (based on QMG score: ≥4-point increase from baseline at 2 consecutive visits at or after week 9 [following administration of loading dose and 2 maintenance study drug doses]); the change from baseline in QMG and MGC scores during the maintenance phase and at the final visit (MGC only); the percentage of patients showing clinical improvement in MG-ADL at weeks 9 and 15; the change from baseline in MG-ADL at weeks 9, 15, and 24; the MG Foundation of America (MGFA) post-interventional change status at week 24 related to baseline; and the change from baseline in the 15-item MG Quality-of-Life (MG-QOL 15) score at weeks 9, 15, and 24.

2.6 | Safety assessments

Safety variables included reporting of all AEs. In addition, vital signs, physical examinations, and blood hematology and chemistry were recorded. An additional description of safety assessments is included in the Data S1.

2.7 | Determination of sample size

Sample size determination is described in Data S1.

2.8 | Statistical analyses

A detailed description of the statistical analyses is included in the Data S1. There was no adjustment for multiple comparisons/multiplicity in this phase 2 proof-of-concept study.

3 | RESULTS

3.1 | Trial registration

The trial was registered on clinicaltrialsregister.eu (2014–003997-18) and clinicaltrials.gov (identifier NCT02473952).

3.2 | Patient disposition

The first patient was enrolled on August 14, 2015, and the last patient completed the study on January 26, 2018. Enrollment was ended when the target was reached, and the study ended when the last enrolled patient completed the study. A total of 79 patients were screened, and 62 were randomized (intent-to-treat population—Figure 1). The modified ITT (mITT) population ($n = 62$) included all randomized patients that received at least one dose of study medication (active or placebo). These 62 patients were included in efficacy and AE analyses. Fifty-two (52) of these patients (83.9%) completed all study visits: 28 (93.3%) in the IGIV-C group and 24 (75.0%) in the placebo group. Two patients in the IGIV-C group withdrew due to MG exacerbations. Eight patients in the placebo group discontinued from the study (six withdrew consent, and two had MG exacerbations).

3.3 | Baseline characteristics of the treatment and placebo groups

The baseline characteristics of both study groups are shown in Table 1. The treatment groups were similar in terms of demographics, MG status, and prior and present MG treatment (Table 1). The placebo group had a higher percentage of female patients and those less <65 years old than the IGIV-C group. In addition, the time since diagnosis was longer in the placebo group than in the IGIV-C group. MG assessments were comparable between the groups. A similar proportion of patients had previously undergone thymectomy (56.7% and 59.4%, for active and control arms, respectively).

3.4 | Primary and secondary efficacy endpoints

The change in QMG score from baseline at week 24, the primary endpoint, was not significantly different for the IGIV-C group and for the placebo group (Table 2). For the secondary endpoints, there was no evidence of a difference in the percentage of patients who showed improvement (≥3-point decrease) in QMG or MGC scores at week 24 versus baseline for the IGIV-C group compared with the placebo group (Table 2).

An apparent difference in the percentage of patients with a clinically meaningful improvement (≥2-point decrease) in MG-ADL score was observed in the IGIV-C group compared to the placebo group.

3.5 | Exploratory efficacy endpoints

The percentage of patients showing clinical improvement in QMG scores was higher, the change from baseline was larger in the IGIV-C treatment group at all measured time points, and there was evidence of a greater difference at weeks 9 and 21 (Figure 2A,B).

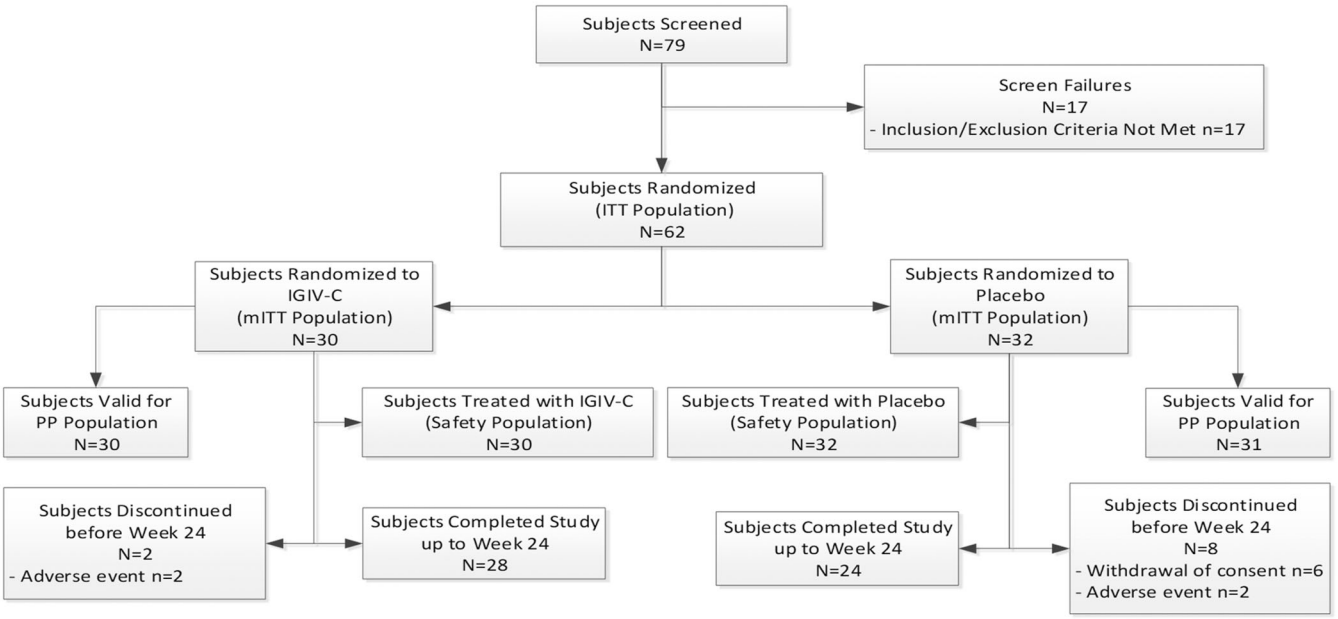

FIGURE 1 Disposition of subjects in a multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of intravenous immunoglobulin (10%, caprylate/chromatography-purified; IGIV-C) in patients with symptomatic myasthenia gravis. ITT, intent to treat; mITT, modified intent to treat; PP, per protocol.

TABLE 1 Demographics and baseline characteristics of the modified intent-to-treat study population.

Demographics	IGIV-C ($n = 30$)	Placebo ($n = 32$)	Total ($n = 62$)
Age (years)—mean (SD)	54.6 (17.1)	48.0 (13.7)	51.2 (15.6)
Age category (years)—*n* (%)			
<65	20 (66.7)	29 (90.6)	49 (79.0)
≥65	10 (33.3)	3 (9.4)	13 (21.0)
Sex—*n* (%)			
Female	14 (46.7)	19 (59.3)	33 (53.2)
Male	16 (53.3)	13 (40.6)	29 (46.8)
Race—*n* (%)			
White (Caucasian)	29 (96.7)	30 (93.8)	59 (95.2)
Black (African American)	1 (3.3)	0	1 (1.6)
Asian	0	1 (3.1)	1 (1.6)
American Indian or Alaskan Native	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (3.1)	1 (1.6)
Ethnicity—*n* (%)			
Hispanic or Latino	2 (6.7)	3 (9.4)	5 (8.1)
Non-Hispanic or Latino	28 (93.3)	29 (90.6)	57 (91.9)
Geographic region—*n* (%)			
North America	11 (36.7)	12 (37.5)	23 (37.1)
Europe	19 (63.3)	20 (62.5)	39 (62.9)
Screening weight (kg) - mean (SD)	86.4 (21.6)	81.1 (20.3)	83.7 (20.9)
Height (cm) - mean (SD)	172.1 (8.6)	170.0 (8.8)	171.0 (8.7)
Screening BMI (kg/m^2) - M	29.1 (6.5)	27.9 (6.1)	28.5 (6.3)
Baseline			
Time since MG diagnosis (years) - mean (SD)	8.1 (7.0)	11.3 (10.1)	9.8 (8.9)
MGFA classification—*n* (%)			
Class IIa	11 (36.7)	9 (28.1)	20 (32.3)
Class IIb	5 (16.7)	5 (15.6)	10 (16.1)
Class IIIa	12 (40.0)	14 (43.8)	26 (41.9)
Class IIIb	1 (3.3)	3 (9.4)	4 (6.5)
Class Iva	1 (3.3)	1 (3.1)	2 (3.2)
Baseline QMG total score - mean (SD)	14.6 (2.8)	16.2 (4.5)	
Baseline MG Composite total score - mean (SD)	14.3 (6.9)	16.8 (7.3)	
Baseline MG-ADL total score - mean (SD)	7.4 (3.2)	7.8 (3.4)	
Baseline MG-QOL 15 total score - mean (SD)	27.9 (14.4)	30.8 (15.0)	
Stratification based on MG Regimen at screening - *n (%)*			
Only ChEI	8 (26.7%)	10 (31.3%)	18 (29.0%)
CS only I/I	6 (20%)	4 (12.5%)	10 (16.1%)
Any non-CS I/I	16 (53.3%)	18 (56.3%)	34 (54.8%)

Abbreviations: ADL, Activities of Daily Living; ChEI, cholinesterase inhibitor; CS, corticosteroid; I/I, immunosuppressant/immunomodulator; IGIV-C, caprylate/chromatography-purified IVIG; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; QMG, Quantitative Myasthenia Gravis; QOL, Quality of Life; SD, standard deviation.

There was no evidence of a difference in the time to first clinical improvement in the IGIV-C group versus the placebo group (see Table 2). The percentage of patients with clinical improvement in MGC scores and change from baseline were relatively constant over time (Figure 3A). Similar results were seen in change from baseline in MGC scores, with evidence of a larger difference between the treatment groups at 9 weeks (Figure 3B).

The percentage of patients who showed improvement in MG-ADL scores showed no apparent difference between the IGIV-C treatment group and the placebo group.

TABLE 2 Primary, secondary, and exploratory endpoints for the effects of IGIV-C.

L	IGIV-C ($n = 30$)	Placebo ($n = 32$)	Mean difference	p value
Primary endpoint				
QMG score—Δ from baseline (least squares mean ± SE; last observation carried forward)	−5.1 ± 1.1	−3.1 ± 1.1	−2.0 ± 1.5	.187
Secondary endpoints			Risk ratio (95% CI)	
QMG score—*n* (%) Pt with clinical improvement	21/30 (70.0)	19/32 (59.4)	1.16 (0.80, 1.68)	.442
MG composite—*n* (%) Pt with clinical improvement	18/30 (60.0)	17/32 (53.1)	1.12 (0.73, 1.73)	.610
MG-ADL—*n* (%) Pt with clinical improvement	21/30 (70.0)	13/32 (40.6)	1.70 (1.06, 2.73)	.025
Exploratory endpoints				
Time to first clinical improvement (weeks: median, IQR)	6.1 (3.1, 15.1)	9.3 (6.0, 24.1)	ND	.195
Time to treatment failure (weeks)	NA	NA	NA	NA
MGFA post-interventional Δ in status - *n (%)*				
Improved	20 (71.4)	13 (54.2)		NA
Unchanged	7 (25.0)	9 (37.5)	ND	NA
Worse	1 (3.6)	2 (8.3)	ND	NA

Abbreviations: ADL, Activities of Daily Living; IGIV-C, caprylate/chromatography-purified IVIG; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; NA, not applicable; ND, not determined; QMG, Quantitative Myasthenia Gravis.

There was no evidence of a difference between the treatment groups in the mean decrease from baseline in MG-ADL score at weeks 9, 15, and 24.

There was evidence of a larger change from baseline in the MG-QOL 15 score (measured at weeks 9, 15, and 24) at week 24 (−7.1 vs. −1.6; $p = .032$).

The analysis of MGFA post-interventional change in status at week 24 compared to baseline showed that a higher percentage of patients in the IGIV-C group were classified as improved compared to the placebo group (Table 2).

3.6 | Subgroup analyses

Subgroup analysis of change from baseline QMG scores, stratified by median overall baseline (entry) QMG score (<15 or ≥15), at week 24, showed no evidence of a difference between the IGIV-C group (≥15 QMG = −4.7; <15 QMG = −4.6) and the placebo group (≥15 = −2.8; <15 QMG = −2.6).

Subgroup analysis of the baseline MG treatment regimen showed that for the regimen containing a non-corticosteroid immunosuppressant/immunomodulator, there was no evidence of a change from baseline in QMG score for this subgroup between the IGIV-C and placebo groups (Figure 4). The other 2 strata were not of sufficient size for analysis.

3.7 | Safety endpoints

IGIV-C was well tolerated. A similar percentage of patients in the IGIV-C treatment group experienced at least one treatment-emergent AE (TEAE) as in the placebo group. The two most frequently reported TEAEs were headache and nasopharyngitis (Table 3). Most TEAEs were mild or moderate in both treatment groups. Few TEAEs were reported as severe for IGIV-C or placebo (Table 3).

TEAEs considered by the investigator to be potentially related to treatment were more common in the IGIV-C group (53.3% of patients) than in the placebo group (25.0% of patients). The perceived relationship of TEAEs to the study medications is shown in Table 3.

The percentage of patients experiencing serious AEs (SAEs) was similar in the IGIV-C group (16.7%; $n = 5/30$) and the placebo group (12.5%; $n = 4/32$). MG exacerbation/relapse/worsening occurred in three patients in the IGIV-C group (one evolving to MG crisis) and one patient in the placebo group. Three of the four MG exacerbations requiring hospitalization and intensive management occurred in subjects in the IGIV-C arm and one in the placebo arm.

Two patients in each treatment group experienced MG AEs that led to discontinuation from the study. One death occurred in the IGIV-C treatment group. At the week 24 visit, the patient was hospitalized for a myasthenic crisis requiring mechanical ventilation. The patient developed pneumonia and *Staphylococcus aureus* septicemia and died due to cardiopulmonary failure 15 days later.

No clinically significant overall changes in laboratory values were seen in either treatment group, but shifts from normal baseline values to low values for hemoglobin, hematocrit, and erythrocyte count were more common in the IGIV-C group than in the placebo group; these effects were usually transient.

Six patients in the IGIV-C treatment group and four patients in the placebo group had laboratory TEAEs. None were considered SAEs.

In the IGIV-C treatment group, 10 patients met the predefined parameters in the algorithm for hemolysis. Seven were not overtly

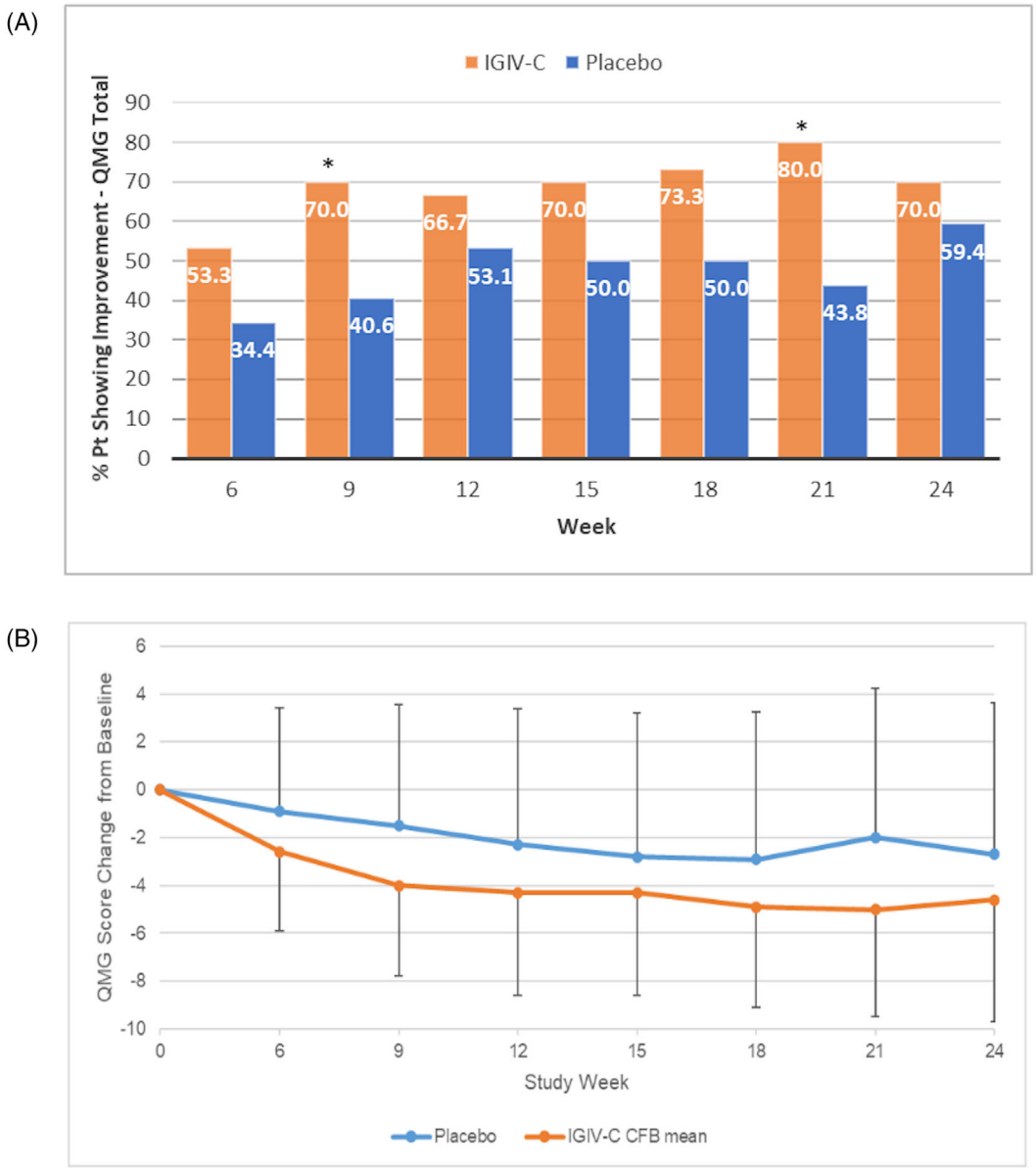

FIGURE 2 (A) Percentage of patients showing improvement in Quantitative Myasthenia Gravis (QMG) score in patients treated with caprylate/chromatography-purified IVIG (IGIV-C) or placebo (LOCF). Improvement was defined as at least a three-point decrease in QMG total score. For IGIV-C, $n = 30$ patients, and for placebo, $n = 32$ patients.*$p < .05$ ($p = .029$ at week 9 and $p = .005$ at week 21). (B) Change from baseline in Quantitative Myasthenia Gravis (QMG) score in patients treated with caprylate/chromatography-purified IVIG (IGIV-C) or placebo. For IGIV-C, $n = 30$ patients, and for placebo, $n = 32$ patients. Data shown are mean ± standard deviation. Treatment group comparisons showed significant differences between the groups at week 9 and week 21 ($p < .05$: $p = .023$ at week 9 and $p = .025$ at week 21).

anemic (hemoglobin values within normal limits), and three had treatment-emergent anemia. One case was reported as an AE. In the placebo group, no incidence of a positive direct antiglobulin test was accompanied by other markers of hemolysis.

4 | DISCUSSION

In this study, the effect of IGIV-C on the primary efficacy endpoint was not statistically significant. The absolute change in QMG score in the placebo group in this study (−3.1) was larger than the placebo-induced change in similar studies investigating treatments for MG (−1.6 and −2.37),[29,30] but similar to the placebo group in a study of tacrolimus in MG (−3.3).[31] These differences in QMG score changes may be due to dissimilarities in the study populations in terms of demographics, disease severity at baseline, baseline regimen, and other factors.

It should also be pointed out that the clinical significance of the QMG score change depends on MG severity at baseline. According to Katzberg et al., a 3-point change is clinically significant for severe MG

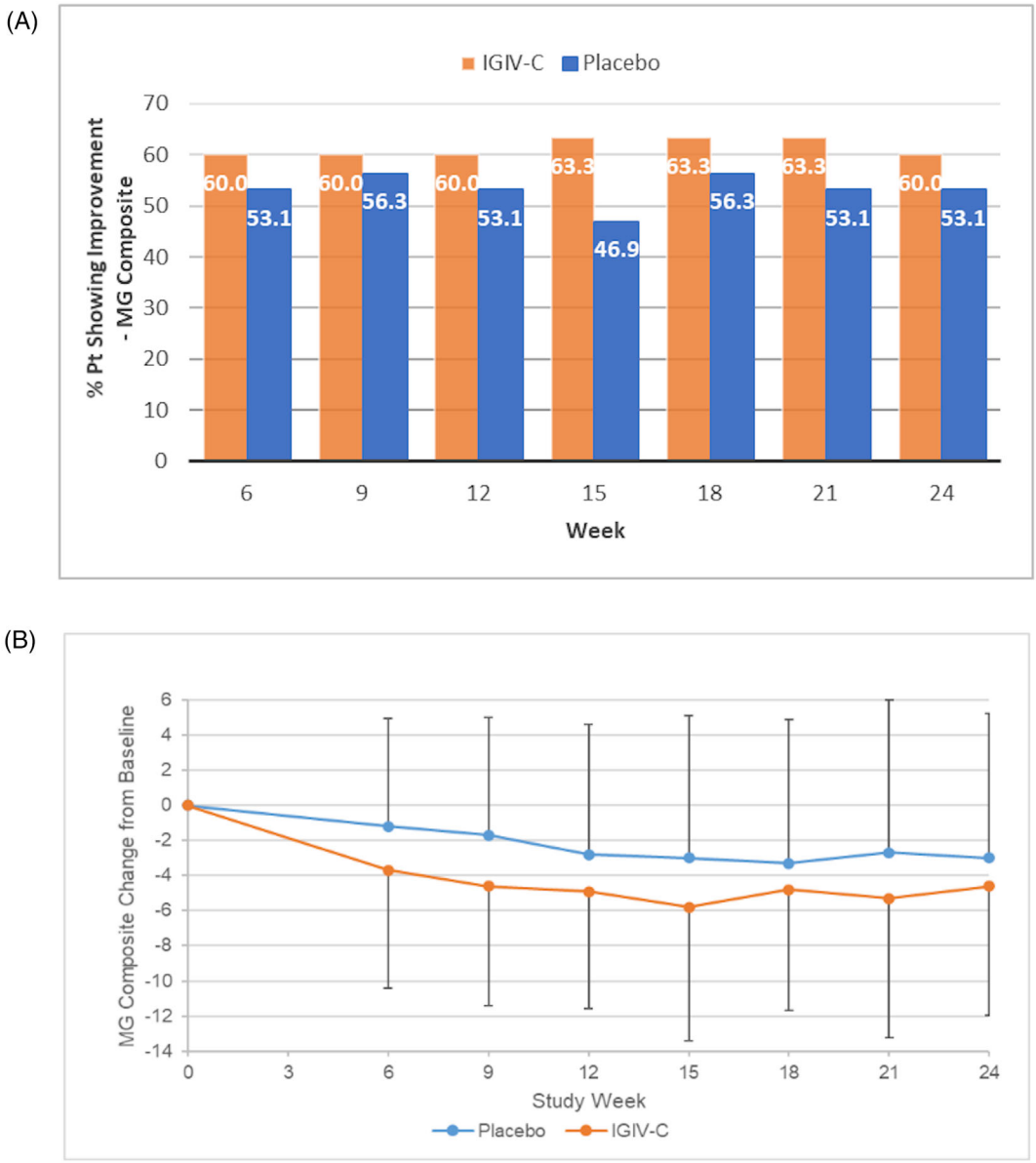

FIGURE 3 (A) Percentage of patients showing improvement in myasthenia gravis (MG) composite score in patients treated with caprylate/chromatography-purified IVIG (IGIV-C) or placebo (LOCF). Improvement was defined as at least a three-point decrease in MG Composite score. For IGIV-C, $n = 30$ patients, and for placebo, $n = 32$ patients. (B) Change from baseline in Myasthenia Gravis (MG) Composite score in patients treated with caprylate/chromatography-purified IVIG (IGIV-C) or placebo. For IGIV-C, $n = 30$ patients, and for placebo, $n = 32$ patients. Data shown are mean ± standard deviation. Treatment group comparisons showed a significant difference only at week 9 ($p = .042$).

(QMG >16).[24,25] Since baseline QMG score in our patient population was on the threshold of severe MG (14.6 in the IGIV-C group and 16.2 in the placebo group), we cannot discount the clinical relevance of the observed 2-point change in the IVG-C group compared to the placebo group (−5.1 improvement vs. −3.1, respectively).

There was an apparent difference in the percentage of patients with a two-point decrease in MG-ADL between the IGIV-C group and the placebo group, although there was no adjustment for multiple comparisons. MGL-ADL is a robust and validated tool for use in MG clinical trials.[32]

Subgroup analysis showed that the change in QMG from baseline in the subgroup with a non-corticosteroid immunosuppressant/immunomodulator in their baseline regimen was greater in the IGIV-C group than in the placebo group—a clinically meaningful difference. The observation warrants consideration for further research.

In summary, there were several efficacy parameters in this study that showed numerical results greater than those seen in the placebo group. Since this was a relatively small study, it is possible that it may have been underpowered to see a significant difference between arms in QMG change from baseline. However, what is more likely is

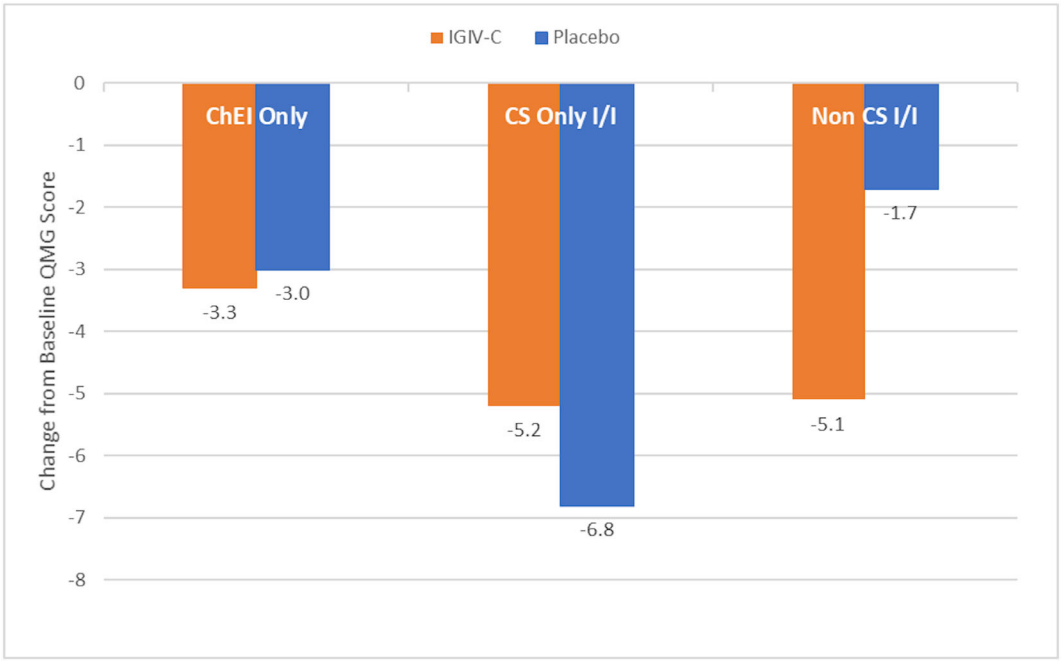

FIGURE 4 Change from baseline in Quantitative Myasthenia Gravis (QMG) score in patients treated with caprylate/chromatography-purified IVIG (IGIV-C) or placebo (LOCF). For this analysis, patients were analyzed as a priori stratified by baseline treatment regimen: cholinesterase inhibitor (ChEI) only, corticosteroid (CS) as the only immunosuppressant/immunomodulator (I/I), or non-CS I/I. For the ChEI-only subgroup: IGIV-C $n = 8$ and placebo $n = 10$; for the CS-only I/I subgroup: IGIV-C $n = 6$ and placebo $n = 4$; and for the non-CS I/I subgroup: IGIV-C $n = 16$ and placebo $n = 18$.

TABLE 3 Summary of treatment emergent adverse events (TEAEs).

	IGIV-C ($n = 30$)	Placebo ($n = 32$)
Patients with any TEAE—*n* (%)	22 (73.3)	22 (68.8)
Total number of TEAEs—*n*	142	71
Patients with any SAE—*n* (%)	5 (16.7)	4 (12.5)
Total number of SAEs—*n*	9	5
Patients with AE leading to withdrawal—*n* (%)	2 (6.7)	2 (6.3)
Total number of AEs leading to withdrawal—*n*	2	2
Severity of TEAEs—*n* (%)		
Mild	79 (55.6)	49 (69.0)
Moderate	46 (32.4)	17 (23.9)
Severe	17 (12.0)	5 (7.0)
TEAEs reported in >10% of treatment group—*n* (%)		
Headache	9 (30.0)	4 (12.5)
Nasopharyngitis	3 (10.0)	4 (12.5)
Myasthenia gravis	3 (10.0)	3 (9.4)
Diarrhea	3 (10.0)	2 (6.3)
Hypertension	3 (10.0)	2 (6.3)
Nausea	3 (10.0)	1 (3.1)
Cough	3 (10.0)	0 (0)
Causal relationship of TEAE to study medication—*n* (%)		
Unrelated	67 (47.2)	48 (67.6)
Doubtful/unlikely	19 (13.4)	5 (7.0)
Possible	20 (14.1)	11 (15.5)
Probable	22 (15.5)	5 (7.0)
Definite	14 (9.9)	2 (2.8)

that the assumed effect size for IGIV-C may have been overestimated in the MG maintenance treatment setting.

It should also be noted that there were some differences in baseline demographics. The placebo group had a higher percentage of females and younger patients than the IGIV-C treatment group. The time since diagnosis of MG was also longer in the placebo group. These factors may have affected the study outcomes. Further studies may be warranted to fully elucidate the efficacy of IVIG as maintenance therapy in MG while carefully monitoring all patients for MG exacerbations.

AUTHOR CONTRIBUTIONS

All authors met the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE). Conceptualization: RG, MQC, and EM. Methodology: RG, MQC, and EM. Formal analysis: RG, MQC, and EM. Investigation: VB, TB, AS, MWN, JB, PH, AV, TV, CR, TM, GP, TT, MP, TM. MF, UR, LV, NS, TL, RMP, MCD, MR, RG, MQC, and EM. Resources: RG, MQC, and EM. Data curation: RG, MQC, and EM. Writing—original draft: VB, RG, and EM. Writing—review and editing: VB, TB, AS, MWN, JB, PH, AV, TV, CR, TM, GP, TT, MP, TM. MF, UR, LV, NS, TL, RMP, MCD, MR, RG, MQC, and EM.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material from other published sources was included in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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