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A 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 (CS) and intravenous immunoglobulin (IVIG). This study was conducted to determine if immune globulin (human), 10% caprylate/chromatography purified (IGIV-C) could facilitate CS dose reduction in CS-dependent MG patients.

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 Patients were withdrawn if worsening failed to improve within 6 weeks or if a second CS increase was required.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

Results: The primary endpoint (≥ 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 endpoints. 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 effects of IGIV-C and CS are not synergistic and may be mechanistically different.

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 to placebo.

1. Introduction

Myasthenia gravis (MG) results from autoimmune-mediated dysfunction at the neuromuscular junction. This dysfunction manifests through autoantibodies to post-synaptic proteins - commonly the acetylcholine receptor (85-90%) and less frequently lipoprotein-related protein 4 (LRP4) and muscle-specific kinase (MuSK). 1, 2

For MG unresponsive to cholinesterase inhibitors, the primary treatment is immunosuppression. The drugs of first choice are frequently corticosteroids (CS).

Treatment of severe MG or exacerbations frequently includes plasma exchange or intravenous 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 neurological 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. Due to 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 MG patients to determine if IGIV-C administration could increase the percentage of patients achieving a \(\geq 50\%\) CS dose reduction compared to placebo.

2. Materials and methods

2.1. 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 MG patients. Sites were in Canada, Czech Republic, Estonia, Germany, Hungary, Lithuania, Poland, and United States. The primary objective was to evaluate the efficacy of IGIV-C as compared to placebo (sterile 0.9% sodium chloride injection, USP or equivalent) in reducing the maintenance dosage of corticosteroids in CS-dependent subjects 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 endpoint was the percentage of subjects achieving a 50% or greater reduction in CS dose (prednisone-equivalent) at Week 39 from Baseline/Week 0. \(^{17}\) The study had four 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: (15mg/day to 40 mg/day of prednisone-equivalent or 41 mg/day to 60/day mg of prednisone-equivalent).

2.2. Treatments

Patients randomized to IGIV-C treatment, received a loading dose (2 g/kg) at the baseline visit (week 0) (see 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/day) or to increase tolerability. Maintenance doses of 1 g/kg over one day were given every three weeks through week 36. A longer dosing period (two days) was allowed to allow for higher doses (maximum dose 80 g/day) 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 three 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 three weeks). If the patient’s CS dose was ≤ 40 mg prednisone equivalent/day, the dose was reduced by 5 mg equivalent/day every three weeks. Patients on every-other-day CS dosing tapered by a commensurate amount, e.g., if > 80 mg/every-other-day the decrease every three 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 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 six weeks (next two 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 six-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.

2.3. Selection of study patients

Male and female patients 18-85 years old, positive for anti-AChR antibody and with a confirmed diagnosis of generalized MG (MGFA Class II, III, IV, or V) were eligible for screening. 18 At screening, potential patients 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/day for one month prior to screening. For potential patients 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 one 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 six months prior to screening or any change in CS dose or acetylcholinesterase inhibitor dose in the month prior to screening. A three-point change in QMG score (increase or decrease) between the screening and baseline (week 0) visits was disqualifying. A myasthenic crisis (MC) episode in the month prior to 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 five years, thymoma requiring potential surgery, thymectomy in the prior six 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 three months, or current anti-coagulant therapy were disqualifying. A history of non-response to IVIG for MG, immunoglobulin therapy in the three months prior to 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.
2.4. 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, USA). 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.

2.5. Study endpoints

The primary efficacy endpoint 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 endpoints 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 endpoints related to CS therapy included: percent of patients achieving a ≥75% reduction in CS dose at week 39, percent of patients achieving a CS dose ≤7.5mg (prednisone-equivalent) at week 39, percent of patients CS free at week 39, change in fasting serum glucose at week 39 versus baseline, percent of patients with fasting glucose ≤125 mg/dL at week 39 versus baseline and a change in hemoglobin A1c at week 39 compared to baseline (week 0).

Exploratory endpoints related to MG were: percent of patients experiencing a 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 to 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, USA). In addition, the change in serum IgG levels at weeks 9, 24, and 39 from baseline (week 0).

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

2.6. Safety assessments

Safety assessment included reporting of all adverse events (AEs), serious adverse events and discontinuations due to adverse events. Patients were also monitored for thromboembolic events and hemolysis. Thromboembolic risk was assessed at screening, baseline (week 0; prior to infusion), after completion of the first loading dose infusion, after completion of the last loading dose infusion, and at weeks 3, 6, and 24 upon completion of the maintenance infusion (hemolysis assessments were at these times plus 1 week post-infusion.
2.7. 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 Fisher’s exact test. The stratified treatment comparison was made using the Cochran-Mantel-Haenszel test adjusted for baseline CS dose (15-40 mg/day versus 41-60 mg/day). Analyses on secondary efficacy endpoints were performed using analysis of covariance (ANCOVA). Missing data from patients who withdrew from the study were handled using the last observation carried forward (LOCF) method.

For the exploratory endpoints, Fisher’s 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 subjects 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. Note: For the OC method: Subjects with missing CS dose at Week 39 are excluded from this analysis.

Safety analyses were performed on data from the safety population and were analyzed descriptively.
2.8. **Data availability**

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

2.9. **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 subjects 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).

3. **Results**

3.1. **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).

3.2. **Patient disposition**

Seventy patients were screened for this study at 24 sites and 60 were randomized (intent-to-treat population) (see Figure 2). All 60 of these patients were included in the modified intent-to-treat population for efficacy analyses and the safety population for adverse event 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, six were due to AEs, four for MG worsening and two withdrew consent (Table 3). Of the ten premature withdrawals in the placebo group, four were due to AEs, one was due to MG worsening, three withdrew consent and two were due to investigator decision (non-AE). MG worsening refers to protocol-directed discontinuation due to failure of the CS taper, (see Treatments section).

3.3. Efficacy endpoints

The primary efficacy endpoint was the percentage of patients that achieved a 50% reduction in CS dose (week 39 versus baseline (week 0)). There was no significant difference between the treatment groups in this primary endpoint (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 endpoint was also conducted with patients stratified by CS dose at baseline. However, since 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 or equal to or above the baseline median CS dose (20 mg/day prednisone or equivalent). For both treatment groups, patients on higher CS doses (>20mg/day) were more likely to achieve a 50% reduction
in their CS dose at week 39 than patients on lower CS doses (≤ 20 mg/day). This finding was seen in both arms: IGIV-C: 70.0% versus 55.0% and placebo: 66.7% versus 60.0%) (Figure 3) with no meaningful between-arm difference in either subgroup (p = 1.00).

Secondary endpoints 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: 52.04 ± 44.49% reduction (mean ± SD) in the IGIV-C arm; 54.69 ± 51.36% reduction in the placebo arm and 25th percentile of time to first worsening (≥ +4 points QMG score) 33.10 weeks IGIV-C; 30.10 weeks placebo.

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 endpoints 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 endpoints except three prior to Week 9 (one active; two placebo).

3.4. Safety endpoints

The safety data showed that IGIV-C treatments were well tolerated. The mean number of doses administered, the mean duration of exposure, and 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 one treatment-emergent adverse event (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%.

Serious adverse events (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 one death in the IGIV-C group and two deaths in the placebo group. One death was associated with MG in each arm. The deaths were attributed to a MG exacerbation, sepsis, and cardiac arrest in the setting of MG crisis, staphylococcal pneumonia, and acute respiratory failure. Serious adverse events of MG exacerbations or MG crises were reported in seven patients: four patients (13.3%) in the IGIV-C treatment group and three in the placebo group (10.0%).

Among 4 subjects 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 subjects, 1 subject died despite increased CS dose and administration of commercial immunoglobulin, and one subject unresponsive to eight plasma exchanges developed a permanent disability (tracheal narrowing) from prolonged intubation.

Among a total of three subjects in the placebo treatment group with SAEs of MG exacerbation/MG crisis, one subject was completely tapered off to 0 mg CS at the time
of MG exacerbation/crisis. Although hospitalized and treated with IV immunoglobulin, CS was not reintroduced, and he died despite interventions. The other two placebo subjects 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 subjects in the IGIV-C treatment group and 4/30 (13.3%) subjects in the placebo treatment group had AEs leading to withdrawal. The AEs resulting in discontinuation were most commonly worsening of myasthenia gravis, MG exacerbations, and MG crisis. Other AEs leading to withdrawal included hemolysis, dizziness, sepsis, and cardiac arrest.

3.5. 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 to placebo.

4. Discussion

The primary objective of this study was to determine if IGIV-C could facilitate the tapering of CS doses in CS-dependent MG patients. No significant difference was seen in the primary endpoint of the number of patients achieving ≥ 50% reduction in CS dose at week 39 compared to baseline between IGIV-C treatment and placebo. It is important to note that this result may have been influenced by one of the selection criterion: eligible patients must have completed at least one 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 endpoints 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 MG patients 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 endpoints regarding CS dose reduction. According to the protocol, patients were required to discontinue the study if they experienced MG worsening (QMG increase ≥ four 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 employed and for all CS-related endpoints WOCF was used if discontinuations were due to treatment-emergent MG SAEs. In fact, all discontinued patients effectively contributed to the CS tapering efficacy endpoint except for three that discontinued prior to week 9 (one IGIV-C, two placebo). Thereby premature discontinuations did not affect the robustness of the efficacy results.

CS are an important tool for treating MG not completely responsive to acetylcholinesterase inhibitors. A retrospective analysis showed that 74% of MG patients responded to CS therapy. The efficacy of CS for treating MG may be due to their immunosuppressive effects. Long-term use of CS, 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.\textsuperscript{13, 28} The impact of these adverse events can be reduced by dose reduction\textsuperscript{13}. Therefore, the goal of CS therapy for MG is a minimum effective dose.

IVIG is also an effective treatment for MG\textsuperscript{3, 4} in certain settings, and has anti-inflammatory and immunosuppressive effects.\textsuperscript{29} The exact mechanisms are unclear but may include the inhibition of dendritic cell maturation, modulation of pro-inflammatory cytokine production,\textsuperscript{30} reduced activation of complement pathways\textsuperscript{31} and blockade of Fc receptors on macrophages.\textsuperscript{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\textsuperscript{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 endpoint 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 timeframe. The duration of the CS taper portion of the study (starting at week 9 and ending at week 36) was 27 weeks or approximately seven 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 seven months – a practical time period to assess the clinically relevant impact 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 that have been started relatively recently, as the criteria for trial inclusion required at least three months of CS dosing prior to entry though one 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 intravenous). 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 MG patients, 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 (versus placebo. MG-related SAE’s in both treatment groups during CS tapering emphasizes 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/day prednisone equivalent) were more likely to achieve 50% reduction in dose than patients on lower baseline doses (< 20 mg/day 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.

5. References


Table 1: Demographics of the modified intent-to-treat study population.

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

IGIV-C = intravenous immunoglobulin – caprylate/chromatography process; SD = standard deviation.
Table 2. Baseline or screening data on the modified intent-to-treat study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IGIV-C (n = 30)</th>
<th>Placebo (n = 30)</th>
<th>Total (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Weight (kg)</td>
<td>78.6 (18.8)</td>
<td>79.7 (20.5)</td>
<td>79.1 (19.5)</td>
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<td>Height (cm)</td>
<td>171.2 (9.6)</td>
<td>167.8 (8.9)</td>
<td>169.5 (9.4)</td>
</tr>
<tr>
<td>Screening BMI (kg/m^2)</td>
<td>26.7 (5.8)</td>
<td>28.1 (5.5)</td>
<td>27.4 (5.7)</td>
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<tr>
<td>Baseline QMG Total Score</td>
<td>12.1 (7.0)</td>
<td>11.2 (6.5)</td>
<td>11.6 (6.7)</td>
</tr>
<tr>
<td>Baseline MG Composite Total Score</td>
<td>11.4 (9.7)</td>
<td>11.3 (9.4)</td>
<td>11.3 (9.5)</td>
</tr>
<tr>
<td>Baseline MG-QOL 15 Total Score</td>
<td>27.2 (13.8)</td>
<td>21.8 (13.3)</td>
<td>24.5 (13.7)</td>
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<tr>
<td>Baseline MG-ADL Total Score</td>
<td>5.3 (3.8)</td>
<td>5.1 (4.2)</td>
<td>5.2 (4.0)</td>
</tr>
<tr>
<td>Baseline Fasting Serum Glucose (mg/dL)</td>
<td>98.0 (27.7)</td>
<td>106.6 (47.7)</td>
<td>102.3 (38.9)</td>
</tr>
<tr>
<td>Baseline Serum IgG Trough (g/L)</td>
<td>8.702 (2.616)</td>
<td>8.685 (1.962)</td>
<td>8.693 (2.292)</td>
</tr>
<tr>
<td>Baseline AChR Binding Ab (nmol/L)</td>
<td>68.02 (145.68)</td>
<td>71.56 (188.20)</td>
<td>69.79 (166.87)</td>
</tr>
<tr>
<td>Baseline AChR Blocking Ab (%)</td>
<td>28.6 (19.5)</td>
<td>22.0 (19.3)</td>
<td>25.3 (19.5)</td>
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<tr>
<td>Baseline AChR Modulating Ab (%)</td>
<td>47.9 (25.2)</td>
<td>51.5 (24.8)</td>
<td>49.7 (24.9)</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>5.83 (0.71)</td>
<td>5.84 (0.89)</td>
<td>5.84 (0.80)</td>
</tr>
<tr>
<td>Daily Prednisone Dose Prescribed (mg)</td>
<td>24.5 (10.0)</td>
<td>26.9 (11.3)</td>
<td>25.7 (10.6)</td>
</tr>
<tr>
<td>Stratification Based on Prednisone Dose* – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-40 mg/day</td>
<td>29 (96.7)</td>
<td>28 (93.3)</td>
<td>57 (95.0)</td>
</tr>
<tr>
<td>41-60 mg/day</td>
<td>1 (3.3)</td>
<td>3 (6.7)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Other non-steroidal Immunosuppressant Therapy n (%)**</td>
<td>14 (46.7)</td>
<td>21 (70.0)</td>
<td>35 (58.3)</td>
</tr>
</tbody>
</table>

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IGIV-C = intravenous immunoglobulin – caprylate/chromatography process; SD = standard deviation; BMI = body mass index; QMG = quantitative myasthenia gravis score; MG = myasthenia gravis; QOL = quality of life; ADL = activities of daily living; IgG = immunoglobulin G; AChR = acetylcholine receptor; Ab = antibodies; HbA1c = hemoglobin A1c. *Prednisone or equivalent dose of another corticosteroid. **Non-steroidal immunosuppressants that were part of the background regimen included azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, and cyclophosphamide.

Table 3. Patient disposition over the course of the study.

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>IGIV-C n (%)</th>
<th>Placebo n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>Randomized (ITT Population)</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td>60 (100.0)</td>
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<tr>
<td>mITT Population</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td>60 (100.0)</td>
</tr>
<tr>
<td>Per Protocol Population</td>
<td>30 (100.0)</td>
<td>28 (93.3)</td>
<td>58 (96.7)</td>
</tr>
<tr>
<td>Safety Population</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td>60 (100.0)</td>
</tr>
<tr>
<td>Discontinued Prematurely</td>
<td>12 (40.0)</td>
<td>10 (33.3)</td>
<td>22 (36.7)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>6 (20.0)</td>
<td>4 (13.3)</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>MG Worsening</td>
<td>4 (13.3)</td>
<td>1 (3.3)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>2 (6.7)</td>
<td>3 (10.0)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td>Physician Decision</td>
<td>0</td>
<td>2 (6.7)</td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

IGIV-C = intravenous immunoglobulin – caprylate/chromatography process; ITT = intent-to-treat; mITT = modified intent-to-treat;
Figure Legends.

Figure 1. Timeline for evaluation of potential steroid-sparing effects of intravenous immunoglobulin (IGIV-C) in myasthenia gravis. Additional information on patient disposition throughout the study is included in Figure 2. CS = corticosteroid.
Figure 2. Disposition of Subjects. a All discontinuations effectively contributed to corticosteroid (CS) tapering efficacy endpoints except 3 subjects who withdrew prior to Week 9 (1 subject on intravenous immunoglobulin (IGIV-C) and 2 subjects 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).
Figure 3. Percent of patients achieving the primary efficacy endpoint: 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 endpoint if entering in the higher CS dose quantile.

![Bar graph showing the percent of patients achieving the primary efficacy endpoint by entry CS dose quantile.]

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 the Quantitative MG (QMG) Score.

![Kaplan-Meier curve showing the probability of MG worsening over time.]

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A Randomized, Double-Blind, Placebo-Controlled Trial of the Corticosteroid-Sparing Effects of Immunoglobulin in Myasthenia Gravis
Vera Bril, Andrzej Szczudlik, Antanas Vaitkus, et al.

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