Treatment of Myasthenia Gravis Exacerbation With Intravenous Immunoglobulin

A Randomized Double-blind Clinical Trial

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Background: The optimal dose of intravenous immunoglobulin (IVIG) in acute exacerbation of myasthenia gravis remains unknown. Increasing the treatment duration might provide added efficacy.

Objective: To determine the optimal dose of IVIG for treating myasthenia gravis exacerbation.

Design: Randomized double-blind placebo-controlled multicenter trial designed to demonstrate superiority of the 2 g/kg dose over the 1 g/kg dose of IVIG, conducted between November 13, 1996, and October 26, 2002.

Participants: One hundred seventy-three patients aged 15 to 85 years with acute exacerbation of myasthenia gravis.

Intervention: Participants were randomly assigned to receive 1 g/kg of IVIG on day 1 and placebo on day 2 (group 1) vs 1 g/kg of IVIG on 2 consecutive days (group 2).

Main Outcome Measure: Improvement in the myasthenic muscular score after 2 weeks.

Results: The mean improvements in the myasthenic muscular scores after 2 weeks were 15.49 points (95% confidence interval, 12.09-18.90 points) in group 1 and 19.33 points (95% confidence interval, 15.82-22.85 points) in group 2. However, the difference between the 2 groups was not significant (effect size, 3.84 [95% confidence interval, −1.03 to 8.71]; P=.12).

Conclusion: This trial found no significant superiority of 2 g/kg over 1 g/kg of IVIG in the treatment of myasthenia gravis exacerbation.

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Myasthenia gravis (MG) is an autoimmune disease. Up to 90% of patients with generalized MG have detectable serum anti-acetylcholine receptor antibodies (anti-AChR ab). Skeletal muscle weakness and fatigability that fluctuate rapidly or slowly are the characteristic symptoms. Acute exacerbation can cause life-threatening swallowing impairment or respiratory failure. Plasma exchange and intravenous immunoglobulin (IVIG) have been proposed for the treatment of MG.1 A randomized controlled clinical trial comparing the efficacy and safety of plasma exchange vs IVIG (0.5 g/kg per day for 3 or 5 days) in patients with severe exacerbation of MG found no significant difference between the efficacy of plasma exchange vs IVIG.2 Furthermore, the 2 IVIG doses had no significantly different effects, although this was perhaps ascribable to the small sample sizes. For treatment of other autoimmune diseases, IVIG has been administered as a single daily dose of 0.8 g/kg or 1 g/kg or administered as 2 g/kg or 1 g/kg per day on 2 consecutive days.

Given the risk of adverse events and the high cost of IVIG, the optimal dose for treating MG should be determined. Therefore, we performed a randomized double-blind placebo-controlled multicenter trial in patients with exacerbation of MG to test the hypothesis that 1 g/kg of IVIG would be more effective when given on 2 consecutive days than as a single dose.

METHODS

PATIENTS

Consecutive patients presenting to any of the 12 study centers with exacerbation of MG were eligible. The following criteria were required for the diagnosis of MG: (1) acquired weakness of skeletal muscles, including those supplied by the cranial nerves; (2) fluctuation of muscle fatigability; and (3) a concentration of serum anti-AChR ab greater than 1 nmol/L or a decremental electromyographic response (≥10% decrease in compound muscle action potential amplitude after stimulation at 3-5 Hz), in addition to a positive response to an anticholinesterase drug.
Myasthenic exacerbation was defined as development within the last month of at least 1 of the following symptoms: difficulty swallowing, acute respiratory failure, and major functional disability precluding physical activity.

Exclusion criteria were corticosteroid treatment initiated or modified within the last month, plasma exchange within the last 6 weeks or IVIG within the last 3 months, known allergy to IVIG, serum creatinine level greater than 1.4 mg/dL (>120 mmol/L), or creatinine clearance less than 60 mL/min (1 mL/s), body weight greater than 100 kg, pregnancy, and age younger than 15 years. The study protocol was approved by the local ethics committee. All patients gave written informed consent.

RANDOMIZATION
Randomization was centralized by fax and stratified by center and by history of corticosteroid or other immunosuppressive therapy. The details of the randomization were unknown to the investigators and the trial coordinator. At each study center, pharmacists who were not involved in the trial dispensed the active drug or the placebo according to the randomization list.

TREATMENTS
Patients were randomly assigned to receive 1 g/kg of IVIG (Tegeline; LFB Laboratories, Les Ulis, France) on day 1 and placebo on day 2 (group 1) vs 1 g/kg of IVIG on 2 consecutive days (group 2). The IVIG and the placebo were prepared and dispensed by the pharmacists in identical bottles. Anticholinesterase drugs were given as necessary. In patients previously treated with corticosteroids or immunosuppressive drugs, these treatments were continued unchanged.

MEASUREMENTS
At baseline, the disease duration, number of previous exacerbations, presence of thymoma, history of thymectomy, and current treatment were recorded. Clinical severity before the exacerbation was graded as follows: grade 1, complete remission; grade 2, minor symptoms allowing normal everyday physical activities; grade 3, moderate symptoms allowing part-time work or some daily activities; grade 4, major disability requiring discontinuation of work; and grade 5, major disability requiring continuous help from others or mechanical ventilation. The myasthenic muscular score (MMS), ranging from 0 points (major weakness) to 100 points (no weakness), was measured as previously described. Other measurements included forced vital capacity, serum creatinine level, blood cell counts, liver function tests, serum anti-AChR ab level, and serological tests for hepatitis viruses and human immunodeficiency virus. Subsequently, the MMS was measured on days 2, 4, 6, 9, 12, and 15; forced vital capacity on day 15; serum creatinine level on days 2, 3, 5, 9, and 15; blood cell counts on days 3, 5, 9, and 15; liver function tests and anti-AChR ab level on day 15; and serological tests for hepatitis viruses and human immunodeficiency virus after 4 months. Clinical adverse events were recorded daily, coded according to the Medical Dictionary for Regulatory Activities on standardized forms, and graded for intensity (1, mild; 2, moderate; 3, severe; and 4, very severe life-threatening). All measurements were undertaken by blinded observers.

EVALUATION CRITERIA
The primary end point was the MMS change from baseline (day 0) to day 15. Secondary end points included the following: the time course of the MMS increase and the response rate, with a response being defined as at least a 20-point MMS increase, as in earlier work; the time to treatment response within the first 15 days; the absolute difference in forced vital capacity between day 0 and day 15; the absolute difference in serum anti-AChR ab levels between day 0 and day 15; and the need for mechanical ventilatory assistance or a nasogastric tube within the first 15 days.

The cumulative incidence of adverse events was analyzed. Noncompliance was defined as administration of less than 0.8 g/kg of IVIG on day 1 in group 1 or less than 0.8 g/kg on day 1 or day 2 in group 2.

SAMPLE SIZE CALCULATION
The minimum sample size was computed to detect an 8-point difference in absolute mean MMS variation from day 0 to day 15, from 16 points in group 1 to 24 points in group 2, assuming an SD of 16 points as assessed from a previous study. At a 2-sided 5% level and 90% power, 85 patients were required for each study group; therefore, we planned to enroll 170 patients.

STATISTICAL ANALYSIS
The intention-to-treat approach was used. Unadjusted differences (with the 95% confidence intervals [CIs]) in outcomes were compared between the randomized groups. We used the nonparametric Wilcoxon rank sum test for continuous variables, the Fisher exact test for categorical outcomes, and the log-rank test for time-to-failure data. To consider the repeated measures over time of the MMS change and the treatment response, we used a mixed linear model and a linear model with generalized estimating equations, respectively, with an unstructured covariance matrix. Missing data were handled using the last observation carried forward procedure.

Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC) and S-PLUS 2000 (Insightful Corporation, Seattle, Wash). Two-sided significance tests were used throughout, with $P \leq .05$ considered statistically significant.

RESULTS

PATIENT FLOW
From November 13, 1996, to October 26, 2002, a total of 173 patients with acute exacerbation of MG, aged 15 to 85 years, were randomized to the trial, 84 to group 1 and 89 to group 2. Four patients (3 in group 1 and 1 in group 2) with erroneous diagnoses were excluded from the analysis. Another patient in group 2 was excluded because of a lost hospital record. This left 168 patients for the intention-to-treat efficacy analysis, 81 in group 1 and 87 in group 2 (Figure 1). Of these 168 patients, 8 patients (4 in each group) were not treated according to the protocol. The safety analysis was done in the 172 patients for whom hospital records were available.
**Table 1** gives the baseline clinical characteristics of the patients in the 2 randomization groups. The groups were well balanced.

**COMPLIANCE**

In group 1, the mean ± SD IVIG dose on the treatment day was 0.983 ± 0.145 g/kg. In group 2, the mean ± SD IVIG doses were 1.003 ± 0.079 g/kg on the first day and 0.990 ± 0.135 g/kg on the second day. The mean ± SD infusion durations on the first day were 15.9 ± 5.3 hours in group 1 and 15.4 ± 4.7 hours in group 2; on the second day, the mean durations were 14.3 ± 4.6 hours and 15.3 ± 4.9 hours, respectively.

**Efficacy Outcomes**

On day 15, the mean MMS changes from baseline were 15.49 points (95% CI, 12.09-18.90 points) in group 1 and 19.33 points (95% CI, 15.82-22.85 points) in group 2 (P < .001 for both, Wilcoxon signed rank test) (**Table 2**). However, the mean MMS variation in the groups was similar (effect size, 3.84 [95% CI, −1.03 to 8.71]; P = .12).

**Figure 2** shows the mean MMS changes over time in each group; there was no evidence of a time × treatment interaction (P = .10). Similarly, no time × treatment interaction was found for the treatment response rates (P = .36) (**Figure 3A**). Similar numbers of patients (44 in group 1 and 52 in group 2) responded at least once within the first 2 weeks. The median times to response were similar between the 2 groups (13.5 days in group 1 and 12.0 days in group 2) (P = .48) (**Figure 3B**). No significant differences were found for the other secondary efficacy criteria.

**Clinical and Laboratory Safety Data**

A total of 138 clinical adverse events were recorded among 75 patients within the first 15 days of treatment, including 59 among 34 patients in group 1 and 79 among 41 patients in group 2 (**Table 3**). Most of these events were mild and self-limited, with grade 4 events occurring in 4 patients in group 1 and in 6 patients in group 2. Headaches were the most frequent adverse events. They were more common in group 2, beginning more often on or after the second day of IVIG infusion.

Elevation of the serum creatinine level to more than 1.4 mg/dL (>120 µmol/L) occurred within the first 15 days in 7 patients in group 1 and in 13 patients in group 2 (P = .20) (**Table 3**). Six patients in group 2 had values exceeding this cutoff on day 15.

Elevations in alanine aminotransferase or aspartate aminotransferase levels more than twice the upper limit of normal occurred in 7 patients in each group (P > .99).
Our results show no significant superiority of 2 g/kg compared with 1 g/kg of IV immunoglobulin infused on a single day in patients with exacerbation of MG, although there was a slight trend toward superiority of 2 g/kg. The 95% CI of the effect size for the MMS change was −1.03 to 8.71; therefore, the MMS change with 2 g/kg of IVIG was between −1.03 and 8.71 points, with a 5% type 1 error. Although the maximum 8.71-point superiority of the 2 g/kg dose is consistent with the expected 8-point effect size, most MMS changes within the observed CI are clinically meaningless.

In a randomized clinical trial comparing the efficacy of plasma exchange vs IVIG, the mean MMS changes on day 15 were similar, 16.6 points (95% CI, 11.6-21.6 points) in the plasma exchange group and 15.6 points (95% CI, 10.6-20.3 points) in the IVIG (given as 0.4 g/kg per day for 3 or 5 days) group. The number of patients with a treatment response was similar to that found in the present trial. Furthermore, the MMS improvement rate in the present trial is in agreement with previous results of administration of IVIG, generally infused as 0.4 g/kg per day for 5 days, among patients with MG.

The present trial was double blind. The clinical results were evaluated using the MMS, which has a high intraclass correlation coefficient (r = 0.91) and is closely correlated with the quantitative MG strength score used in other investigations (r = 0.87). Our results do not rule out a lesser benefit from the 2 g/kg IV immunoglobulin dose (ie, <50% difference in the MMS increase between the 1 g/kg and the 2 g/kg doses). However, such a small difference would not be clinically relevant. Furthermore, the low prevalence of MG is a major obstacle to the recruitment of patient populations large enough to allow detection of small between-group differences.

Many adverse events occurred in this trial. However, most were minor and self-limited, and occurrence rates were similar between the 2 groups except for headaches. Serum creatinine level elevations occurred in both groups, slightly more common with the higher dose, but levels returned to normal by day 15 in 70% of cases. Physicians should be alert to these adverse effects, most notably in patients with renal failure.

**Table 3. Main Adverse Events in the Study Groups Within the First 15 Days After Randomization**

<table>
<thead>
<tr>
<th>Event</th>
<th>Group 1 (n = 84)</th>
<th>Group 2 (n = 88)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence ± SD of patients with clinical adverse events on day 15</td>
<td>40.48 ± 5.36</td>
<td>46.59 ± 5.32</td>
<td>.39</td>
</tr>
<tr>
<td>Patients with ≥1 episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>10 (11.9)</td>
<td>13 (14.8)</td>
<td>.66</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (3.6)</td>
<td>5 (5.7)</td>
<td>.72</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (1.2)</td>
<td>1 (1.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Headaches</td>
<td>11 (13.1)</td>
<td>2 (22.7)</td>
<td>.05</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>5 (6.0)</td>
<td>6 (6.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>1 (1.2)</td>
<td>1 (1.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Other</td>
<td>16 (19.0)</td>
<td>16 (18.2)</td>
<td>.69</td>
</tr>
<tr>
<td>Laboratory result changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine level &gt;1.4 mg/dL</td>
<td>7 (8.3)</td>
<td>13 (14.8)</td>
<td>.20</td>
</tr>
<tr>
<td>Increase in serum AST or ALT level &gt;2 times the upper limit of normal</td>
<td>7 (8.3)</td>
<td>7 (8.0)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

SI conversion factor: To convert serum creatinine levels to micromoles per deciliter, multiply by 88.4.

*Data are given as number (percentage) unless otherwise indicated.
CONCLUSIONS

The results of this trial comparing IV immunoglobulin infusion of 2 g/kg during 2 days vs 1 g/kg on 1 day in patients with MG exacerbation demonstrate no statistically significant differences. Furthermore, the results were not different from those reported previously with administration of 0.4 g/kg per day for 5 days.\(^1\) Therefore, 1 g/kg may be the best dose for general clinical practice. This may have implications on the cost of IVIG infusion for acute exacerbation of MG.

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Disclaimer: Drs Gajdos and Chevret had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES