Comparison of IVIg and PLEX in patients with myasthenia gravis

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ABSTRACT

Objective: Both IV immunoglobulin (IVIg) and plasma exchange (PLEX) are immunomodulatory treatments used to treat patients with myasthenia gravis (MG), but the choice of which treatment to administer to patients is limited due to lack of evidence from adequately powered, masked, randomized, standardized trials.

Methods: We randomized 84 patients with moderate to severe MG defined as a Quantitative Myasthenia Gravis Score for disease severity (QMGS) of >10.5 and worsening weakness to IVIg (Gamunex[®], Talecris Biotherapeutics) 1 g/kg/day for 2 consecutive days or PLEX (Caridian Spectra) 1.0 plasma volume exchanges for 5 exchanges. The patients were evaluated at day 14 after treatment for the primary efficacy parameter of change in QMGS and secondary clinical and electrophysiologic parameters and were followed for a total of 60 days.

Results: Both IVIg and PLEX reduced the QMGS, and IVIg was comparable to PLEX in efficacy. The dropout rate was the same for both treatment arms and both treatments were well-tolerated. The presence of acetylcholine receptor antibodies and greater baseline disease severity predicted a better response to therapy. The postintervention status revealed that the same proportion of patients improved with treatment: 69% on IVIg and 65% on PLEX. The duration of improvement was similar with both treatments.

Conclusions: IVIg has comparable efficacy to PLEX in the treatment of patients with moderate to severe MG. Both treatments are well-tolerated, and the duration of effect is comparable. Either treatment may be offered to patients depending on availability of resources.

Classification of evidence: This study provides Class I evidence that IVIg and PLEX have comparable efficacy and are equally tolerated in adult patients with moderate to severe MG within 2 weeks of treatment. *Neurology*[®] 2011;76:2017-2023

GLOSSARY

AChRab = acetylcholine receptor antibodies; **ANCOVA** = analysis of covariance; **ANOVA** = analysis of variance; **CI** = confidence interval; **ICU** = intensive care unit; **IVIg** = IV immunoglobulin; **MG** = myasthenia gravis; **MGFA** = Myasthenia Gravis Foundation of America; **MuSK** = muscle-specific tyrosine kinase; **PLEX** = plasma exchange; **QMGS** = Quantitative Myasthenia Gravis Score for disease severity; **RNS** = repetitive nerve stimulation; **SFEMG** = single-fiber EMG testing; **UHN** = University Health Network; **VAS** = visual analog scale.

Myasthenia gravis (MG) is a disorder caused by acetylcholine receptor antibodies (AChRab) and antibodies to muscle-specific tyrosine kinase (anti-MuSK antibodies) in most patients.¹⁻⁴ Definitive treatment requires immunosuppression or immunomodulation therapy such as IV immunoglobulin (IVIg) or plasma exchange (PLEX).^{5,6} Immunomodulation is used when rapid improvement is required, i.e., MG exacerbation,⁷⁻¹¹ preoperative optimization of strength prior to thymectomy,¹² and in patients who cannot tolerate or do not respond to immunosuppressive medications.^{5,10,11}

The benefits of immunomodulation with PLEX and IVIg have been demonstrated in several studies.^{10,11,13,14} A recent double-blind, placebo-controlled, randomized clinical trial demonstrated the efficacy of IVIg in patients with MG and worsening weakness with greater response in patients with more severe MG.⁷ While both IVIg and PLEX appear to be useful in worsen-

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ing MG, there is insufficient evidence available as to which treatment is more effective. An unmasked study compared a short course of PLEX with 2 different doses of IVIg and showed no significant difference between treatments.¹⁵ Smaller studies have suggested PLEX may be superior and faster acting than IVIg.^{16,17} The small numbers, unmasked assessments, lack of standard treatment protocols, and lack of standardized assessments raise questions about the conclusions of these studies. Since immunomodulation treatments are costly, it is important to determine whether the treatments are comparable to help guide therapy of patients with MG.

We carried out a randomized, evaluator-masked study in patients requiring immunomodulation for moderate to severe MG to determine whether IVIg was comparable to PLEX.

METHODS **Standard protocol approvals, registrations, and patient consents.** This single-center protocol received ethics approval from the University Health Network (UHN) Research Ethics Board in 2007 and was conducted at UHN and concluded in 2010. The study is a randomized clinical trial with masked evaluators. Informed consent was obtained from all study subjects. Clinical trials ID: NCT01179893.

Patients aged 18 years or older with a diagnosis of moderate to severe MG, defined as Quantitative Myasthenia Gravis Score (QMGS) >10.5, and worsening weakness requiring a change in treatment modality as judged by a neuromuscular expert, were considered for the study. The diagnosis of MG was made upon clinical assessment, abnormal electrodiagnostic studies on single-fiber EMG testing (SFEMG), and abnormal repetitive nerve stimulation (RNS). The presence of AChRab and anti-MuSK antibodies supported the diagnosis, while negative antibody results did not exclude patients from the diagnosis of MG. Worsening weakness was outlined as increase in diplopia, ptosis, blurred vision, dysarthria, dysphagia, difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Increasing weakness had to be sufficiently severe to suggest that adjustment of current medications would not adequately control the symptoms and QMGS was >10.5 at time of screening. Prior QMGS information was not available in all patients so a change in QMGS could not be used as an index of worsening.

Exclusion criteria included MG worsening secondary to concurrent medications (e.g., aminoglycosides) or infection, change in corticosteroid dosage in the 2 weeks prior to screening, other disorders causing weakness, known immunoglobulin A deficiency, active renal or hepatic disease, clinically significant cardiac disease, known hyperviscosity, or hypercoagulable state. Patients with a history of anaphylaxis, severe systemic response to IVIg or albumin, known refractory status to previous IVIg or PLEX, poorly controlled hypertension, pregnancy, or breastfeeding were also excluded.

Clinical evaluation. Once the diagnosis was confirmed and informed consent obtained, patients were screened for the study

by a neurologist (V.B.) who remained masked throughout the study. The baseline clinical assessments included the QMGS, Myasthenia Gravis Foundation of America (MGFA) clinical classification of MG score, and subjective patient visual analog scale (VAS). QMGS is a validated, ordinal scale testing sentinel muscle groups endorsed by the MGFA and is the current gold standard of prospective studies in MG.^{18,19} A change of 3.5 out of 39 units on the QMGS for disease severity is considered clinically meaningful, and was the effect size used in determining the sample size for this study.²⁰ The QMGS, MGFA classification, and VAS were repeated at days 14, 21, and 28 after treatment was completed. Quality of life was assessed using the Myasthenia Gravis Quality of Life Questionnaire at baseline, and days 14, 21, 28, and 60 after treatment was completed.²¹ Postintervention status was also reported, rating the patient's clinical status on a 5-step scale as improved, unchanged, worse, exacerbation, and died from MG.

Patients receiving pyridostigmine were instructed not to take medication 12 hours prior to assessment and for those receiving slow-release pyridostigmine, the medication was held the night before the assessment. No change in cholinesterase inhibitors or other immunosuppressant medications were made from study initiation to the primary outcome measure on day 14.

At day 60, an unmasked QMGS was performed and the patient evaluated for clinical worsening of MG during the study, time interval after initial PLEX or IVIg to additional treatment in case of worsening MG, or the need for any of the following: intensive care unit (ICU) admission, positive pressure ventilation, hospitalization, nasogastric tube feeding, and adverse events. If the patient terminated early, regardless of reason, day 60 assessments were performed.

Electrodiagnosis. SFEMG and RNS studies were done at baseline and days 14, 21, and 28 on the same day as the clinical assessments using methods published previously.⁷

Laboratory measures. Laboratory measures included AChRab and Anti-MuSK antibody levels for all patients at baseline and days 28 and 60, if abnormal at baseline.

Intervention. Subjects were randomized in blocks of 4 to receive either IVIg (Gamunex[®], Talecris Biotherapeutics, Mississauga, Canada) or PLEX (Caridian Spectra). Patients randomized to IVIg received 1 g/kg/day of IVIg for 2 consecutive days. Patients received preinfusion Benadryl 50 mg PO and Tylenol ES 2 tablets to reduce potential side effects of IVIg. IVIg was administered in the medical day unit at UHN for outpatients, or on a hospital unit for inpatients. Patients randomized to PLEX received 1.0 plasma volume exchanges with 5% albumin replacement fluid. Five plasma exchange procedures were performed every second day with breaks over the weekend allowed. Outpatients were treated in the apheresis unit at UHN and inpatients were treated in hospital units. A hematologist (D.B.) conducted the randomization, administered IVIg and PLEX treatments, and provided care for complications of treatments so that the neurologist (V.B.) would remain masked to the treatment allocation.

Efficacy measures. The primary outcome measure of the study was the change in QMGS from baseline to day 14 after full treatment. The secondary outcome measures included the change in QMGS from baseline to days 21 and 28, change in SFEMG jitter, abnormal pairs, blocking pairs, % decrement in RNS from baseline to days 14, 21, and 28, postintervention status at days 14, 21, and 28, and change in AChRab titers from baseline to days 28 and 60. Need for ICU admission, positive

pressure ventilation or intubation, any hospitalization, and additional therapy for MG were also considered secondary outcome measures. All efficacy evaluations were masked.

Adverse events occurring within 30 days after treatment were recorded and assessed for relation to study treatment. Additional MG therapy was permitted after day 14, if necessary. Although these patients were nonresponders to treatment, they were not removed from follow-up, unless adverse events prevented their further participation.

Statistical analyses. All analyses were performed using JMP SAS version 5. Baseline demographic variables were described by means $\pm$ standard deviations for continuous variables and compared by t test, and percents or ranges for categorical values and compared by χ^2 . For the primary outcome of change in QMGs at day 14, analysis of variance (ANOVA) was used. Responders were defined as those who had a decrease in QMGs of ≥ 3.5 units and a responder analysis was performed by contingency table with χ^2 . For secondary outcome measures, multivariate ANOVA for repeated measures, analysis of covariance (ANCOVA), and χ^2 were performed. A p value <0.05 was considered statistically significant. The effects of baseline covariates (disease severity, age, gender, MG duration, presence of thymoma, thymectomy, presence of AChRab or anti-MuSK antibodies, jitter, decrement, and immunosuppressive medications)

were examined by ANCOVA. Kaplan-Meier survival analyses were used to analyze the duration of treatment effects.

Data for the primary efficacy parameter were analyzed in an intent-to-treat analysis in treated patients. The power analysis showed a 90% probability that the study would detect a treatment difference at a 2-sided 0.05 significance level if the true difference in QMGs between treatments was 3.5 (SD 4.0) with 29 patients per arm of the study. Additional patients were recruited to maintain the power of the study in case of early withdrawals.

RESULTS Eighty-six patients were recruited for the study. Two withdrew consent prior to being randomized and their data were excluded from further analysis. Eighty-four patients were randomized to treatment and 4 of these patients failed to return for follow-up after treatment (3 on PLEX and one on IVIg). Eighty patients were assessed at day 14 for the primary efficacy parameter. Another 15 patients withdrew from the study prior to day 60. Of those withdrawing from the study, 10 were randomized to IVIg and 9 to PLEX. An intent-to-treat analysis for

Figure 1 CONSORT flow chart for IV immunoglobulin (IVIg) compared to plasma exchange (PLEX) randomized study

Table 1 Baseline demographic data^a

Clinical characteristics	IVIg (n = 41)	PLEX (n = 43)	p Value ^b
Age, y			
Mean ± SD	57 ± 18	58 ± 17	0.75
Range	19-84	20-84	
Female sex	24 (58)	24 (55)	0.89
MG duration, mo			
Mean ± SD	71 ± 90	64 ± 89	0.75
Range	3-450	5-456	
Previous IVIg treatment	9 (21)	6 (13)	0.33
Previous PLEX treatment	4 (10)	8 (20)	0.15
History of thymectomy	13 (31)	19 (44)	0.40
History of thymoma	11 (27)	14 (32)	0.78
Current pyridostigmine	32 (78)	32 (74)	0.69
Current prednisone	14 (34)	21 (48)	0.17
Current azathioprine	6 (14)	7 (16)	0.83
Current mycophenolate mofetil	2 (5)	4 (10)	0.42
Baseline QMGSc			
Mean ± SD	14.26 ± 4.0	14.44 ± 3.8	0.83
Range	11-29	11-30	
MGFA classification			
Grade 2	22 (53)	26 (60)	
Grade 3	17 (41)	15 (34)	0.60
Grade 5	0 (0)	1 (2.3)	
AChRAB (positive)	28 (70)	34 (79)	0.34
Baseline AChRAB, nmol/L			
Mean ± SD	149 ± 142	198 ± 132	0.11
Range	0-429	0-457	
Anti-MuSK AB (positive)	2 (5)	2 (4)	0.94
Seronegative	10 (25)	7 (19)	0.32
Decrement at baseline, %			
Mean ± SD	13.8 ± 14.6	17.2 ± 18.5	0.38
Range	0-61	0-63	
Baseline SFEMG jitter, μs			
Mean ± SD	110 ± 52	118 ± 39	0.47
Range	29-247	40-233	
Baseline SFEMG abnormal pairs, %			
Mean ± SD	66 ± 27	77 ± 21	0.06
Range	10-100	19-100	
Baseline SFEMG blocking pairs, %			
Mean ± SD	15.4 ± 13.1	20.8 ± 13.2	0.09
Range	0-60	0-60	

Abbreviations: AChRAB = acetylcholine receptor antibodies; IVIg = IV immunoglobulin; MG = myasthenia gravis; MuSK = muscle-specific tyrosine kinase; PLEX = plasma exchange; QMGSc = Quantitative Myasthenia Gravis Score for disease severity; SFEMG = single-fiber electromyography.

^a The values are mean ± SD for continuous variables and n (%) for categorical variables.

^b p Values for categorical variables were calculated with the χ^2 test, and analysis of variance was used for continuous variables.

^c The QMGSc is out of 39.

the change from baseline in the QMGSc at day 14 was done on the data from the 84 patients who received study treatment (figure 1).

Baseline demographic information is provided in table 1. The treatment groups were balanced in all respects. The mean age of all patients was 58 ± 17 years and 57% were female. The mean duration of disease was 68 ± 89 months. Current medications were similar in both treatment groups: 73% of the patients were on pyridostigmine, 40% on prednisone, 14% on azathioprine, and 6% on mycophenolate mofetil. Seventy-four percent (n = 63) of the patients were AChRAB-positive, and of 22 who were AChRAB-negative, 18% (n = 4) were anti-MuSK antibody-positive. Disease severity by QMGSc was the same: 14.30 ± 4.0 for IVIg and 14.35 ± 3.8 for PLEX.

The primary outcome measure of change in QMGSc at day 14 from baseline was 4.0 ($p = < 0.0001$) for the whole patient group, without a significant difference between treatments: 3.2 ± 4.1 (95% confidence interval [CI] 2–4.5) unit decrease in QMGSc for the IVIg group and 4.7 ± 4.9 (95% CI 3.2–6.2) unit change for the PLEX group ($p = 0.13$) as shown in table 2. Responders, defined as those who changed by at least 3.5 units on the QMGSc, were 51% of patients on IVIg compared to 57% of the patients on PLEX ($p = 0.5$, χ^2). Absolute risk reduction for the responder rate of PLEX compared to IVIg was 7% (number needed to treat 14). The reduction in QMGSc persisted until day 28 in both treatment groups (table 2). A repeated measures analysis of the change in QMGSc from baseline showed no difference between treatments throughout the 28-day study ($p = 0.26$).

At day 14, the postintervention status was as follows: 69% improved on IVIg and 65% improved on PLEX ($p = 0.74$, χ^2), 17.5% worsened on IVIg and 2% worsened on PLEX ($p = 0.10$, χ^2), and 10% remained stable on IVIg and 31% on PLEX ($p = 0.07$, χ^2). Hospitalization or intubation were not required by any of the patients in the study by day 14.

Analysis of baseline covariates by ANCOVA showed that disease severity by QMGSc and seropositivity predicted response to therapy. Patients with more severe disease (higher QMGSc), and the presence of antibodies, had a better response to treatment ($p = 0.0005$ and $p = < 0.0001$, respectively). The AChRAB decreased with treatment from 170 ± 139 at baseline to 152 ± 123 at day 60 ($p = 0.01$) but did not differ between groups. Other baseline factors such as age, gender, duration of MG, thymoma status, thymectomy status, and electrodiagnostic status did not predict the response to therapy.

Table 2 Mean $\pm$ SD change in QMGs for disease severity from baseline to days 14, 21, and 28^a

	IVIg (n = 41)	PLEX (n = 43)	p Value ^b
Baseline QMGs	14.2 $\pm$ 4	14.4 $\pm$ 3.8	0.83
Δ QMGs			
Day 0-14 ^c	3.2 $\pm$ 4.1	4.7 $\pm$ 4.9	0.13
Day 0-21	3.3 $\pm$ 3.6	5.3 $\pm$ 5.5	0.07
Day 0-28	2.6 $\pm$ 4.0	4.7 $\pm$ 5.7	0.08

Abbreviations: IVIg = IV immunoglobulin; PLEX = plasma exchange; QMGs = Quantitative Myasthenia Gravis Score for disease severity.

^a This table demonstrates that the changes of QMGs for disease severity did not differ between the 2 treatment groups for the 28-day study duration.

^b p Values are for QMGs differences from baseline with IVIg compared to PLEX.

^c Primary efficacy parameter.

Electrophysiology showed changes with treatment as seen in table 3. RNS showed a reduction in decrement with both treatments ($p = 0.0006$). Although the improvement in RNS with IVIg was maintained at day 28, the positive effects with PLEX were not maintained, as shown in table 3 ($p = 0.001$). Similarly, the jitter decreased in both groups at day 14 and the decrease was maintained in the IVIg group at day 28, but not in the PLEX group ($p = 0.03$). The same pattern was observed for % blocking pairs with an initial decrease in the PLEX group at day 14 ($p = 0.03$), followed by an increase of the % blocking pairs at day 28 compared to patients on IVIg who showed a change at day 14 that was maintained to day 28 ($p = 0.08$). Percent abnormal pairs on SFEMG showed no specific pattern with time or with treatment.

Persistence of treatment effect, analyzed by the Kaplan-Meier survival analysis, showed no difference between groups: 10 patients withdrew early in the IVIg group (8 due to worsening and 2 withdrew con-

sent) compared to 9 patients in the PLEX group (7 due to worsening and 2 withdrew consent) ($\chi^2 = 0.79$) (figure 2).

Adverse effects observed with IVIg were allergic reaction (2), nausea and vomiting (7), headache (8), chills (2), fever (3), hemolytic anemia (1), and hypertension (1). One patient in the IVIg group had pneumonia and required intubation, but this was not considered to be treatment-related. The treatment-related adverse effects in the PLEX group were citrate reaction (6), poor venous access delaying treatment (4), vasospasm (8), and vasovagal reaction (2). One patient in the PLEX group had congestive heart failure and this adverse event was thought to be unlikely related to the treatment, and one patient had a myocardial infarction and this was considered possibly related to PLEX treatment.

Eighteen (20%) of the patients required additional treatment, 10 in the IVIg group and 8 in the PLEX group. None of the patients had any change in therapy in the first 14 days after initial treatment. In the IVIg group, 3 received additional IVIg and 2 of these withdrew early due to worsening and one stayed to day 60 after additional IVIg. One patient received PLEX and still withdrew due to worsening. The other 6 in the IVIg arm were treated with changes in medications (azathioprine, pyridostigmine, prednisone). In the PLEX group, 4 received additional PLEX and 3 of these still left early due to worsening status, and one other completed the study. One patient received IVIg but left early due to worsening. Three patients had a change in medications (pyridostigmine, prednisone, mycophenolate mofetil).

DISCUSSION Immunomodulation for MG can be accomplished with either IVIg or PLEX. This study demonstrates that IVIg has comparable efficacy to a full course of PLEX as a treatment for MG; both forms of immunomodulation produce similar improvement in the clinical state of patients with worsening disease as measured by the QMGs for disease severity (-3.2 for IVIg and -4.7 for PLEX, $p = 0.13$).

PLEX is the historical standard of immunomodulation in patients with MG although randomized, placebo-controlled trials for efficacy have not been done.^{10,13} Patients respond with rapid improvement that is temporary and treatment availability is limited to centers with apheresis devices and trained nursing staff. Standard PLEX requires 5 exchanges over the course of 2 weeks and may require central vascular access with potential infection and thrombosis. Despite limitations, PLEX is accepted as a therapy that acts rapidly and often enables patients to discontinue ventilator assistance or regain normal strength.

Table 3 Electrophysiologic characteristics at baseline and days 14, 21, and 28

Treatment	Decrement, %	Jitter, μ s	Abnormal pairs, %	Blocking pairs, %
IVIg				
Baseline	13.8	110	66	15
Day 14	9.9	76.4	49.2	9
Day 21	9.2	75.3	52.5	8.8
Day 28	6.5	72.6	47.6	7.1
PLEX				
Baseline	17.2	118	77	20.8
Day 14	8.9	78.3	49.6	10
Day 21	12.0	83.6	57.3	13.6
Day 28	13.4	97.7	67.9	16.4
p Value ^a	0.001	0.03	0.11	0.08

Abbreviations: IVIg = IV immunoglobulin; PLEX = plasma exchange.

^a The p value is for difference in treatment effect at different time intervals.

Figure 2 Duration of treatment effect with IV immunoglobulin (IVIg) and plasma exchange (PLEX) in patients with myasthenia gravis (MG)

Kaplan-Meier survival curves for IVIg and PLEX treatment in patients with myasthenia gravis. No significant difference between relapse or worsening of MG was observed between the treatment groups.

IVIg, used as an alternative to PLEX,^{8,11} does not require volume shifts and is more easily administered. In patients with MG with worsening weakness, a randomized, double-blind, placebo-controlled trial showed IVIg to be efficacious compared to placebo treatment,⁷ with greater improvement observed in patients with more severe MG at baseline. Another study had failed to show a clinical benefit with IVIg, but only 15 patients were studied.²²

While IVIg and PLEX are both useful in treating patients with worsening myasthenic weakness, the evidence as to which treatment is more effective was limited. Gajdos et al.¹⁵ performed a randomized trial of 87 patients with acute myasthenic worsening treated with 3 days of PLEX or 2 doses of IVIg. This study showed no difference among the 3 treatments,¹⁵ but the assessments were unmasked and a full course of PLEX was not administered, resulting in a study bias toward the benefits of IVIg. Stricker et al.¹⁶ reported that PLEX was superior to IVIg in a small, uncontrolled series of patients with an acute exacerbation of myasthenic weakness. Ronager et al.¹⁷ studied 12 patients with MG in a controlled crossover study of PLEX and IVIg and observed no difference in outcomes at 1 month although PLEX worked more rapidly as clinical differences were observed at 7 days after treatment. An American Academy of Neurology recently updated evidence-based guideline on PLEX noted the lack of sufficient evi-

dence to support or refute the use of PLEX for MG,²³ but the current study provides strong evidence that IVIg and PLEX have comparable efficacy in treatment of patients with worsening MG.

Since both IVIg and PLEX have different implications with respect to side effect profiles, costs, availability, and time commitment for the patient and medical staff, it was desirable to determine if IVIg had comparable efficacy to the older standard of PLEX in a randomized, masked study involving a large number of patients with moderate to severe MG using standard therapeutic protocols, validated clinical assessment tools, objective electrodiagnostic testing, and antibody testing. These aims were addressed by the current study and new information on the duration of the treatment effect was obtained. The observations that both treatments are well-tolerated and that the dropout rate is the same with either treatment demonstrates similar patient tolerance for both forms of immunomodulation.

This study provides evidence for the choice of either IVIg 1 g/kg/day for 2 consecutive days or PLEX 1.0 plasma volume exchanges for 5 exchanges as effective immunomodulatory treatment for patients with worsening myasthenic weakness, and shows a similar duration of benefit and acceptable safety profile with both treatments. The results suggest that patients with worse myasthenic weakness at baseline and a positive AChRAb status may respond better to immunomodulation.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Maryam Nabavi Nouri.

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DISCLOSURE

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