ABSTRACT: Failure to induce and maintain remission in severe exacerbations of myasthenia gravis (MG), despite optimal care, is a common problem. We evaluated the efficacy and safety of high-dose intravenous immunoglobulin (IVIg) therapy in an open-label study of 10 patients with severe generalized myasthenia and an acute deterioration unresponsive to conventional therapy including high-dose corticosteroids, cyclosporine, and azathioprine. Intravenous Ig at a loading dose of 400 mg/kg was administered daily for 5 consecutive days, with maintenance IVIg treatment at a dose of 400 mg/kg, once every 6 weeks. Significant improvement occurred in all patients, beginning at 6 ± 2 days of treatment as measured by the Osserman scale, fatigue variables, muscle strength, and respiratory function tests. No side effects were observed during induction of remission. Further IVIg treatments were highly efficacious in maintaining the remission. The severity of the disease decreased by 2.5 ± 0.8 grades of the Osserman scale over a period of 1 year (P <0.001), in parallel with reduction of immunosuppressive therapy as well as a decrease in acetylcholine receptor antibody titers (P < 0.01). Intravenous Ig therapy seems to be highly potent for inducing rapid improvement in refractory myasthenia during acute deterioration as well as for maintaining remission.
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IMMUNOGLOBULIN TREATMENT IN REFRACTORY MYASTHENIA GRAVIS

ANAT ACHIRON, MD, PhD, YORAM BARAK, MD, SHMUEL MIRON, MD, PhD, and IDA SAROVA-PINHAS, MD

Neuroimmunology Unit, Sheba Medical Center, Tel-Hashomer, 52621 Israel

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Various treatments are currently available for myasthenia gravis (MG), including acetylcholine esterase inhibitors, corticosteroids, immunosuppressive cytotoxic drugs, plasmapheresis, and thymectomy.[4,5,17,21,23] However, these may be ineffective in a subgroup of patients defined as refractory myasthenics. Because acute worsening of MG is associated with a mortality rate of 5 to 24%,[12,24] additional efficacious therapeutic strategies are needed. Intravenous immunoglobulin (IVIg) has been used to treat a variety of autoimmune disorders,[3,22] and several reports exist on the potential role of IVIg in MG.[1,2,7,9–11,15] We report on rapid improvement and maintenance of remission induced by IVIg treatment in 10 patients suffering from an acute worsening of generalized MG.

Abbreviations: AChR, acetylcholine receptor; IVIg, intravenous immunoglobulin; FEV, forced expiratory volume; MG, myasthenia gravis

Key words: immunoglobulins; myasthenia gravis; remission; treatment

Correspondence to: A. Achiron; e-mail: achiron@post.tau.ac.il

PATIENTS AND METHODS

The study was approved by our Hospital Internal Review Board and the Israeli Ministry of Health Ethical Committee. All participants signed an informed consent agreement following extensive explanation of the study's aim. The primary outcome objectives were (1) induction of remission, defined as decrease in Osserman score of 1 point; and (2) maintenance of remission, defined as sustained Osserman score equal to or lower than grade 2. A secondary outcome measure was reduction in concomitant medications.

Patients were included in the study according to the following inclusion criteria: (1) onset of acute myasthenic worsening, characterized by worsening of myasthenic symptoms such as fatigue, generalized muscle weakness, ptosis, diplopia, dysarthria, dysphagia, or respiratory difficulties; (2) increase in Osserman score[25] of at least 2 points from previous examination; (3) objective findings in the neurologic examination; and (4) lack of response to an increased dose of steroids within 1 week or rapid clinical deterioration accompanied by severe respiratory difficulties.

Exclusion criteria were: (1) intercurrent infection; (2) IgA deficiency; and (3) previous allergic reaction to blood products.

The IVIg (Octagam, Omrix, Israel) in a sterile, liquid, 4.5 to 5.5% solution of human protein in 9 to 11% maltose—inactivated by Cohn fractionation, solvent/detergent treatment and low pH—was given intravenously once daily for 5 consecutive days at a dose of 0.4 g/kg/day. The daily dose was infused slowly (4 to 6 h). Patients were further treated with IVIg 0.4 g/kg, once every 6 weeks for the following year.

Clinical Evaluation. Disease severity was scored according to Osserman's classification (University of Virginia's modification[25]). Grade I involves focal disease (restricted to ocular muscles); grade II, generalized disease that is either mild (IIa) or moderate (IIb); grade III, severe generalized disease; and grade IV, severe generalized disease with life-threatening impairment of respiration. Isometric muscle strength was tested by manual muscle testing.[9] Forced expiratory volume (FEV) was measured by a spirometer. Fatigue parameters included: (1) timed forward legs extensions while lying supine; (2) timed forward arms abduction while sitting; (3) maximal palpebral fissures width before and after 30 s of upward gaze; and (4) shortest time to count from 1 to 40, for evaluation of voice fatigue.

Clinical evaluation was performed at onset of IVIg treatment and daily during the first week, then once weekly for the first month, and once every 6 weeks for a period of 1 year. Neurologic examinations were always performed during morning hours, 2 hours after anticholinesterase medication and before IVIg administration at 6-week intervals.

Laboratory Tests. Complete blood count and chemistry, serological tests for anti–human immunodeficiency virus and hepatitis A and B antibodies, immunoelectrophoresis, and urinalysis were performed before first IVIg treatment. Acetylcholine receptor (AChR) antibody titer was measured before IVIg treatment, 10 days later, and once every 6 weeks for the following year.

Statistical Analysis. Two-sample *t*-test and nonparametric test were applied for testing differences between patients' baseline and follow-up parameters. All tests applied were two-tailed, and P values of 0.05 or less were considered statistically significant. The data were analyzed using SAS software.

RESULTS

We treated 10 consecutive patients (7 women) with an acute exacerbation of MG. Age range was 25–70 years (mean, 44.7 ± 15 years), and disease duration ranged from 2 to 8 years. Three patients underwent thymectomy 2 to 4 years prior to the study; one had a thymoma and two patients had thymic hyperplasia. Patients were admitted because of an acute myasthenic exacerbation not attributable to concomitant infection and deteriorated while on therapy with pyridostigmine (240–360 mg/day, 8 patients), prednisone (30–60 mg/day, 9 patients), or azathioprine (100–300 mg/day, 5 patients). In all patients, the exacerbation was generalized and was characterized by moderate to severe muscle weakness associated with respiratory difficulties and ocular and bulbar muscle involvement with ptosis, diplopia, dysarthria, and dysphagia. All had high levels of plasma AChR antibodies (mean value, 95 ± 112; range, 15–326 pg/mL; normal values in our laboratory, 0–6 pg/mL).

Induction of Remission. All 10 patients benefited from IVIg treatment. Initial improvement was observed at 6.4 ± 2.2 days after the start of IVIg treatment and became maximal at 10.5 ± 1.6 days. Severity of disease decreased from a mean score of 3.7 ± 0.5 (severe generalized weakness) to 2.2 ± 0.7 (mild to moderate disease) ($P = 0.001$). Forced expiratory volume improved from a mean of 1148 ± 568 to 1810 ± 722 mL. Corrected for age and height, FEV increased by a mean of 18%. Performance in fatigue tests improved significantly after IVIg treatment. The timed forward arms abduction increased from 15 ± 6.7 s to 64 ± 39.1 s ($P < 0.05$) and the timed forward legs extension increased from 6.7 ± 8.3 s to 21.8 ± 19 s ($P < 0.05$). Ptosis evaluated by palpebral fissure width after 30 s of upward gaze improved from 6.7 ± 3.9 mm to 9.5 ± 2.4 ($P < 0.01$), and counting time (evaluating dysarthria and facial weakness) decreased from 44 ± 7.4 s to 25.7 ± 3 ($P < 0.01$). Acetylcholine receptor antibody titers decreased during IVIg induction period by a mean of 63%. The duration of IVIg single-course beneficial effects lasted for 32 ± 5 days, and clinical examination immediately prior to the second administration of IVIg (6 weeks from study entry) reflected worsening of MG symptoms (Fig. 1).

Maintenance of Remission. All patients completed the 1-year treatment according to the study's protocol. Individual Osserman scores for all 10 patients changed significantly throughout the study period, as presented in Figure 1. Decreased disease severity

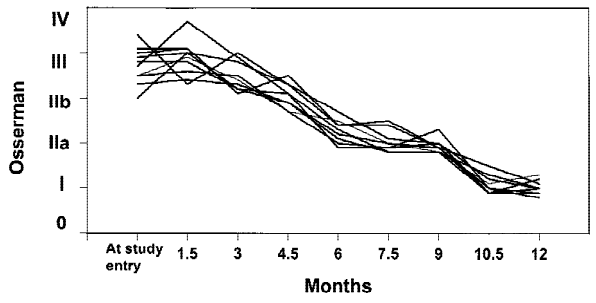

FIGURE 1. Individual Osserman scores for the 10 patients throughout the study.

as reflected by Osserman's score significantly correlated with treatment duration ($r = -0.79$; $P = 0.003$). Muscle strength for the face and neck musculature, upper limb girdle, and lower limb girdle increased significantly over time. Face and neck muscles improved in strength by a mean of 1.3 ± 0.6; $P = 0.003$; mean upper limb girdle improvement was 0.9 ± 0.5; $P = 0.001$; and mean lower limb girdle strength improved by 1.2 ± 0.5; $P = 0.0001$.

During the maintenance period, no exacerbations occurred and gradual decrease in corticosteroids and immunosuppressive medication was achieved (Fig. 2). For pyridostigmine, prednisone, and azathioprine, the decrease in daily dose correlated with treatment duration ($r = -0.56$, -0.66, and -0.69, respectively; $P < 0.005$). During the induction phase, no attempt was made to change concomitant medication regimen. Azathioprine was the first medication to be tapered, beginning at a mean of 3 months, followed by prednisone, at a mean of 4.5 months, while pyridostigmine was the last to be tapered. Not only did the mean dose of concomitant medications decrease during the maintenance phase, but at the end of the study, the number of patients using azathioprine decreased from 5 to 1 patient, prednisone from 9 to 8 patients, and pyridostigmine from 8 to 3 patients.

Acetylcholine receptor antibody titers remained fairly constant throughout the maintenance period ($r = 0.11$; P = nonsignificant), whereas, at the same time, disease severity (Osserman's scale score) significantly improved ($r = -0.77$; $P = 0.001$).

No complications or adverse reactions were encountered during the treatment. Minor transient side effects were recorded in three of 130 IVIg infusions. These included increased blood pressure (one patient) and headaches (two patients).

Attempt to discontinue IVIg maintenance treatment following completion of the study was successful in seven patients within 1.5 to 3 years.

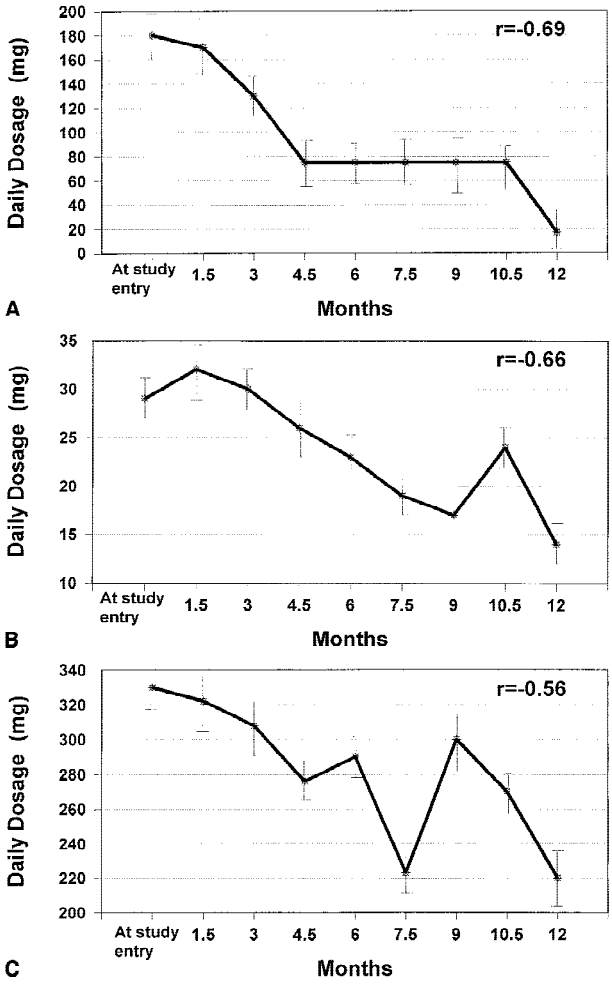

FIGURE 2. Mean dose of concomitant medications throughout the study period (r = correlation with duration of IVIg treatment). **(A)** Azathioprine. **(B)** Prednisone. **(C)** Pyridostigmine.

DISCUSSION

The present study demonstrates that treatment with IVIg induces remission of generalized MG and helps to maintain the achieved remission. Gajdos et al.[11] were the first to describe treatment with IVIg in five patients with MG. In four, improvement was significant between days 10 and 15 and remained stable up to day 25. This study was followed by several similar reports in relatively small groups of MG patients.[2,7,10,15] Arsura et al.[1] reported the effects of repeated doses of IVIg in nine myasthenic patients in whom improvement began at a mean of 4.3 days and was sustained up to 106.6 days. In the present study, improvement occurred in all patients, beginning 6 days after initiation of treatment, and was maintained with further IVIg dosing every 6 weeks for a period of 12 months, enabling significant reduction in mean daily dosages of concomitant medications.

The benefit of steroid reduction is obvious and has also been reported in other autoimmune diseases, such as chronic inflammatory demyelinating polyneuropathy and systemic vasculitis, wherein IVIg treatment was administered. This may be related to shared mechanisms of action for both IVIg and steroids, such as Fc receptor blockade, anticytokine effects, or a direct effect on the glucocorticoid receptor.[13,20]

During the induction phase, a significant reduction in AChR antibodies titer was noted. However, similarly to other drug studies in MG,[9] we could not demonstrate a consistent effect on the amount of AChR antibodies during the maintenance phase.

The mechanism of action of IVIg in MG is not fully elucidated. It may act directly by competing with antibodies for the AChR binding site. Another possibility is that IVIg activates idiotypic–anti-idiotypic network. This network shares cross-reactivity with the AChR and thus suppresses the immune response. Lefvert[18] produced anti-idiotypic antibodies against two purified AChR antibodies in rabbits and found cross-reaction with several myasthenic IgG fractions. Inhibition of receptor antibody binding to neurotoxin–human receptor complex by anti-idiotypic IgG fractions was reported by Lefvert and Bergstrom.[19] Intravenous Ig increases levels of anti-idiotypic antibodies that bind and neutralize a large array of autoantibodies, thus interfering with their cross-reactivity with the autoantigen. By 1990, Dietrich and Kazatchkine[8] had already shown that normal IVIg contains cross-reactive anti-idiotypic antibodies. Among the many autoantibodies neutralized by IVIg are anti-AChR antibodies.[16] However, two other mechanisms of action have been proposed to explain the beneficial effect of IVIg in MG. First, binding of IgG to B cells may result in decreased autoantibody production, and second, IVIg may cause reduction in the production of autoantibodies because it contains antibodies against CD5, which would inactivate CD20 B cells.[6,14]

Remission of myasthenic crisis in open trials is reported to be in the range of 70 to 80%.[9] However, this effect is transitory and is sustained only for periods of weeks, necessitating an approach that will allow long-term therapy. Our patients benefited from IVIg treatment during a 1-year maintenance period. Stability of clinical status and reduction in dose of steroids and cytotoxic medications during the maintenance phase are encouraging. For the subgroup of MG patients in whom steroids and cytotoxic treatment is required for a considerable length of time, serious side effects frequently develop. Thus, use of IVIg directly affects patient well-being and reduces the negative consequences associated with immune-suppressing drugs.

The limitations of the present study are the small number of patients involved and the open-label design, but the inherent bias was countered by the use of objective parameters (e.g., FEV, fatigue parameters) and the long duration of treatment. Thus, the results of the present study together with previous reports support the role of IVIg as an adjunctive therapy for inducing and maintaining remission of acute exacerbations of MG.

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