Intravenous immunoglobulin improved clinical outcomes in patients with myasthenia gravis and worsening weakness

Zinman L, Ng E, Bril V. **IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial.** Neurology. 2007;68:837-41.

Clinical impact ratings: Neurology ★★★★★★☆

QUESTION

In patients with myasthenia gravis (MG) and worsening weakness, is intravenous immunoglobulin (IVIG) more effective than placebo for improving clinical outcomes?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: 28 days.

Setting: A university clinic in Toronto, Ontario, Canada

Patients: 52 patients ≥ 18 years of age (mean age 55 y, 61% women) who had MG and worsening weakness. Exclusion criteria were respiratory distress requiring intensive care unit admission, vital capacity < 1 L, severe swallowing difficulties with a high risk for aspiration, corticosteroid dosage changed within 2 weeks, disorders causing weakness or fatigue, immunoglobulin A deficiency, active renal or hepatic insufficiency, clinically significant cardiac disease, hyperviscosity or hypercoaguable state, pregnancy or breast-feeding, or worsening weakness secondary to concurrent infections or medications.

Intervention: IVIG 2 g/kg (n = 24) or IV dextrose 5% in water (n = 27).

Outcomes: Change in the Quantitative Myasthenia Gravis (QMG) score for disease severity from day 1 to 14. Secondary outcomes included changes in the QMG score from day 1 to 28, the postintervention status (PIS) on days 14 and 28, and adverse events.

Patient follow-up: 98%.

MAIN RESULTS

IVIG led to a lower QMG score for disease severity on day 14 than placebo, and the effect remained on day 28 (Table). More patients in the IVIG group than in the placebo group had improved the PIS on day 14 (25% vs 6%, P < 0.004) but not on day 28. IVIG resulted in a higher incidence of headache (Table).

CONCLUSION

In patients with myasthenia gravis and worsening weakness, intravenous immunoglobulin (2 g/kg) was more effective than placebo for improving clinical outcomes on day 14, and the effect remained on day 28.

Source of funding: Talecris.

For correspondence: Dr. V. Bril, Toronto General Hospital, Toronto, Ontario, Canada. E-mail: vera.bril@utoronto.ca.

*See Glossary.

Intravenous immunoglobulin (IVIG) vs placebo in patients with myasthenia gravis and worsening weakness†

Outcomes	IVIG	Placebo	Difference between groups (P value)	
Change in QMG score (day 1 to 14)	−2.54	−0.89	−1.65 (0.047)‡	
Change in QMG score (day 1 to 28)	−3.00	−1.19	−1.81 (0.055)‡	
			RRI (95% CI)	NNH (CI)
Headache	75%	19%	305% (93 to 840)	2 (2 to 4)

†QMG = quantitative myasthenia gravis; other abbreviations defined in Glossary. RRI, NNH, and CI calculated from data in article.
‡Favors IVIG (lower QMG score is better).

COMMENTARY

Acute severe bulbar or respiratory weakness, a myasthenic crisis, can be life-threatening. MG is effectively treated with immunosuppressive medications, although significant improvement can take months—an unacceptable delay in a myasthenic crisis (1, 2).

Several trials and consensus "expert" opinion suggest that IVIG and plasma exchange (PLEX) are equally effective in cases of significant weakness, especially of bulbar or respiratory muscles (1). Because the optimal benefit from IVIG occurs in 1 to 2 weeks and lasts up to 2 months, it bridges the gap until immunosuppression works. However, there is no evidence that IVIG or PLEX changes the long-term outcome, and their roles in management of chronic MG are limited to those who cannot tolerate or do not respond to immunosuppression (3).

The trial by Zinman and colleagues compared IVIG with placebo and found that MG patients with IVIG improved at 14 days, albeit only 25%, which is lower than most studies suggest (4). In addition, the degree of improvement did not meet their predetermined and widely accepted criteria for clinical significance. However, the study sample was not representative of patients with MG in whom IVIG might be used. First, many patients were seronegative or had ocular or mild MG. Second, the percentage of patients who were positive for muscle-specific tyrosine kinase antibody was high. Third, they excluded patients with severe bulbar or respiratory weakness. All of these factors dilute the sample of very weak patients who are seropositive for acetylcholine-receptor antibody (AChRAb) in whom IVIG is arguably most effective and diminish application of the results to clinical practice. An analysis by disease severity showed more convincing improvement in weaker patients.

Do these results show that IVIG is more effective than placebo in patients with MG? Perhaps—provided that the right population is treated. It is difficult to find benefit in patients who are mildly weak or who have a form of MG that does not respond as well. However, the results suggest, as do other studies, that IVIG might be effective at the right time (sufficiently severe weakness) and place (definitely proven AChRAb-positive MG).

Michael W. Nicolle, MD
University of Western Ontario
London, Ontario, Canada

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