Monthly immunoglobulin therapy improved relapsing-remitting multiple sclerosis

Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B, for the Austrian Immunoglobulin in Multiple Sclerosis Study Group. **Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis.** Lancet. 1997 Mar 1;349: 589-93.

Objective
To evaluate the effectiveness of monthly intravenous immunoglobulin (IVIg) therapy in improving the clinical course of relapsing-remitting multiple sclerosis (MS).

Design
Randomized, double-blind, placebo-controlled trial with 2-year follow-up.

Setting
13 neurologic centers throughout Austria.

Patients
150 patients (mean age 37 y, 75% women) with relapsing-remitting MS, a baseline Kurtzke expanded disability status scale (EDSS) score between 1.0 and 6.0, and a history of ≥ 2 relapses during the previous 2 years. Exclusion criteria were use of immunotherapy in the previous 3 months or corticosteroids in the previous 2 weeks, lack of reliable contraception, a primary or secondary course of MS, or a benign progressive course of MS.

Intervention
75 patients were allocated to IVIg, 0.15 to 0.2 g/kg body weight once per month, and 73 were allocated to saline placebo, both for 2 years.

Main outcome measures
The primary outcome measure was difference in absolute change in clinical disability between treatment groups measured with the EDSS. The secondary outcome measure assessed relapse rates.

Main results
Analysis was by intention to treat. The final EDSS score decreased (improved) from baseline in patients in the IVIg group but increased in the placebo group (mean change – 0.23 [95% CI – 0.43 to – 0.03] vs 0.12 [CI – 0.13 to 0.37], $P = 0.008$). 23 patients (31%) in the IVIg group improved by ≥ 1.0 grade on the EDSS compared with 10 patients (14%) in the placebo group {$P = 0.01$}* (Table). Overall, 24% of patients in the IVIg group did better than those who received placebo in terms of improvement (17%) and prevention of deterioration (7%). The number of confirmed relapses in the IVIg group was half that in the placebo group. IVIg was well tolerated.

Conclusion
Monthly intravenous immunoglobulin improved the course of clinical disability and reduced the frequency of relapses in relapsing-remitting multiple sclerosis.

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*P value calculated from data in article.

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Intravenous immunoglobulin (IVIg) vs placebo†

Outcome at 2 years	IVIg EER	Placebo CER	RBI (95% CI)	ABI |EER – CER|	NNT (CI)
Improvement of ≥ 1 grade on the EDSS	31%	14%	124% (17 to 337)	17%	6 (3 to 27)

†Abbreviations defined in Glossary; RBI, ABI, NNT, and CI calculated from data in article.

Commentary

To date, the only disease-modifying therapies shown to be effective in relapsing-remitting MS are the β-interferons (1, 2) and copolymer 1 (3). These therapies reduce relapse frequency by about one third and may slow disability progression.

In this interesting Austrian study by Fazekas and colleagues, several comments are in order. Previous attempts at IVIg therapy in MS have yielded mixed results, and most studies have been uncontrolled or unblinded (4, 5). The primary end point in this study was the difference in the absolute change in EDSS score between groups rather than relapse frequency. These changes were very modest, although statistically significant. The authors chose to measure disability level at the end of the study rather than the more conservative sustained disability change, and this would tend to overstate the likelihood of progression in both treatment groups. Finally, magnetic resonance imaging was not done.

Nonetheless, the findings from this work strongly suggest the need for a large multicenter trial of this therapy in relapsing-remitting MS in which change in disability and relapse frequency are the primary end points and magnetic resonance imaging analysis is a secondary outcome measure. From the perspective of cost, convenience, side effects, and safety, IVIg is a potentially attractive treatment for patients with MS.

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