

Review: In relapsing-remitting multiple sclerosis, recombinant interferon reduces exacerbations in the first 2 treatment years

Rice GP, Incorvaia B, Munari L, et al. *Interferon in relapsing-remitting multiple sclerosis*. Cochrane Database Syst Rev. 2001;(4):CD002002 (latest version 30 Jul 2001).

QUESTION

In patients with relapsing-remitting multiple sclerosis (MS), is recombinant interferon more effective than placebo for reducing clinical relapse and disease progression?

DATA SOURCES

Studies were identified by searching 3 databases; hand searching references in identified trials and symposia reports (1990 to 2000); and contacting trialists and 5 drug manufacturers.

STUDY SELECTION

Studies were included if they were randomized, double-blind, placebo-controlled trials of α - or β -recombinant interferons given subcutaneously or intramuscularly to patients who had a diagnosis of MS and who were in a relapsing-remitting phase (i.e., ≥ 1 exacerbation followed by complete or partial recovery).

DATA EXTRACTION

Reviewers independently extracted data on participant characteristics, intervention (type of interferon, dose, duration of treatment, and follow-up), outcome measures, use of corticosteroids, need for hospitalization, side effects, and adverse events. Primary outcomes were the number of patients with exacerbations during scheduled treatment and follow-up, the number of patients whose disease progressed during the first 2 years of treatment, mean change in disability score, and

the number of patients unable to walk without aid at the end of follow-up.

MAIN RESULTS

7 trials ($n = 1215$) met the selection criteria. Overall, 240 patients (20%) were excluded after randomization or were lost to follow-up. Meta-analysis showed that patients receiving interferon had a reduced risk for new exacerbations after 1 and 2 years of treatment (Table); however, at 2 years, the result became nonsignificant when interferon-treated patients who dropped out were assumed to have had exacerbations {relative risk increase (RRI) 11%, 95% CI -27 to 68 }*. Fewer patients who received interferon had disease progression over the first 2 years of treatment (Table), but this result became nonsignificant when interferon-treated patients who dropped out were assumed to have progressed {RRI 31%, CI -40 to 189 }*. Patients who received interferon also had

lower disability scores at 2 years than did patients who received placebo (2 trials, $n = 618$, weighted mean difference 0.25, 95% CI 0.05 to 0.46). No data were available for the number of patients able to walk unaided at 2 years. Patients receiving interferon had a higher risk for flu-like symptoms, fever, fatigue, nausea and vomiting, headache, injection site reactions, and hair loss (all $P \leq 0.05$).

CONCLUSION

In patients with relapsing-remitting multiple sclerosis, recombinant interferon treatment results in a modest reduction in exacerbations during the first 2 years of treatment.

Sources of funding: Multiple Sclerosis Society of Canada and Fondazione Italiana Sclerosi Multipla.

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*Calculated from data in article.

Recombinant interferon vs placebo for relapsing-remitting multiple sclerosis†

Outcomes (number of trials, patients)	Weighted event rates		RRR (95% CI)	NNT (CI)
	Interferon	Placebo		
≥ 1 exacerbation at 1 y (5, 667)	45%	68%	27 (3 to 45)‡	5 (3 to 14)
≥ 1 exacerbation at 2 y (3, 919)	56%	70%	20% (12 to 27)§	8 (6 to 13)
Disease progression at 2 y (3, 919)	20%	29%	31% (13 to 45)§	12 (7 to 30)

†Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article.

‡Meta-analysis was done using a random-effects model.

§Meta-analysis was done using a fixed-effects model.

COMMENTARY

The conclusion of the review by Rice and colleagues might sound bland after years of enthusiastic trumpeting by pharmaceutical firms, but the message is clear. The benefits of interferon therapy for relapsing-remitting MS are modest, with only small reductions in relapses at 1 and 2 years and a small reduction in disease progression. Results may improve in the future as patients are being treated much earlier in the course of the disease.

The authors' assumption that those who dropped out did so because of relapses or progression may be unjustified because patients drop out of interferon therapy for many reasons, including needle phobia, side effects, and costs. High expectations of patients are fueled by the enthusiastic publicity surrounding these drugs. Although patients believe that their symptoms and disability will improve, this has not been shown in any studies. Patients who do not feel better or have side effects stop therapy. Paradoxically, some patients stop therapy that requires frequent subcutaneous or intramuscular injections because they are doing well and have no relapses or progression.

The most positive result of this review is the small but encouraging reduction in progression. If the only result of these expensive and

inconvenient therapies is a modest reduction in relapses, then it is not worth the large expense to health care systems. The hope that reduction in relapses (and the rather striking reduction in new lesions seen on magnetic resonance imaging) will result in a reduction in eventual progression has not been proved. The small reduction of progression in such short-term studies is encouraging and needs to be tested in long-term studies assessing reduction in disability rather than in relapses.

Obtaining the long-term results needed to justify interferon and glatiramer acetate therapy will not be easy. Patients are not interested in entering long-term clinical studies when therapy is now widely available. The ethical concerns about placebo trials in MS when therapies are available has caused some to consider the use of long-term observational studies of the natural history of the disease, despite the obvious limitations. Many clinicians are increasingly unsettled about the use of such expensive therapy on the basis of short-term data and on the unproven hypothesis that short-term results will reduce disease progression in the long term.

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