Interferon-β1b reduced the progression of secondary progressive multiple sclerosis


Question
In patients with secondary progressive multiple sclerosis (MS), does interferon-β1b delay the 3-year progression of MS?

Design
Randomized, double-blind, placebo-controlled trial.

Setting
32 European centers.

Patients
768 outpatients were screened, and 718 were studied (mean age 41 y, 61% women, mean duration of disease 13 y). Inclusion criteria were clinically or laboratory-confirmed MS that was considered to be secondary progressive (a period of deterioration, independent of relapses, sustained for ≥ 6 mo after a period of relapsing-remitting MS), age 18 to 55 years, baseline Kurtzke Expanded Disability Status Scale (EDSS) score 3.0 to 6.5, and a history of ≥ 2 relapses or an increase ≥ 1 point on the EDSS in the previous 2 years. Patients were excluded if they had recently used immunosuppressive or immunomodulatory treatment or other putative agents for MS. Steroids could be used for relapses. Follow-up was 92%.

Intervention
360 patients were allocated to subcutaneous interferon, 4 million IU every other day for 2 weeks and then 8 million IU every other day for 33 months. 358 patients were allocated to placebo.

Main outcome measures
Time to confirmed progression of disability that was sustained for ≥ 3 months (≥ 1 point on the EDSS scale for patients with a baseline score of < 6.0 or a 0.5-point increase for patients with a baseline score of 6.0 or 6.5).

Main results
270 patients in the interferon group and 261 in the placebo group completed treatment. Fewer patients had confirmed progression during follow-up (P < 0.001) (Table) and the time to progression was longer in the interferon group than in the placebo group (median 644 vs 403 d, P < 0.001). The effect was independent of baseline EDSS scores and occurrence of relapses in the 2 years before or during the study. Patients in the interferon group also had longer time to and less chance of becoming wheelchair bound (P = 0.01), less change in EDSS scores (P = 0.03), fewer relapses (P < 0.001), fewer moderate or severe relapses (44% vs 54%, P = 0.008), less steroid use (54% vs 68%, P < 0.001), fewer hospital days (P = 0.04), and more adverse effects (13 measures).

Conclusion
Patients with secondary progressive MS were less likely to have disease progression with interferon-β1b.

Source of funding: Schering AG, Berlin.
For correspondence: Professor L. Kappos, Department of Neurology, University Hospital Basel, Kantonsspital, Petersgraben 4, CH-4031 Basel, Switzerland.
Abstract and Commentary also published in ACP J Club. 1999;130:69.

Interferon-β1b vs placebo in secondary progressive multiple sclerosis*

<table>
<thead>
<tr>
<th>Outcome at 33 mo</th>
<th>Interferon-β1b</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
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<tbody>
<tr>
<td>Progression</td>
<td>39.1%</td>
<td>49.7%</td>
<td>21.3% (7.2 to 33.5)</td>
<td>9 (6 to 30)</td>
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*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

Commentary (continued from page 74)

Increased from 403 to 644 days. Interferon-β1b also reduced relapse frequency and severity and had favorable effects on MRI. The authors were careful to include patients who were progressing and were able to show that the treatment effect on progression was similar regardless of baseline EDSS scores or relapses.

Clinical trials should note 2 strategies that helped to achieve a modest effect: a high degree of statistical significance, a large sample size for a 2-arm study and the practice of sending examiners off to "EDSS school" so that the neurologic end point determination would be standardized and less prone to variability.

This study does not resolve the controversy over the importance of antibody development with β-interferon. Neutralizing antibodies were seen in 28% of treated patients, usually in the first 6 months of therapy. Many of these patients, however, subsequently had ≥ 1 negative antibody test result. Oddly, patients who were antibody positive tended to lose the beneficial therapeutic effect of Betaseron on relapse rate, but no change in disability was seen over time. It seems fair to say that although antibody development may not be bad, it is unlikely to be good.

The ideal dose of interferon-β1b also remains to be identified. The upcoming results of the North America Betaseron Secondary- Progressive MS trial may provide this information. We can also look forward to data from the Rebif Secondary-Progressive MS trial (Europe and Canada) and the Avonex Secondary-Progressive MS trial (North America). The long-term efficacy of these drugs will not be assessed by these short-term clinical trials. But for patients struggling with secondary progressive MS, these studies provide reason for hope.

Paul O'Connor, MD, MSc
St. Michael's Hospital
Toronto, Ontario, Canada

References