Placebo-controlled multicentre randomised trial of interferon β-1b in treatment of secondary progressive multiple sclerosis

European Study Group on Interferon β-1b in Secondary Progressive MS*

Summary
Background The beneficial effects of interferon β have only been shown for patients in the relapsing-remitting phase of multiple sclerosis (MS). The role of interferon β in the treatment of patients who are in the secondary progressive phase of the disease (SP-MS), and for whom no effective drug treatment is available, has not been assessed.

Methods In this multicentre, double-masked, randomised, placebo-controlled trial, outpatients with SP-MS having scores of 3–0–6–5 on the Expanded Disability Status Scale (EDSS) received either 8 million IU interferon β-1b every other day subcutaneously, or placebo, for up to 3 years. The primary outcome was the time to confirmed progression in disability as measured by a 1–0 point increase on the EDSS, sustained for at least 3 months, or a 0–5 point increase if the baseline EDSS was 6–0 or 6–5. A prospectively planned interim analysis of safety and efficacy of the intention-to-treat population was done after all patients had been in the study for at least 2 years.

Findings 358 patients with SP-MS were allocated placebo and 360 were allocated interferon β-1b; 57 patients (31 placebo, 26 interferon β-1b) were lost to follow-up. There was a highly significant difference in time to confirmed progression of disability in favour of interferon β-1b (p=0.0008). Interferon β-1b delayed progression for 9–12 months in a study period of 2–3 years. The odds ratio for confirmed progression was 0–65 (95% CI 0.52–0.83). This beneficial effect was seen in patients with superimposed relapses and in patients who had only progressive deterioration without relapses. Positive results were also obtained regarding time to becoming wheelchair-bound, relapse rate and severity, number of steroid treatments and hospital admissions, as well as on magnetic resonance imaging variables. The drug was safe and side effects were in line with previous experience with interferon β-1b. The study was stopped after the interim results gave clear evidence of efficacy.

Interpretation Treatment with interferon β-1b delays sustained neurological deterioration in patients with SP-MS. Interferon β-1b is the first treatment to show a therapeutic effect in patients with SP-MS.

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See Commentary page xxx

Introduction
In 1993, interferon β-1b emerged as a therapeutic option in multiple sclerosis (MS) and has been hailed as a major advance in the management of this disorder. Three products containing interferon β are available, and phase III trials for each product have shown a reduction in relapse rate by 18–34% in patients with relapsing-remitting MS.1–3 This reduction in disease activity was associated with a striking effect on abnormalities detected by magnetic resonance imaging (MRI), particularly on the development of new and contrast enhancing lesions.

A major concern of patients with MS and their physicians, is accrual of disability when the disease has reached the secondary-progressive (SP-MS) phase. In SP-MS, disability becomes the dominant factor and determines the level of support required and costs incurred. Three studies1–3 have given some indication of an effect of interferon β on the accrual of disability but such an effect was difficult to address persuasively: the patient groups studied were in the early stage of the disease with little if any disability, reflected by low Expanded Disability Status Scale (EDSS) scores, and at a time when disability was unlikely to develop over a 2–3 year period. The EDSS measured impairment rather than disability in the group of patients who had scores in the lower part (0–3–0) of the scale.4,5 The one study6 in which time to sustained change on the EDSS was used as the primary outcome measure, recruited patients with the lowest EDSS scores and was of the shortest duration.

Disability in MS can result from two distinct, though in many cases, overlapping mechanisms: failure to recover from relapse (incomplete remission) and slow insidious progression. These mechanisms may have different underlying pathologies.7 In patients with relapsing-remitting disease, the failure to recover from relapse is the sole cause of disability, while patients with secondary progressive MS accrue disability from both relapses and insidious progression.

To address the effects of interferon β-1b on disease progression in patients with SP-MS, we started a large placebo-controlled multicentre European study in 1994.8 The main clinical findings of a prospectively planned interim analysis are presented here.

Methods
Design
This is a European, multicentre, double-blind, placebo-controlled study of two parallel-treatment groups of outpatients with SP-MS. The study was planned to have a 36-month period of treatment, followed by a drug-free follow-up of 3 months. Regular visits were scheduled for days 1, 3, 5, and 15, months 1–3, and thereafter every 3 months until month 36 (end of

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elsewhere. Patients provided written informed consent.

The complete eligibility criteria have been published elsewhere. Immunomodulatory treatment and other putative treatments for EDSS in the previous 2 years. Immunosuppressive or non-steroidal anti-inflammatory drugs or paracetamol were recommended to reduce flu-like symptoms or for patients sensitive to changes in body temperature. Systemic steroid treatment was standardised (1 g methylprednisolone intravenously for 3 days—with or without tapering with decreasing oral doses). Patients injected 0·5 mL interferon-1b to blocks of six patients in a 1/1 ratio. Access to the code was strictly limited according to study protocol. Patients injected 0·5 mL interferon-1b (4 million IU) or placebo subcutaneously for the first 2 weeks, thereafter increasing their dose to 1·0 mL (8 million IU interferon-1b or placebo) every other day. Interferon-1b was indistinguishable from placebo. Treatment had to be discontinued in cases of intolerable adverse events or clinically relevant laboratory deviations, pregnancy, use of prohibited medication, or if the code was broken.

A central randomisation schedule assigned placebo or interferon-1b to blocks of six patients in a 1/1 ratio. Access to the code was strictly limited according to study protocol. Patients injected 0·5 mL interferon-1b (4 million IU) or placebo subcutaneously for the first 2 weeks, thereafter increasing their dose to 1·0 mL (8 million IU interferon-1b or placebo) every other day. Interferon-1b was indistinguishable from placebo.

Non-steroidal anti-inflammatory drugs or paracetamol were recommended to reduce flu-like symptoms or for patients sensitive to changes in body temperature. Systemic steroid treatment was standardised (1 g methylprednisolone intravenously for 3 days—with or without tapering with decreasing oral doses of prednisone or prednisolone) and restricted to treatment of relapses. Courses of steroids were limited to a maximum of three per patient.

Functional system and EDSS scores were determined as described by Kurtzke. The functional-system scores measure function within individual neurological systems including visual, pyramidal, cerebellar, brainstem, sensory, bowel and bladder, cerebral (mental), and other functions. The EDSS comprises 20 grades from 0 (normal) to 10 (death due to MS) progressing in a single-point step from 0–1 and in 0·5 point steps upward, and is based on the combination of functional-system scores and the patient’s degree of mobility, need for walking assistance, or help in the activities of daily living. Because ambiguities in the original definitions resulted in poor inter-rater reliability, physicians rating EDSS underwent training at a central EDSS reference centre that provided standardised rules for assessment of individual functional systems, ambulation distance, and EDSS scoring.

The EDSS reference centre trained raters before the start of the study and in yearly follow-up sessions to reinforce uniformity of assessments, and provided testers with videotapes, manuals, and written guidelines. New EDSS raters underwent training at the EDSS reference centre before assessing patients. Whenever possible, the same EDSS rater did all scheduled neurological assessments for a given patient throughout the study.

To avoid unmasking as a result of the well-characterised side-effects of interferon-1b,13 designated treating physicians were responsible only for general medical care, safety assessments, and treatment of relapses, while designated EDSS physicians did the standardised neurological tests. EDSS physicians received no potentially unmasking information from the treating physicians, and were allowed to speak to patients only as necessary to carry out neurological tests. During EDSS assessments all potential injection sites were covered. Documentation of neurological examinations and functional system and EDSS scores were kept separately by the EDSS physicians.

A questionnaire to test the success of masking was filled out at the end of the study by treating physicians, EDSS physicians, and patients.

Disability

The primary outcome measure was the time from baseline to the first scheduled quarterly visit at which an increase by at least 1·0 point of the EDSS (0–5 points if the baseline EDSS was 6·0 or 6·5) was recorded, provided the increase was confirmed at the next scheduled study visit (at least 60 days apart). The visit at month 33 was the last after which confirmation could be obtained (at month 36). EDSS scores recorded during an investigator-verified relapse were not considered valid except for those collected after day 90 of an ongoing relapse.

Further EDSS-related variables included time to becoming wheelchair-bound (ie, reaching an EDSS score of ≥7·0). For this criterion no confirmation was required because the number of patients reaching EDSS of 7 or more was expected to be much lower and to occur later, because this criterion was more difficult to reach than the primary endpoint for all those patients who had a baseline EDSS of 6·0 or lower. Additional variables were proportion of patients with confirmed progression, proportion of patients becoming wheelchair-bound, and EDSS at the endpoint.

Table 1: Summary of statistical methods

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Statistical method</th>
<th>Stratification/covariance adjustment</th>
<th>Supportive modelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to confirmed progression</td>
<td>Nonparametric analysis of covariance (primary), Mantel-Cox log-rank test (secondary)</td>
<td>Baseline EDSS*</td>
<td>Piecewise logistic model</td>
</tr>
<tr>
<td>Time to becoming wheelchair-bound</td>
<td>Mantel-Haenszel test</td>
<td>Centre/baseline EDSS</td>
<td>Piecewise logistic model</td>
</tr>
<tr>
<td>Proportion of patients becoming wheelchair bound</td>
<td>Nonparametric analysis of covariance</td>
<td>Centre/relation in previous years</td>
<td>Logistic model</td>
</tr>
<tr>
<td>Annual relapse rate</td>
<td>Nonparametric analysis of covariance</td>
<td>Centre/baseline EDSS</td>
<td>Centre/baseline EDSS</td>
</tr>
<tr>
<td>Percentage change in annual T2 lesion volume</td>
<td>Nonparametric analysis of covariance</td>
<td>Centre/baseline EDSS</td>
<td>Centre/baseline EDSS</td>
</tr>
<tr>
<td>Number of newly active lesions months 1–6 and months 19–24</td>
<td>Nonparametric analysis of covariance</td>
<td>Centre/baseline number of lesions</td>
<td>Centre/baseline number of lesions</td>
</tr>
<tr>
<td>Proportion of patients with confirmed progression</td>
<td>Mantel-Haenszel test</td>
<td>Baseline EDSS*</td>
<td>Logistic model</td>
</tr>
<tr>
<td>Change in EDSS from baseline</td>
<td>Extended Mantel-Haenszel test</td>
<td>Baseline EDSS*</td>
<td>Logistic model</td>
</tr>
<tr>
<td>EDSS at endpoint</td>
<td>Mantel-Cox log-rank test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
<tr>
<td>Time to first relapse</td>
<td>Extended Mantel-Haenszel test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
<tr>
<td>Proportion of patients with moderate or severe relapse</td>
<td>Mantel-Haenszel test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
<tr>
<td>Proportion of patients with steroid use</td>
<td>Mantel-Haenszel test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
<tr>
<td>Proportion of patients admitted to hospital</td>
<td>Mantel-Haenszel test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
<tr>
<td>Number of MS-related hospital admissions per patient</td>
<td>Extended Mantel-Haenszel test</td>
<td>Centre</td>
<td>Centre</td>
</tr>
</tbody>
</table>

*Baseline EDSS categories <3·5, 4·0–5·5, >6·0.
Relapse-related variables
A relapse was defined as the acute or subacute appearance or reappearance of a neurological abnormality, immediately preceded by a stable, improving, or slowly progressive neurological state for 30 days before deterioration, present for at least 24 h, and occurring in the absence of fever, known infection, or concurrent steroid withdrawal. Patients were instructed to contact the study centre if any symptom, suggestive of a relapse occurred. The treating physician did the relapse-related assessments including the date of onset, symptoms, and estimate of relapse severity (mild, moderate, or severe), as well as functional-system and EDSS scoring for the relapse assessments. Only relapses verified by the treating physician were considered valid for efficacy analyses.

Relapse-related variables were annual relapse rate (number of relapses divided by days in study, multiplied by 365), time to first relapse, and proportion of patients with moderate or severe relapses.

Other assessments
MS-related steroid use and hospital admissions were assessed. For MRI assessments, all patients had an annual scan, and 125 patients (61 placebo, 64 interferon β-1b) also underwent monthly MRI including T1-weighted gadolinium-enhanced scans in months 0–6 and 18–24. MRI assessments done by one evaluating centre, included annual lesion volume and newly active lesions.

Patients were tested at scheduled visits for titres of neutralising antibodies to interferon β-1b with the MxA protein assay;\(^1\) positivity was defined by two consecutive titres of 1:20 or more.

Safety assessments included adverse events, vital signs, physical examinations, and concomitant medication. Standard laboratory tests were done at all regular visits by a central laboratory. An electrocardiogram was done at the beginning and end of the study. The Montgomery Asberg Depression Rating Scale (MADRS),\(^1\) an observer rating scale, was used to assess mood changes and suicidal risk at all regular quarterly visits.

Statistical analyses
Sample size was determined, assuming that the proportion of patients with confirmed progression in the placebo group would be 50% at 3 years, and a treatment difference of 12.5% was to be detected in a two-sided log-rank test at α=0.029 and 80% power using the Pocock method to adjust for the planned interim analysis. 355 patients per group, including adjustment for an expected 20% loss of patients, were required. \(\hat{\alpha}\) adjustment for the interim analysis of efficacy was later based upon a Lan-DeMets adaptation of \(\hat{\alpha}\) spending (\(\hat{\alpha}=0.048\) for final analysis and \(\hat{\alpha}=0.0133\) for interim assuming an information fraction of 83% EDSS data). All statistical analyses were based on the intention-to-treat population, including all data of all patients as randomised without any restrictive criteria.

Baseline characteristics were analysed with the Wilcoxon’s rank-sum test for comparison of ordinal and continuous variables, and Fisher’s exact test for comparisons of dichotomous or non-ordinal categorical variables.

Efficacy variables were analysed with nonparametric methods addressing the non-linearity of the EDSS scale.\(^1\) The primary method for time to confirmed progression was an analysis of covariance\(^1\) with adjustment for centre and baseline EDSS and stratification adjustment for centre, and covariance-adjusted log-rank scores for the follow-up information on confirmed progression were compared between groups with an extended Mantel-Haenszel test with stratification adjustment for centre.

Life-table estimates were generated and treatment groups compared with the Mantel-Cox log-rank test stratified for baseline EDSS categories (<3.5, 4.0–5.5, and >6.0). The odds ratio was estimated from a piecewise logistic regression model including baseline EDSS, centre, and time as factors other than treatment.\(^1\) In expanded models, duration of MS, age, sex, and body-surface area were also included and interaction with treatment was tested. Progression confirmed after 3 and 6 months irrespective of concomitant relapses was also explored. Other efficacy outcomes were analysed with Mantel-Haenszel, extended Mantel-Haenszel, or Mantel-Cox log-rank tests adjusted for baseline EDSS, pre-study relapse, baseline MRI, or centre (table 1).

A longitudinal analysis with the generalised estimating equations approach was used to address the question whether the change from neutralising-antibodies negative to neutralising-antibodies positive status was associated with an attenuation of treatment effects.\(^1\) Tables and analyses were done with SAS software (version 6.12).

Results

Study population
As shown in figure 1, 718 of 768 patients screened in 32 European centres were randomly assigned interferon β-1b (n=360) or placebo (n=358). The mean follow-up time at interim cut-off was 892 study days in the placebo group and 901 days in the interferon β-1b group, comprising about 85% of EDSS information anticipated over the planned study duration of 3 years. Treatment groups were comparable for all baseline variables (table 2). Of these, 57 patients (18 [5·7%] placebo, 26 [7·2%] interferon β-1b) dropped out of the study (table 3). There were no significant differences for the reasons given between treatment groups. Altogether, 130 patients (66 placebo, 64 interferon β-1b) stopped treatment but were followed up according to the protocol (table 3).
ARTICLES

Table 3: Reasons for dropping out of study and stopping treatment

Overall, 531 patients (placebo 261 [72·9%], interferon β-1b 270 [75·0%]) either completed 3 years of treatment or were still being treated at interim cut-off (figure 1).

More protocol deviations were reported in the placebo group (73 patients [23·5%]) than in the interferon β-1 group (58 patients [17·2%]). Reasons for protocol deviations were equally distributed between treatment groups except for a significantly more frequent use of prohibited medication, including excessive use of steroids or treatment with immunosuppressants or open label interferon β, in the placebo group (33 vs 15 patients, p=0·0071). Only 11 protocol deviations were related to EDSS measurements.

Reasons for treatment discontinuation that differed significantly in frequency between groups were: adverse events (placebo 15 [4·2%] interferon β-1b 45 [12·5%]); patient uncooperative or treatment rejection (placebo 19 [5·3%], interferon β-1b eight [2·2%]); and inefficacy of trial medication as perceived by physician or patient (placebo 44 [12·3%] interferon β-1b 23 [6·4%]; table 3).

Clinical efficacy variables

For the primary efficacy variable, time to confirmed neurological deterioration, the nonparametric analysis of covariance showed a significant difference between the two groups (p=0·0008) in favour of interferon β-1b (figure 2, table 4). Of the 358 patients taking placebo 178 (49·8%) had confirmed progression (days to event [40% quantile] 549, CI 463–642). Of the 360 patients taking placebo 1494 THE LANCET • Vol 352 • November 7, 1998

Figure 2: Time to confirmed progression, life-table estimate

*Month 36 visit for confirmation only.

also supported the primary analysis with an odds ratio of 0·65 (95% CI 0·52–0·83) and did not reveal any interactions between treatment and the variables included in the expanded model confirming a homogeneous treatment effect over time.

The estimated probabilities of remaining progression free (estimated survival rates) were calculated for each 3-month period throughout 33 months (table 4). Treatment effects became visible after 9 months of treatment (p=0·059) and were significant after 12 months (p=0·003), maintaining significance for each 3-month period throughout the remainder of the study (33 months, p=0·0015). The delay in progression can be described by comparing the periods at which a given estimated probability is reached. Delay ranged from 9 to 12 months for 65% and 60% probability of remaining progression-free (figure 2, table 4). Estimation of quantiles of time to confirmed progression using the Kaplan-Meier method showed increasing delay of progression over time with a difference of 344 days for the 40th quantile.

In the placebo group, 49·7% of patients had confirmed progression compared with 38·9% in the treatment group over the total study period (p=0·0048), which represents a relative reduction of 21·7% in the proportion of patients with progression (table 5). Logistic regression modelling showed that patients on placebo had a 1·6 times higher probability of progression (odds ratio 0·65, 95% CI [0·46–0·85]). The time to becoming wheelchair-bound (ie, reaching EDSS 7·0) was also significantly delayed (odds ratio 0·66, 0·47–0·93; table 5); the comparison of life-table estimates showed a delay of up to 9 months in the interferon β-1 group versus placebo, the difference being significant as of month 12. In the placebo group,

<table>
<thead>
<tr>
<th>Time period</th>
<th>Placebo</th>
<th>Interferon β-1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival rate</td>
<td>Number at risk</td>
<td>Survival rate</td>
</tr>
<tr>
<td>Month 1-3</td>
<td>0·93</td>
<td>358</td>
</tr>
<tr>
<td>Month 4-6</td>
<td>0·87</td>
<td>332</td>
</tr>
<tr>
<td>Month 7-9</td>
<td>0·79</td>
<td>305</td>
</tr>
<tr>
<td>Month 10-12</td>
<td>0·71</td>
<td>275</td>
</tr>
<tr>
<td>Month 13-15</td>
<td>0·65</td>
<td>244</td>
</tr>
<tr>
<td>Month 16-18</td>
<td>0·60</td>
<td>226</td>
</tr>
<tr>
<td>Month 19-21</td>
<td>0·55</td>
<td>206</td>
</tr>
<tr>
<td>Month 22-24</td>
<td>0·53</td>
<td>188</td>
</tr>
<tr>
<td>Month 25-27</td>
<td>0·50</td>
<td>148</td>
</tr>
<tr>
<td>Month 28-30</td>
<td>0·48</td>
<td>95</td>
</tr>
<tr>
<td>Month 31-33</td>
<td>0·47</td>
<td>65</td>
</tr>
</tbody>
</table>

*Mantel-Cox log-rank test with stratification adjustment for baseline EDSS categories (secondary method of statistical evaluation); cumulative comparison of survival curves.

Table 4: Time to confirmed progression: estimated probability to remain progression free by the life-table method
**Efficacy variable** | **Placebo** (n=358) | **Interferon -1b** (n=360) | **p**
--- | --- | --- | ---
Proportion of patients with confirmed EDSS progression* | 49·7% | 38·9% | 0·0048

**Loss of mobility**

| Time to becoming wheelchair-bound | 0·0133
--- | --- | --- |
Estimated probability of not becoming wheelchair-bound:

| Year 1 | 0·90 | 0·96 | 0·0129
| Year 2 | 0·81 | 0·89 | 0·0094
| Year 3 | 0·66 | 0·77 | 0·0132

**Mean EDSS**

| At endpoint | 5·84 | 5·57 | 0·0750
| Change at endpoint† | 0·60 | 0·47 | 0·0299

**Mean annual relapse rate**

| Overall | 0·64 | 0·44 | 0·0002
| Year 1 | 0·82 | 0·57 | 0·0095
| Year 2 | 0·47 | 0·35 | 0·0201
| Year 3 | 0·35 | 0·24 | 0·1624

**Median time to first relapse (days)** | 403 | 644 | 0·0030

**Proportion of patients with moderate or severe EDSS** | 53·1% | 43·6% | 0·0083

*Patients lost to follow-up counted as not progressed.
†Endpoint minus baseline.

Table 5: Results of secondary and tertiary efficacy variables

88 (24·6%) patients reached an EDSS score of 7 or more, compared with 60 (16·7%) patients in the interferon -1b group (p=0·00277), which represents a reduction by 32·1% in the proportion of patients becoming wheelchair-bound during the study period. Comparison of EDSS at the endpoint (last visit available) between treatment groups was not significant (p=0·075), but change in EDSS score at endpoint minus baseline showed a significant difference in favour of interferon -1b (p=0·0227).

The treatment effect on progression was similar, irrespective of baseline EDSS or superimposed relapses before or during the study, with relative reductions of sustained progression of about 20% in the interferon -1b group (table 6).

Mean annual relapse rate was reduced overall by about 30% in the treatment group (placebo 0·64 vs interferon -1b 0·44, p=0·002). The rates dropped annually in both groups (table 5), maintaining the treatment effect over time, although this was not significant in the third year. The time to first relapse was prolonged in the interferon -1b group (median 644 days) compared with placebo (median 403 days; p=0·0030) and the proportion of patients with moderate or severe relapses was lower (190 [53·1%] patients on placebo, 157 [43·6%] patients on interferon -1b, p=0·0083, table 5).

Both the proportion of patients admitted to hospital (189 [52·8%] patients on placebo, 167 [46·4%] patients on interferon -1b, p=0·0435) and the number of MS-associated hospital admissions per patient were significantly reduced in the patients on active treatment (p=0·0003). The proportion of patients with MS-associated steroid use was significantly lower in the interferon -1b group (67·9% vs 53·6%, p=0·0001).

The questionnaire to assess effectiveness of masking was received from 84–86% of the treating physicians, EDSS physicians, and patients. As expected, treating physicians often guessed correctly whether the patients were on placebo 148 (48·4%) of 306 or interferon -1b 176 (56·2%) of 313, although they did not know or guessed incorrectly for 225 (36·3%) of 619 and 70 (11·3%) of 619 of patients, respectively. Similarly 165 (54·3%) of 304 patients guessed correctly that they were on placebo and 202 (65·6%) of 308 that they were on active treatment. However, 71 (23·4%) of 304 on placebo thought they were on interferon -1b, 36 (11·7%) of 308 on interferon -1b thought they were on placebo, and 138 (22·5%) of 612 did not know. Most importantly, EDSS physicians guessed correctly for only 54 (18·6%) of 291 of patients on placebo and 65 (20·8%) of 312 patients on interferon -1b. They stated “do not know” for 401 (66·5%) of 603 patients.

**MRI variables**

Treatment with interferon -1b resulted in a significant reduction of mean MRI T2 lesion volume, which increased by about 8% in the placebo group and there was a 5% decrease in the interferon -1b group (p<0·0001). In the frequent MRI cohort (n=125), patients receiving interferon -1b showed a 65% reduction of newly active lesions from months 1–6 (p<0·0001) and a 78% reduction from months 19–24 (p=0·0008) compared with placebo.

**Neutralising antibodies to interferon -1b**

Of 100 (27·8%) patients positive for neutralising antibodies, 66 became so in the first 6 months of treatment. 47 patients positive for neutralising antibodies subsequently had at least one negative titre, and 37 of them remained negative for neutralising antibodies after reverting to a neutralising-antibody-negative status. Longitudinal analyses with the generalised estimating equations approach indicated a significant decrease of the therapeutic effect in terms of relapse rate in patients positive for neutralising antibodies. But for parameters directly associated with the primary endpoint (EDSS changes over time) there was not a decrease in therapeutic effect.

**Safety**

Clinically relevant and common adverse events significantly associated with interferon -1b included injection-site events and flu-like symptoms, the latter particularly in the early treatment phase. Injection-site necrosis was observed in 4·7% of patients on interferon -1b. Other reported adverse events significantly associated with interferon -1b were muscle hypertonia (37·8% vs 27·4%, p=0·0032) and hypertension (3·9% vs 0·8%, p=0·0117). Standardised neurological examinations and vital-sign findings associated with...
treatment with interferon

one patient had a cardiac arrest, and one a massive

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scale. Suicides or suicide attempts were reported in five

depression, neither as a spontaneously reported adverse

superimposed relapses following an initial relapsing-

group, including patients who progressed with or without

enzymes and white-blood-cell counts in the interferon

proportions of patients with abnormal values of liver

1b group. In general, liver-enzyme abnormalities resolved

1b. In general, liver-enzyme abnormalities resolved

more than one adverse event are counted more than once. The table does not count

hypertonia and hypertension showed no differences

between treatment groups (table 7).

As anticipated from other studies, there were higher proportions of patients with abnormal values of liver enzymes and white-blood-cell counts in the interferon β-1b group. In general, liver-enzyme abnormalities resolved spontaneously or were well managed by dose reduction or intermittent treatment discontinuation. Clinically relevant laboratory abnormalities occurred rarely and were only clearly associated with interferon β-1b for lymphopenia.

There were four deaths in the study, three of which occurred in the interferon β-1b group. Two patients (one on placebo, one on interferon β-1b) committed suicide, one patient had a cardiac arrest, and one a massive pulmonary embolism (55 days after prematurely stopping treatment with interferon β-1b). Patients on interferon β-1b had no increased incidence of new or worsened depression, neither as a spontaneously reported adverse event nor in the quarterly monitoring with the MADRS scale. Suicides or suicide attempts were reported in five patients on placebo and three on interferon β-1b.

Table 7: Adverse events significantly associated with interferon β-1b treatment

<table>
<thead>
<tr>
<th>Body system/adverse events</th>
<th>Placebo (n=358)</th>
<th>Interferon β-1b (n=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>133 (37·2%)</td>
<td>213 (59·2%)</td>
</tr>
<tr>
<td>Fever</td>
<td>47 (13·1%)</td>
<td>142 (39·4%)</td>
</tr>
<tr>
<td>Chills</td>
<td>26 (7·3%)</td>
<td>79 (21·9%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23 (6·4%)</td>
<td>38 (10·8%)</td>
</tr>
<tr>
<td>Chills and fever</td>
<td>1 (0·3%)</td>
<td>13 (3·6%)</td>
</tr>
<tr>
<td>Hemic and lymphatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>18 (5·0%)</td>
<td>36 (10·0%)</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (0·8%)</td>
<td>14 (3·9%)</td>
</tr>
<tr>
<td>Injection site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>37 (10·3%)</td>
<td>157 (43·6%)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>15 (4·2%)</td>
<td>180 (50·0%)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0</td>
<td>17 (4·7%)</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>38 (10·6%)</td>
<td>77 (21·4%)</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>32 (8·9%)</td>
<td>82 (22·8%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonia</td>
<td>98 (27·4%)</td>
<td>136 (37·8%)</td>
</tr>
</tbody>
</table>

Patients were counted for each individual adverse event term so patients who had more than one adverse event are counted more than once. The table does not count multiple occurrences of the same event in one patient.

Regarding the primary outcome, a highly significant delay in the time to disease progression (p=0·0008) was observed in the interferon β-1b group, as seen in the life-table curves, which show a delay of progression of up to 12 months in the study period. These results are supported by equally clear benefits across the secondary and tertiary variables and led to the independent advisory board’s recommendation to stop the study early.

The outcome of any study is invariably influenced by the behaviour of the placebo group. The proportion of treatment failures and time to treatment failure in the placebo arm of this study fell within the range of the results of previous studies including patients with SP-MS.

The results of the questionnaire on masking provide encouraging evidence that the specific measures taken—ie, having a separate EDSS physician excluded from patient management and masked from all clinical information, recommending the use of anti-inflammatory drugs, and covering injection sites at all EDSS assessments—were effective.

Interestingly, in this study the therapeutic benefit appeared to be as strong in the severely disabled patients as in those with mild-to-moderate disability. However, it has been suggested that using a more clinically appropriate definition of worsening for patients with baseline EDSS of 6·0 or greater, as described above, essentially removes the dependence of treatment failure on baseline EDSS.

As expected from previous studies of interferon β, the relapse rate was significantly lower in the treated group and decreased in both groups over time, as might be anticipated in SP-MS. The effect on disability progression continued to be significant at each time point and similar treatment effects were seen irrespective of on-study relapses, giving further evidence that the effect of interferon β-1b slows the progression of disability in addition to its effect on relapses.

These findings raise important issues in relation to the mechanism of disability progression in MS and the mode of action of interferon β. In this study, an effect was observed on both aspects of deterioration—ie, incomplete recovery from relapse and slow insidious progression. While the former is likely to be associated with demyelination and axonal loss secondary to acute inflammation, the latter may be associated with continuous damage either due to low-grade inflammatory activity or some other independent process. Two possible modes of action may be in play, one inhibition of disability progression by suppressing low-grade inflammation or, less probably, an additional hitherto unrecognised protective effect on myelin and axonal integrity.

Steroids were more frequently used in the placebo group. This probably reflects the fact that placebo

at these levels are frequently prolonged relative to other points on the scale, a fact that reflects the usually more extended period of deterioration leading to loss of ability to walk. This issue was addressed in the present study by counting 0-5 point steps from a baseline EDSS of 6·0 or 6·5 as full steps. This definition has been suggested as a clinically appropriate definition of worsening because each half-point step captures significant progression in this EDSS range. A further limitation of the EDSS scale, its poor inter-rater reliability, was addressed by repeated standardised audiovisual training sessions for the EDSS physicians, which resulted in improved consistency of ratings.

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Table 7: Adverse events significantly associated with interferon β-1b treatment

hypertonia and hypertension showed no differences between treatment groups (table 7).

As anticipated from other studies, there were higher proportions of patients with abnormal values of liver enzymes and white-blood-cell counts in the interferon β-1b group. In general, liver-enzyme abnormalities resolved spontaneously or were well managed by dose reduction or intermittent treatment discontinuation. Clinically relevant laboratory abnormalities occurred rarely and were only clearly associated with interferon β-1b for lymphopenia.

There were four deaths in the study, three of which occurred in the interferon β-1b group. Two patients (one on placebo, one on interferon β-1b) committed suicide, one patient had a cardiac arrest, and one a massive pulmonary embolism (55 days after prematurely stopping treatment with interferon β-1b). Patients on interferon β-1b had no increased incidence of new or worsened depression, neither as a spontaneously reported adverse event nor in the quarterly monitoring with the MADRS scale. Suicides or suicide attempts were reported in five patients on placebo and three on interferon β-1b.

Discussion

This phase III study shows a therapeutic benefit of interferon β-1b in SP-MS. SP-MS is reported to be the most common phase of the disease and the one during which major irreversible disabilities most often appear. The cohort studied was representative for this disease group, including patients who progressed with or without superimposed relapses following an initial relapsing-remitting phase. Patients were in the early stage of progression beginning about 10 years after initial diagnosis of MS and had active disease in the 2 years before entry into the study.

The primary outcome measure in this study was sustained progression of disability as measured by EDSS. Although much criticised, the EDSS remains the most widely accepted measure of disease progression in MS. However, the EDSS is poorly responsive at certain levels and particularly between EDSS 6·0 and 7·0. Times spent
patients had more disease activity, which is supported by
findings from studies of IFNB-1a.\textsuperscript{2,3} no increased
incidence of depression was seen with interferon
beta-1b treatment in the present study. Muscular hypertonia was
reported in a higher proportion of treated patients, but
this was not reflected in the detailed neurological
assessments.

This study provides convincing evidence that treatment with interferon beta-1b delays sustained neurological deterioration in patients with SP-MS. Supportive analyses of disease progression and the consistently positive findings for relapse and MRI-related efficacy variables demonstrate the robustness of the results. Thus, interferon beta-1b is the first treatment to show a therapeutic effect in patients with SP-MS.

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**References**