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PAPER

Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis

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Objective: Interferon (IFN) beta has repeatedly shown benefit in multiple sclerosis (MS) in reducing the rate of relapse, the disease activity as shown with magnetic resonance imaging and, to some degree, the progression of disability; however, it is unknown how much the therapeutic response depends on the dose, the subgroup involved, and the disease stage. This multicentre, double blind, placebo controlled study explored the dose–response curve by examining the clinical benefit of low dose IFN beta-1a (Rebif®), 22 μg subcutaneously once weekly, in patients with secondary progressive MS.

Methods: A total of 371 patients with clinically definite SPMS were randomised to receive either placebo or subcutaneous IFN beta-1a, 22 μg once weekly, for 3 years. Clinical assessments were performed every 6 months. The primary outcome was time to sustained disability, as defined by time to first confirmed 1.0 point increase on the Expanded Disability Status Scale (EDSS). Secondary outcomes included a sensitive disability measure and relapse rate.

Results: Treatment had no beneficial effect on time to confirmed progression on either the EDSS (hazard ratio (HR) = 1.13; 95% confidence interval (CI) 0.82 to 1.57; p = 0.45 for 22 μg *v* placebo) or the Regional Functional Status Scale (HR = 0.93; 95% CI 0.68 to 1.28; p = 0.67). Other disability measures were also not significantly affected by treatment. Annual relapse rate was 0.27 with placebo and 0.25 with IFN (rate ratio = 0.90; 95% CI 0.64 to 1.27; p = 0.55). The drug was well tolerated with no new safety concerns identified. No significant gender differences were noted.

Conclusions: This patient population was less clinically active than SPMS populations studied in other trials. Treatment with low dose, IFN beta-1a (Rebif®) once weekly did not show any benefit in this study for either disability or relapse outcomes, including a subgroup with preceding relapses. These results add a point at one extreme of the dose–response spectrum of IFN beta therapy in MS, indicating that relapses in this phase may need treatment with higher doses than in the initial phases.

The first published study of interferon (IFN) beta-1b (Betaseron/Betaferon®) treatment of secondary progressive multiple sclerosis (SPMS), the European Secondary Progressive MS (EU-SPMS) trial, demonstrated a benefit on disability.[1] However, this was followed by negative studies with both IFN beta-1a (Rebif® in the SPECTRIMS trial)[2 3] and IFN beta-1b (Betaseron/Betaferon® in the North American Secondary Progressive MS trial).[4] Finally, a study of weekly IFN beta-1a (Avonex®) also showed no benefit on disability, as measured by progression on the Expanded Disability Status Scale (EDSS).[5] Debate exists about why the EU SPMS study stands apart; a major contributing factor may be the earlier stage of SPMS studied in the EU SPMS trial compared with subsequent studies,[6] although this was not evident in subgroups within the EU-SPMS trial. However, a post hoc study of the SPECTRIMS trial revealed a borderline therapeutic effect on progression in a subgroup with relapses in the 2 year period before inclusion.

Several studies in relapsing–remitting MS (RRMS) have suggested dose–response effects,[7–11] although one has not.[12] Apart from dose differences between studies, other factors may also explain the different results. A recent direct comparative study of high dose, high frequency IFN beta-1a (Rebif®; 44 μg three times weekly), and low dose, low frequency IFN beta-1a (Avonex®; 30 μg once weekly) regimens indicated a differential effect that could be attributed to the preparation, dose, dose frequency, route of administration, or a combination of these.[13] Results on pharmacokinetic and pharmacodynamic outcomes are controversial. In one study in healthy volunteers, the effect of IFN beta on biological markers was as high after subcutaneous (SC) or intramuscular (IM) injections as after intravenous injections, although the latter resulted in higher IFN blood levels. Injection two or more times a week resulted in more sustained biological markers than one injection per week.[14]

One pharmacokinetic study found no difference between IM and SC injections,[15] while another study showed that the area under the curve for serum IFN activity was two to three-fold higher after IM than after SC injections. However, pharmacodynamic parameters showed a less marked difference.[16]

The primary objective of this study was to determine whether low dose weekly SC IFN beta-1a (Rebif®) could affect disability progression in patients with SPMS.

METHODS

Patients aged 18–65 years were eligible for inclusion in this trial if they had a diagnosis of clinically definite MS[17] for at least 1 year, and which was classified as SPMS with an EDSS score below 7.0. Patients had had a prior history of RRMS

Abbreviations: EDSS, Expanded Disability Status Scale; EU-SPMS, European Secondary Progressive Multiple Sclerosis trial; HR, hazard ratio; IFN, interferon; IM, intramuscular; KFS, Kurtzke Functional System; MRI, magnetic resonance imaging; PH, proportional hazard; RFSS, Regional Functional System Score; RRMS, relapsing–remitting multiple sclerosis; SAE, serious adverse event; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis; TTP, time to progression

and had experienced progressive deterioration of disability for at least 6 months, with an increase of at least 1.0 point on the EDSS in the previous 4 years (or 0.5 points if the entry EDSS score was 6.0 or 6.5), with or without superimposed exacerbations. Patients were in a stable neurological condition for the 4 weeks preceding study day 1. Exclusion criteria were similar to those used in previous IFN beta trials.[2 7]

Treatments and randomisation

Patients were randomised in equal allocation to receive IFN beta-1a (Rebif®; Serono), 22 µg SC once weekly, or matching placebo, for 3 years. The double blind study was terminated during year 3 following the release of results from the SPECTRIMS study using IFN beta-1a (Rebif®), 22 µg and 44 µg three times weekly, which showed a non-significant trend towards benefit on disability.[2] In cases of toxicity, the dose could be reduced or treatment interrupted according to guidelines in the protocol. Steroids were to be given only for disabling acute exacerbations.

Blinding

Patients were instructed to cover injection sites and to discuss only neurological matters during neurological evaluations. Neurologists blinded to dose assignment were responsible for neurological assessments. No blinding questionnaire was conducted at study termination.

Study assessments

Patients underwent complete neurological assessments, including Kurtzke Functional System (KFS),[18] EDSS, Regional Functional System Score (RFSS),[1–6 11–13 17–20] ambulation index,[21] and arm index[22] at entry and then at 6 month intervals, or more frequently in case of exacerbations. Magnetic resonance imaging (MRI) scanning was not performed. Adverse events and concomitant medications were recorded throughout the study, and clinical laboratory evaluation was performed at months 1, 3, and 6, and then at 6 monthly evaluation visits or as needed.

The primary efficacy endpoint (deterioration of disability) was the time to progression on the EDSS, defined as an increase from baseline by at least 1.0 point (or 0.5 points if the baseline EDSS score was 5.5 or higher) and confirmed at two consecutive scheduled visits separated by 6 months. Time to progression on the RFSS was considered a secondary outcome and defined as an increase of 2% or more from baseline on the RFSS. All investigators participated in a pre-study centralised training session to become consistent in the use of the EDSS and RFSS. A relapse was defined as the appearance of a new symptom or worsening of an old symptom attributable to MS, lasting at least 24 hours in the absence of fever and preceded by stability or improvement for at least 30 days. An amendment to the protocol definition of relapse required either an increase of 0.5 points on the EDSS, or a 1.0 point worsening in the score of two KFS or 2.0 points in one functional system.[18] The recruitment status was uneven between countries when this amendment was implemented, and adjustment of results by country was performed. Tertiary endpoints included the proportion of progression free patients, time to first exacerbation, proportion of exacerbation free patients, MS related hospitalisation rate, ambulation index, and arm index.

Study design

The sample size determination was based on interim results from an ongoing study (SPECTRIMS).[2] The median time to progression (TTP) was assumed to be 3.1 years for the placebo group and 5.4 years for the treatment group. To achieve a power of 90% with an estimated 10% of the patients not being evaluable for efficacy, 370 patients (185 in each group) would need to be included in the trial.

The study was conducted in accordance with the Declaration of Helsinki. Consent was obtained from the Ethics Committees of all participating institutions before study initiation. Written informed consent was obtained for all patients before beginning pre-study assessments.

Statistical analyses

Analyses were performed on all randomised patients who received at least one injection (n = 364). Seven randomised patients did not receive study medication. For the analysis of time to event outcomes, patients who dropped out were considered as censored at the time of dropout, and no imputation of their outcome was made. Two pre-planned subgroup analyses on all primary and secondary efficacy outcomes were performed. The subgroups were classified by gender and by the presence or absence of relapses during the 4 years prior to baseline, based on results from the SPECTRIMS study that indicated a treatment by gender interaction and improved outcome for patients with relapses in the 2 years prior to initiation of therapy.[2]

Time to confirmed EDSS progression, confirmed RFSS progression, and to first relapse were analysed using the Cox proportional hazards (PH) model. Covariate adjustment by country rather than centre was employed. Time to event curves were constructed using the Kaplan–Meier approach. Subgroup Cox PH regression analyses were performed for both genders, and for patients with or without one or more relapses in the 4 years prior to baseline. Hazard ratios (HR) <1 indicated a reduced risk of the event compared with the reference group (placebo).

A logistic regression model with treatment and country covariates was used to compare the proportion of progression free and relapse free patients between the treatment groups. The rates of exacerbations and hospitalisations were compared between groups using the negative binomial regression model (also including treatment and country factors as covariates), with the logarithm of time on study included as an offset.

Change in ambulation and arm indices was analysed using one way analysis of variance on ranks with treatment and country in the model.

RESULTS

Patients

This study enrolled 371 patients with clinically definite SPMS in 32 centres in Denmark (4 centres, 48 patients), Finland (6 centres, 123 patients), Norway (12 centres, 120 patients) and Sweden (10 centres, 80 patients). Of 371 patients randomised to therapy, 364 received the study drug: 186 patients received IFN beta-1a (Rebif®) 22 µg once weekly, 178 received placebo once weekly, and 5 patients randomised to placebo and 2 randomised to IFN received no therapy (relapse, withdrew consent). A total of 301 patients (83%) completed the double blind phase of the study (fig 1). Therapy was discontinued prematurely by 63 patients (17%; 25/178 patients (14%) with placebo and 38/186 patients (20%) with IFN). Reasons for discontinuation of study drug included adverse events (6 placebo, 16 IFN), disease progression (2 placebo, 3 IFN), death (2 patients in each group), protocol violation (1 placebo), pregnancy (1 placebo) and patient decision (13 placebo, 17 IFN).

The median time on treatment was 35.2 months (mean 32.0) for placebo and 35.0 months (mean 31.1) for IFN. The double blind phase of the study was completed by 153 patients on placebo and 148 on IFN. The study was terminated during the third year by the Steering Committee

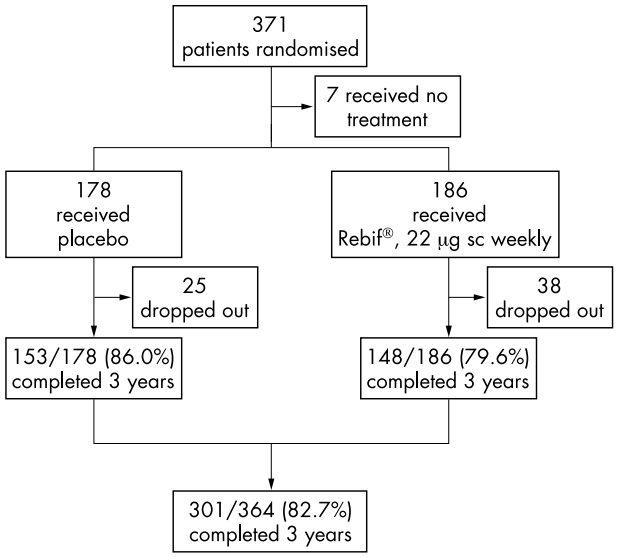

Figure 1 Patient groups.

based on results from a study in SPMS patients using higher, more frequent dosing of the same product.[2]

Demographic characteristics (table 1) were similar between the two groups. Baseline disease characteristics were similar for both groups except that placebo patients had a longer duration of SPMS, and a larger baseline EDSS and ambulation index (table 1). The difference for duration of SPMS was significant ($p = 0.03$). However, duration of SPMS did not significantly affect the primary outcome, nor the treatment impact on primary outcome (assessed via an analysis that included a duration–treatment interaction term).

Disability

Treatment with IFN beta-1a 22 μg once weekly did not show a benefit on the primary outcome, time to sustained disability progression (HR = 1.13; 95% confidence interval (CI) 0.82 to 1.57; $p = 0.45$). Confirmed disability progression was observed in 77/186 (41%) actively treated patients and 68/178 (38%) placebo patients (fig 2). Sensitivity analyses, conducted using a 1.0 point confirmed EDSS change for all patients or a 1.0 point EDSS change for patients with an EDSS score below 6.0, did not alter the findings.

Table 1 Baseline demographics and disease characteristics

	Total	Placebo	IFN
Number of patients	364	178	186
Proportion female	0.60	0.60	0.60
Age (mean, years)	45.7	46.4	45.1
Duration of MS (mean, years)	14.3	14.4	14.2
Duration of SPMS (mean, years)*	5.4	6.1	4.8
Number of relapses in prior 4 years (mean)	1.7	1.6	1.7
Proportion relapse free in prior 4 years	0.37	0.40	0.34
EDSS score (mean)*	4.8	5.0	4.7
RFSS score (mean)	16.5	16.8	16.2
Arm index (mean)	1.4	1.4	1.4
Ambulation index* (mean)	3.3	3.5	3.1

*$p<0.05$.
EDSS, Expanded Disability Status Scale; IFN, interferon (Rebif® 22 μg once weekly); MS, multiple sclerosis; RFSS, Regional Functional Status Scale; SPMS, secondary progressive multiple sclerosis.

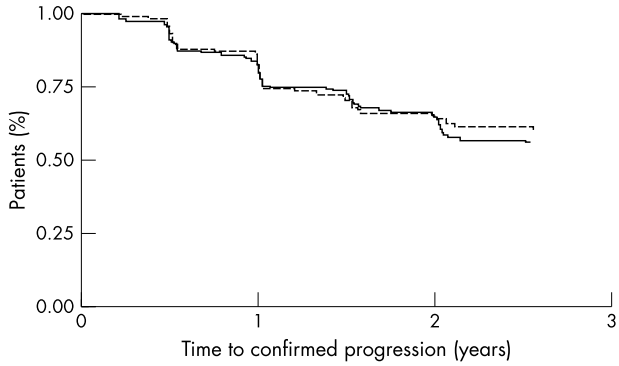

Figure 2 Time to confirmed (6 months) disability progression by 1.0 point (or 0.5 points if baseline Expanded Disability Status Scale score was 5.5 or higher), Kaplan-Meier estimate. Dotted line, interferon beta 1-a (Rebif®), 22 μg subcutaneously once weekly; dashed line, placebo.

Likewise, confirmed increase in RFSS showed no significant treatment benefit, either in the proportion of patients who progressed (80/186 (43%) with IFN beta-1a, compared with 79/178 (44%) with placebo), or time to progression (HR = 0.93; 95% CI 0.68 to 1.28; $p = 0.67$). Mean EDSS and RFSS scores over time showed a similar profile for both treatment groups, with no significant difference in terms of mean EDSS over the 6 months (fig 3, EDSS only). Changes in ambulation index and arm index were similar in both groups (data not shown).

Exacerbations

The annualised relapse rate was 0.25 for IFN and 0.27 for placebo (rate ratio = 0.90; 95% CI 0.64 to 1.27; $p = 0.55$). Time to first relapse was not significantly affected by therapy (data not shown). The proportion relapse free at the end of the study was 110/178 (62%) for placebo and 114/186 (61%) for IFN (odds ratio (OR) = 1.03; 95% CI 0.67 to 1.58; $p = 0.89$). Hospitalisations for MS were similar in both groups (data not shown).

Subgroup analyses

IFN treatment did not significantly affect time to progression of disability in either men (HR = 1.24; 95% CI 0.73 to 2.10; $p = 0.43$) or women (HR = 1.11; 95% CI 0.73 to 1.69; $p = 0.62$). The proportion of patients with progression in treated men (30/75; 40%) was slightly less than for treated women (47/111; 42%). The proportion of patients with

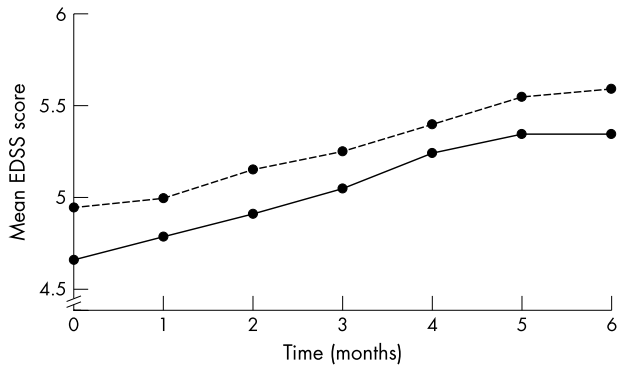

Figure 3 Mean Expanded Disability Status Scale (EDSS) score by treatment group at each 6-monthly visit. Solid line, interferon beta 1-a (Rebif®), 22 μg subcutaneously once weekly; dashed line, placebo.

progression for placebo men (26/72; 36%) was slightly less than placebo women (42/106; 40%) and the 25th percentile time to progression for placebo randomised men was 175 days longer than for placebo randomised women (p = 0.76), similar to the pattern seen in placebo patients in the SPECTRIMS study.[2]

In women, the proportion of exacerbation free patients was slightly higher in the IFN group (69/111; 62%) compared with the placebo group (62/106; 58%), although the difference was not statistically significant (OR = 1.14; 95% CI 0.65 to 1.98; p = 0.65). For men, an opposite trend was seen in that 45/75 (60%) of those on IFN remained free of exacerbations compared with 48/72 (67%) of those on placebo (OR = 0.68; 95% CI 0.34 to 1.36; p = 0.27).

Based on previous results suggesting a difference in treatment effect for those with or without relapses in the 2 years pre-study,[2] similar subgroup analyses were performed for patients with and without bouts in the previous 4 year period in this study. In terms of disability progression, 25/71 (35%) of the non-relapsing placebo patients progressed compared with 42/106 (40%) of relapsing placebo patients, while 27/64 (42%) of IFN treated non-relapsing patients progressed compared with 47/111 (42%) of IFN treated relapsing patients. Compared with placebo, the TTP for treated relapsing patients (HR = 1.01; 95% CI 0.68 to 1.56; p = 0.88) and non-relapsing patients (HR = 1.03; 95% CI 0.75 to 2.30; p = 0.34) was similar.

Safety

Adverse event data are presented in table 2. Laboratory abnormalities on any occasion at any level of severity, independent of whether they were considered to be adverse events, were more common with IFN than placebo. This was particularly the case for typical IFN related events, such as elevation of alanine transaminase (89/186 (48%) on IFN *v* 58/178 (33%) on placebo) and lymphopenia (101/186 (54%) on IFN *v* 76/178 (43%) on placebo). The majority of such laboratory abnormalities were mild and rarely led to dose discontinuation.

No substantial difference between the groups was observed in serious adverse event reporting; 49 placebo patients reported 72 events, compared with 51 IFN patients with 79 events.

DISCUSSION

The results demonstrate that IFN beta-1a (Rebif®; 22 µg weekly), had no significant beneficial impact on clinical disease activity, as measured by either relapse activity or disability progression. As a low progression rate was anticipated in this trial, the progression was also measured by the RFSS, believed to be a more sensitive measure of progression, but only a marginally positive trend was recorded. No effect was seen in the subgroup with relapses during a pre-trial 4 year period, and there was no gender effect.

The inclusion criteria of the present study required less progression than other trials in SPMS, and the lower progression rate during the trial confirmed that the Nordic SPMS population studied was clinically less active than populations studied in other trials in SPMS. While higher doses of Rebif®, 22 µg or 44 µg three times weekly, were ineffective in secondary progression without preceding bouts, the current study was designed to explore low dose IFN beta in this stage of the disease, adding another point to the dose−response curve.

Inflammatory lesions, clinical and MRI, in early MS respond to lower doses of IFN. Thus, IFN beta-1a, 22 µg (Rebif®) or 30 µg (Avonex®) weekly, can reduce both relapse and MRI activity after a clinically isolated syndrome with MRI criteria.[23 24] Whereas 22 µg weekly given to established MS patients only reduced MRI lesion burden, and 44 µg weekly reduced MRI activity with only a marginal reduction of the relapse frequency compared with placebo,[25] both doses administered three times weekly had beneficial effects on all outcome measures including disability.[7 8] The present study has shown that 22 µg weekly was ineffective in advanced MS on all clinical measures and in relevant subgroups. No MRI data were obtained in the present study.

The available data indicate that superimposed relapses during secondary progression, require treatment with higher doses than do relapses in clinically isolated syndrome or early MS. The results from this study provide strong evidence that therapy with IFN beta-1a (Rebif®), 22 µg once weekly, is not effective in reducing clinical activity in SPMS, as measured by either relapse activity or disability progression, not even in a subgroup selected for preceding relapse activity.

Table 2 Selected adverse events considered to be IFN-related

Preferred term	IFN beta-1a (%)	Placebo (%)	p value
Flu like symptoms	37*	22	0.002
Headache	36	20	0.002
Injection site inflammation	31	4	<0.001
Injection site reaction	27	8	<0.001
Depression	20	14	0.128
Fatigue	19	13	0.117
Myalgia	15	8	0.048
Fever	10	4	0.024
Elevation of liver enzymes†	3	0	0.061
Lymphopenia	1	2	0.362

*Percentages represent patients reporting adverse event at least once.
†Includes patients with elevated alanine transaminase, elevated aspartate transaminase, or abnormal hepatic function.
IFN, interferon (Rebif®, 22 µg once weekly).

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An introductory text on the RFSS, its definitions of scoring, and principles of calculation is posted on the following web pages: http://www.neuro.gu.se/swe/forskning/demyel/RFSS%20calculation%20example.xls; http://www.neuro.gu.se/swe/forskning/demyel/RFSS%20overview.doc; http://www.neuro.gu.se/swe/forskning/demyel/RFSS%20recording, %20relationship%20to%20EDSS.ppt; http://www.neuro.gu.se/swe/forskning/demyel/RFSSmanual.pdf; and http://www.neuro.gu.se/swe/forskning/demyel/RFSSscan1-7.doc. An instruction video of the RFSS is available on request to the corresponding author.

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