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Interferon β -1a in relapsing multiple sclerosis: four-year extension of the European IFN β -1a Dose-Comparison Study

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Background: Multiple sclerosis (MS) is a chronic disease requiring long-term monitoring of treatment. **Objective:** To assess the four-year clinical efficacy of intramuscular (IM) IFN β -1a in patients with relapsing MS from the European IFN β -1a Dose-Comparison Study. **Methods:** Patients who completed 36 months of treatment (Part 1) of the European IFN β -1a Dose-Comparison Study were given the option to continue double-blind treatment with IFN β -1a 30 mcg or 60 mcg IM once weekly (Part 2). Analyses of 48-month data were performed on sustained disability progression, relapses, and neutralizing antibody (NAb) formation. **Results:** Of 608/802 subjects who completed 36 months of treatment, 493 subjects continued treatment and 446 completed 48 months of treatment and follow-up. IFN β -1a 30 mcg and 60 mcg IM once weekly were equally effective for up to 48 months. There were no significant differences between doses over 48 months on any of the clinical endpoints, including rate of disability progression, cumulative percentage of patients who progressed (48% and 43%, respectively), and annual relapse rates; relapses tended to decrease over 48 months. The incidence of patients who were positive for NABs at any time during the study was low in both treatment groups. **Conclusion:** Compared with 60-mcg IM IFN β -1a once weekly, a dose of 30 mcg IM IFN β -1a once weekly maintains the same clinical efficacy over four years. Multiple Sclerosis (2004) 10, 139–144

Key words: interferon beta-1a; long-term efficacy; multiple sclerosis; neutralizing antibodies

Introduction

Three interferon beta (IFN β) products – IFN β -1b (Betaseron[®], Berlex Laboratories Montville NJ, USA), IFN β -1a (Avonex[®], Biogen, Inc., Cambridge, MA, USA), and IFN β -1a (Rebif[®], Ares-Serono, Geneva, Switzerland) – have demonstrated beneficial effects in the treatment of patients with relapsing multiple sclerosis (MS). Two-year phase III pivotal trials have shown efficacy in reducing exacerbations, slowing disability progression, and reducing activity on magnetic resonance imaging (MRI).^{1–3} However, MS is a chronic disease requiring long-term treatment. Results of long-term follow-up patients treated with IFN β therefore are important and should be taken into account in clinical practice.

The efficacy and safety of intramuscular (IM) IFN β -1a were recently evaluated in the European IFN β -1a Dose-

Comparison Study, which was conducted to determine whether a higher weekly dose of IM IFN β -1a could improve upon the established efficacy of IM IFN β -1a 30 mcg in reducing the rate of sustained disability progression. Efficacy and MRI data from the first 36 months of the study (Part 1) have been published separately.⁴ In summary, the effect of both doses of IFN β -1a IM seen in Part 1 of the study was similar to that observed in the pivotal phase III trial of IFN β -1a,² and results showed no differences between IFN β -1a 30 mcg and 60 mcg IM on time to sustained disability progression, extent of change in Expanded Disability Status Scale (EDSS) score, relapse rate, and rate of intravenous (IV) steroid use.⁴ In addition, there were no statistically significant differences or trends observed between IFN β -1a 30 mcg and 60 mcg IM with regard to change in T2 lesion volume, change in T1 lesion volume, number of new or enlarging T2 lesions compared with baseline, number and volume of gadolinium-enhanced (Gd+) lesions, and brain atrophy (only one MRI parameter at one time point, i.e., the number of new or enlarging T2 lesions at month 36 compared with month 24, showed a statistically significant difference between the IFN β -1a 30- and 60-mcg doses [$P = 0.004$]).⁴

Patients who completed 36 months of treatment (Part 1) were allowed to enroll in a second phase of double-blind treatment (Part 2). The present paper reports 48-month efficacy data from Part 2 of the European IFN β -1a Dose-Comparison Study.

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³See Appendix for members of the European IFN β -1a (AVONEX[®]) Dose-Comparison Study investigators.

Methods

Detailed design and methodology of the study have been published separately.⁵

Subjects

The European IFN β -1a Dose-Comparison Study enrolled 802 patients with a relapsing form of MS. Patients were included in the study if they had a clinical diagnosis or a laboratory-supported clinical diagnosis of definite MS⁶ for at least one year, at least two medically documented relapses within the three years prior to randomization, and an EDSS score between 2.0 and 5.5, inclusive. Patients were excluded from the study if they had progressive disease for longer than six months, had a relapse within two months prior to randomization, or were pregnant or breastfeeding.

Study design

The European IFN β -1a Dose-Comparison Study was a randomized, double-blind, parallel-group study conducted throughout Europe. Patients were randomized to receive IFN β -1a 30 mcg ($n = 402$) or IFN β -1a 60 mcg ($n = 400$) IM once weekly for at least 36 months. Patients who completed the 36-month planned study period (Part 1) were allowed to participate in a second phase of double-blind treatment, completing 48 months of treatment (Part 2). Thirty-four of the 38 study centres enrolled patients into Part 2 of the study. Each study site designated a primary examining neurologist and at least one treating neurologist. Responsibilities of the examining neurologists included performing EDSS evaluations and neurologic examinations during all scheduled study visits; they were not involved with any other aspect of patient care or management. Treating neurologists were responsible for all other aspects of patient care and management, including the assessment and treatment of adverse events and relapses.

The primary outcome variable was sustained disability progression, defined as time to a sustained increase of ≥ 1.0 point on the EDSS persisting for six months for patients with baseline EDSS scores of ≤ 4.5 , or a 0.5-point increase for patients with a baseline EDSS score of ≥ 5.0 . Additional efficacy outcome variables included the following: rate of sustained progression to an EDSS score of ≥ 4.0 and ≥ 6.0 , and extent of change in EDSS. As relapses do not fully represent the extent of disease activity and do not correlate with disease progression,⁷ they were not predefined in the protocol as an efficacy endpoint. Safety was assessed by the incidence of adverse events and the results of blood chemistry, hematology, and urine testing. EDSS was evaluated every three months. Patients were seen at any time throughout the study for the evaluation of adverse events or relapses.

Serum levels of neutralizing antibodies (NAbs) were measured at baseline and every three months throughout the study at a central laboratory at Biogen, Inc., using a two-step ELISA–cytopathic effect assay. We report the incidence of titers of $\geq 1:20$ – the level that has been associated with reduced biologic activity of IFN β -1a.⁸

Statistical analysis

Analyses were based upon the intent-to-treat population (i.e., all randomized subjects). All reported P values were based on two-tailed statistical tests, with a significance level of ≤ 0.05 . No imputation was performed for missing data.

The primary endpoint, the cumulative probability of sustained disability progression, was calculated for each treatment group using the Kaplan–Meier product-limit method. The treatment groups were compared using the Cox proportional hazards model using baseline EDSS score, prestudy relapse rate, duration of disease, age, and gender as preplanned covariates. Covariates, which did not reach a significance level of 0.05, were dropped from the Cox proportional hazards model. All time-to-event endpoints were analysed in a similar way. The treatment difference on the extent of change in EDSS was analysed using the rank-based analysis of covariance (ANCOVA) model at each predefined time point using the baseline EDSS score as the covariate. Annualized relapse rates were compared between doses using the likelihood ratio test for a Poisson model. Percentages of relapse-free patients were estimated using the Kaplan–Meier method, and the difference between treatment groups was compared using the log-rank test.

Results

Subjects

Six hundred and eight subjects completed 36 months on study in Part 1. As some centres decided not to participate in the extension study, only 493 patients were enrolled in Part 2 (Figure 1). A total of 446 subjects (56%) of the initial cohort who entered Part 2 of the study completed 48 months of treatment and follow-up (Figure 1). The proportion of subjects enrolled in Part 2 who discontinued the study before 48 months was 13% (31/246) in the 30-mcg group and 6% (16/247) in the 60-mcg group. The most common reasons for study discontinuation in both the 30 and 60-mcg groups were perceived worsening of disease (6% [14/246] and 2% [6/247], respectively), other reasons (4% [11/246] and 2% [6/247], respectively), and adverse events or lack of tolerability to study drug (1% [3/246] and $< 1\%$ [1/247], respectively). The ‘other’ category included patient request and the wish to become pregnant. The median time on study was 1447 days (3.96 years) in the 30-mcg group and 1455 days (3.99 years) in the 60-mcg group.

The baseline demographic and clinical characteristics of patients who were originally enrolled in the study are listed in Table 1. There were no differences between treatment groups with regard to age, sex, race, disease duration, EDSS scores, MRI, or prestudy relapse rates. Overall, the mean age at diagnosis of MS was 31.3 years, the mean disease duration was 6.4 years, and the mean EDSS was 3.6 at study entry. The mean relapse rate during the three years prior to enrollment was 1.3 per year. As shown in Table 1, baseline characteristics of patients included in Part 2 were similar to baseline characteristics

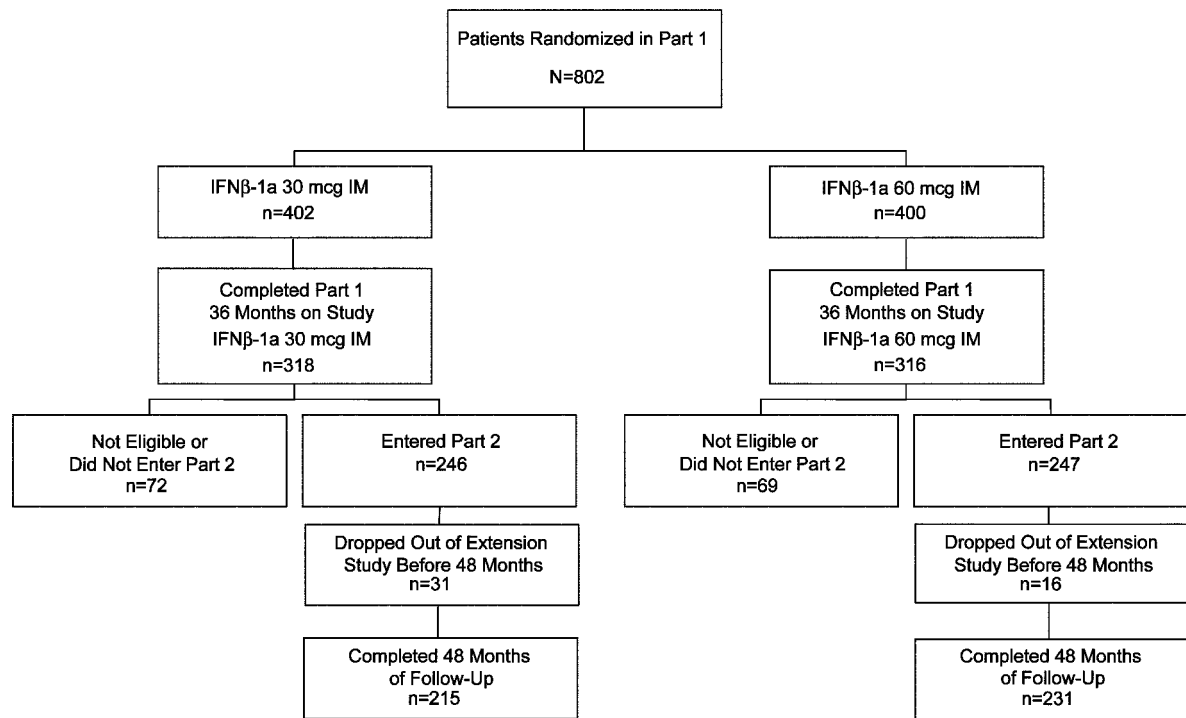


Figure 1 Profile of patients in Part 1 and Part 2 of the European IFN β -1a Dose-Comparison Study.

Table 1 Baseline demographic and clinical characteristics of patients enrolled in Part 1 and Part 2 of the European IFN β -1a Dose-Comparison Study

Characteristic	Part 1		Part 2
	All patients n = 802	IFN β -1a 30 mcg n = 246	IFN β -1a 60 mcg n = 247
Age (years)			
Mean \pm SD	36.8 \pm 7.9	37.6 \pm 7.7	36.9 \pm 7.9
Gender (% female)	68	69	68
Ethnicity (% Caucasian)	97	98	98
Classification of MS (%)			
Relapsing–remitting	85	86	87
Relapsing–progressive ^a	15	14	13
Age at diagnosis (years)			
Mean \pm SD	31.3 \pm 7.8	31.9 \pm 7.8	31.6 \pm 7.7
EDSS score			
Mean \pm SD	3.6 \pm 1.0	3.4 \pm 1.0	3.5 \pm 1.0
Prestudy relapse rate ^b			
Mean \pm SD	1.3 \pm 0.6	1.3 \pm 0.6	1.3 \pm 0.5

SD, standard deviation.

^aPatients with early progressive disease who experienced relapses; patients with confirmed progressive disease and no relapses were excluded from the study.

^bRelapse rate per year during the three years prior to study enrollment.

of patients included in Part 1, suggesting that there was no selection bias to affect the clinical results of patients included in Part 2 who were followed for up to four years.

Disability progression

The cumulative percentage of subjects with sustained disability progression for each treatment group is shown in Figure 2. After 48 months of treatment, the cumulative

rate of sustained disability progression was not different between the IFN β -1a 30-mcg group and the 60-mcg IM group. The cumulative percentage of subjects who progressed at 48 months was 48% in the IFN β -1a 30-mcg group and 43% in the 60-mcg group (rate ratio, 0.94; 95% confidence interval [CI], 0.75–1.17; $P = 0.58$).

The cumulative percentage of subjects who progressed to an EDSS score of ≥ 4.0 or ≥ 6.0 was analysed. There

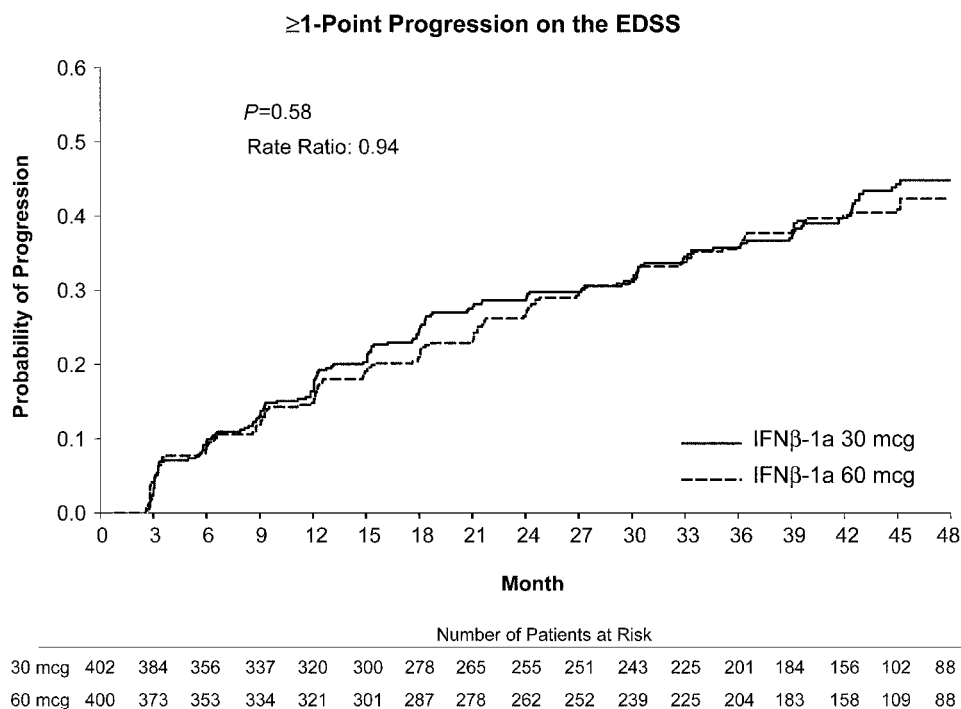


Figure 2 Kaplan–Meier curve of the cumulative probability of disability progression by treatment group (all subjects). The cumulative probability of developing disability progression was similar between the IFN β -1a 30-mcg group and 60-mcg group ($P = 0.58$).

Table 2 Extent of change in EDSS scores from baseline over four years of IFN β -1a treatment

	IFN β -1a 30 mcg n = 402	IFN β -1a 60 mcg n = 400	P value
<i>Mean change \pm SEM</i>			
Months 0–12	0.09 \pm 0.04 n = 376	0.06 \pm 0.04 n = 376	0.86
Months 0–24	0.14 \pm 0.05 n = 347	0.16 \pm 0.05 n = 348	0.99
Months 0–36	0.25 \pm 0.06 n = 328	0.27 \pm 0.06 n = 326	0.47
Months 0–48	0.30 \pm 0.08 n = 192	0.30 \pm 0.08 n = 211	0.69

SEM, standard error of the mean.

were no significant differences between treatment groups for either endpoint (rate ratio for EDSS ≥ 4.0 , 1.01; 95% CI, 0.70–1.45; $P = 0.96$; rate ratio for EDSS ≥ 6.0 , 0.96; 95% CI, 0.69–1.32; $P = 0.79$). By month 48, 30% of subjects in each group progressed to an EDSS score of ≥ 4.0 and 22% of subjects in each group progressed to an EDSS score of ≥ 6.0 . At month 48, the mean change in EDSS score was 0.30 in the 30-mcg group and 0.30 in the 60-mcg group; no significant differences between treatment groups were observed in change in EDSS score at month 12 ($P = 0.86$), month 24 ($P = 0.99$), month 36 ($P = 0.47$), or month 48 ($P = 0.69$) (Table 2).

Disability progression was also analysed according to disease characteristics at baseline, including EDSS score

(≤ 3.5 or ≥ 4.0), presence of Gd+ lesions (0 or ≥ 1), and type of relapsing MS (relapsing–remitting or relapsing–progressive). There were no differences between IFN β -1a 30 mcg and 60 mcg for subjects with baseline EDSS scores of ≤ 3.5 (hazard ratio, 0.84; 95% CI, 0.61–1.16; $P = 0.29$) or baseline EDSS scores of ≥ 4.0 (hazard ratio, 1.04; 95% CI, 0.76–1.42; $P = 0.80$). The proportions of subjects with baseline EDSS scores of ≤ 3.5 who had disability progression by 48 months were 40% in the IFN β -1a 30-mcg group and 34% in the 60-mcg group. The proportions of subjects with baseline EDSS scores of ≥ 4.0 who had disability progression by 48 months were 51% in the 30-mcg group and 53% in the 60-mcg group. Subgroup analyses based on presence (hazard ratio, 0.99; 95% CI, 0.66–1.48; $P = 0.94$) or absence (hazard ratio, 0.80; 95% CI, 0.49–1.31; $P = 0.38$) of Gd+ lesions at baseline also showed no significant difference between IFN β -1a 30 mcg and 60 mcg on progression of disability. In addition, there were no differences between IFN β -1a doses on progression of disability in subjects with relapsing–remitting MS (hazard ratio, 0.95; 95% CI, 0.74–1.22; $P = 0.66$) or relapsing–progressive MS (hazard ratio, 0.89; 95% CI, 0.55–1.45; $P = 0.63$).

An analysis was conducted to determine whether the presence or frequency of relapse would differentially affect disability progression in the IFN β -1a 30 mcg and 60 mcg groups. Results showed no significant differences between IFN β -1a 30 mcg and 60 mcg on disability progression in patients who experienced no relapses ($P = 0.20$), ≥ 1 relapse ($P = 0.82$), or ≥ 3 relapses ($P = 0.93$).

Relapses

Relapse-related data were collected as part of the documentation of adverse events, and relapse rate was not a predefined efficacy endpoint in the study; hence, relapse rate is not a reliable efficacy endpoint. During Part 1 of the study, the mean annualized relapse rate based on self reports over 36 months of treatment was 0.77 in the 30-mcg group and 0.81 in the 60-mcg group ($P = 0.330$, 30 mcg versus 60 mcg). Over 48 months of treatment, the mean annualized relapse rate was 0.75 in the 30-mcg group and 0.77 in the 60-mcg group ($P = 0.527$, 30 mcg versus 60 mcg); relapses tended to decrease over the 48 months. There were no differences between treatment groups in mean self-reported relapse rates during each year. Over the 48 months of treatment, the percentage of relapse-free patients was 18% in the IFN β -1a 30-mcg group and 19% in the 60-mcg group (no significant difference [$P = 0.829$]). The median time to first relapse was 402 days in the 30-mcg group and 347 days in the 60-mcg group ($P = 0.822$, 30 mcg versus 60 mcg). The rate of IV steroid use, a surrogate marker for severe relapses, was 0.66 courses per subject per year in the 30-mcg group and 0.67 in the 60-mcg group after 48 months of treatment.

Safety

Both doses of IFN β -1a were well tolerated over 48 months of treatment. Overall, the safety profile of IFN β -1a was consistent with that observed in other clinical studies and from post-marketing surveillance. The most common treatment-related adverse events in both dose groups were flu-like syndrome, MS exacerbation, asthenia, depression, pharyngitis, and headache. Of all treatment-related adverse events that occurred in $\geq 10\%$ of patients, a difference of more than 5% was identified between the groups with regard to the percentage of patients with arthralgia, hypertonia, and infection (each occurred more often in the 30-mcg group) and flu-like syndrome, which occurred significantly more often ($P = 0.016$) in the 60-mcg group.

Neutralizing antibodies

The proportions of patients who had NAb (titers ≥ 20 LU/mL) at any time during the study were 2.3% in the 30-mcg group and 5.8% in the 60-mcg group ($P = 0.011$).

Discussion

Results from Part 2 of the European IFN β -1a Dose-Comparison Study demonstrated that the clinical efficacy of IFN β -1a 30 mcg and 60 mcg IM is equivalent and is sustained for up to 48 months of treatment. There were no significant differences between the two IFN β -1a doses on any of the clinical endpoints, including sustained disability progression (including subgroup analyses of disability progression), extent of change in EDSS score, and relapse rate. Although relapse rate was not a predefined efficacy endpoint in the study, data on relapses were collected as part of the documentation of adverse events. As such, self-reported neurologic symptoms that did not

necessarily fulfill the usual criteria for a relapse (typically included in relapse-based protocols) were reported throughout the study. Hence, the rates of relapse for each group reported in this paper were likely overestimated. Relapse rate is reported here because it is typically reported as an outcome measure in clinical trials of MS. However, sustained progression in EDSS is a better measure of disease activity, particularly in long-term studies.

The proportion of patients who discontinued treatment because of perceived worsening of disease was higher in the 30-mcg group (6%) compared with the 60-mcg group (2%). It is important to note that this measure of worsening of disease was not always supported by neurologic examination – in some cases, it was simply a ‘feeling’ the patient had. To further explore this issue, a Kaplan–Meier analysis was conducted on a combined endpoint of discontinuation because of perceived worsening of disease or sustained disability progression (≥ 1.0 point on EDSS). There was no statistically significant difference between IFN β -1a 30 mcg and 60 mcg ($P = 0.54$); therefore, it is likely that no bias was introduced due to differences in rates of discontinuation based on perceived worsening of disease.

Although the incidence of NAb was significantly higher in the 60-mcg dose group (5.8%) compared with the 30-mcg dose group (2.3%), the incidence was low in both treatment groups. This result suggests that higher doses of IFN β may produce higher incidences of NAb; however, this issue is still a matter of debate due to inconsistent results among studies.^{3,8,9} The development of NAb to IFN β products has been associated with reduced clinical efficacy in some studies.^{10–12} The impact of NAb on the efficacy of IFN β s in these studies was observed after 18 months and two years, suggesting that long-term follow-up is important for an accurate assessment of efficacy in patients with MS.

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Appendix A

Members of the European IFN β -1a (Avonex[®]) Dose-Comparison Study

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