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Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study

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Objective – To evaluate and compare the long-term efficacy and safety of two different β-interferon preparations (IFN-β-1a vs IFN-β-1b). *Materials and methods* – Two parallel outpatient groups with relapsing–remitting multiple sclerosis (RRMS), according to Poser criteria, were treated with either intramuscular IFN-β-1a 30 μg (group A, $n = 62$) or subcutaneous IFN-β-1b 250 μg (group B, $n = 64$). *Results* – A statistically significant reduction was seen in the relapse rate ($P < 0.0001$) in both groups. No significant difference was found between the two groups ($P = 0.43$). After 6 years of therapy, the mean Expanded Disability Status Scale score was 3.22 ± 1.47 (Δ 1.03 ± 1.35) in group A and 3.34 ± 1.47 (Δ 0.97 ± 1.47) in group B ($P = 0.47$). *Conclusions* – Our study results suggest that the efficacy of IFN-β-1a 30 μg once weekly and SC IFN-β-1b 250 μg every other day is similar. Both IFN-β-1a and IFN-β-1b are effective in slowing disability progression.

F. Patti[1], A. Pappalardo[1], C. Florio[1], G. Politi[2], T. Fiorilla[3], E. Reggio[1], A. Reggio[1†]

[1]Centro Sclerosi Multipla, Università di Catania, Catania, Italy; [2]Centro Sclerosi Multipla, Ospedale Cardarelli, Napoli, Italy; [3]Istituto di Radiologia, Università di Catania, Catania, Italy

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F. Patti, Centro Sclerosi Multipla, Università di Catania, Via S. Sofia 78, 95123, Catania, Italy
Tel.: +39 95 3782822 (ext. 2832)
Fax: +39 95 330943
e-mail: patti@unict.it

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Several studies have demonstrated the beneficial effects of β-interferon (IFN-β) in modifying the course of relapsing–remitting multiple sclerosis (RRMS). Three different IFN-β products are available for the treatment of RRMS: Betaferon® (IFN-β-1b) (Schering, Berlin, Germany), Avonex® (IFN-β-1a) (Biogen Idec, Inc., Cambridge, MA, USA), and Rebif® (IFN-β-1a) (Serono, Inc., Rockland, MA, USA). Phase III clinical trials have shown that all IFN-βs are effective in reducing the relapse rate and slowing the progression of MS (1–3).

Phase III clinical trials have shown the beneficial effects of IFN-β in reducing gadolinium-enhancing (Gd+) lesions and lesion load on magnetic resonance imaging (4, 5). It also has been shown that IFN-β-1a (Avonex) and IFN-β-1b decrease the progression of cerebral atrophy and accumulation of T1-hypointense lesion load (T1-LL), also called black holes (6, 7).

Many studies have focused on the short-term effects of IFN-β therapy on RRMS, but few on its long-term clinical and magnetic resonance imaging (MRI) aspects. Because most phase III clinical trials are of short duration, it has not been possible to evaluate the clinical efficacy or general impact of disease-modifying agents (DMAs) over time. Thus, surveillance studies are needed to evaluate the long-term effects of IFN-β in modifying the disease course, monitoring adverse events, and predicting clinical response to treatment (8).

In this study, we aimed to describe our experience concerning the clinical practice setting of MS patients treated with IFN-β. The main purpose of this study was to evaluate and compare the long-term efficacy and safety of two different IFN-β preparations [IFN-β-1a (Avonex) vs IFN-β-1b (Betaferon)]. We also compared the results of our

[†]Deceased

study with phase III trials, head-to-head studies, and other observational studies.

Materials and methods

Design

This independent, open-label, non-randomized, observational, 6-year follow-up study was retrospective for the first 3 years and prospective for years 4–6. Two parallel outpatient groups with RRMS, according to Poser criteria (9) were treated with either intramuscular (IM) IFN-β-1a (group A) or subcutaneous (SC) IFN-β-1b (group B).

The primary objectives of this study were to verify the sustained efficacy of IFN-β on patients with RRMS and compare the reported clinical efficacy of two different IFN-βs. We also investigated the effects of IFN-β-1a and IFN-β-1b on the relapse rate and in delaying disease progression. A relapse was defined as the appearance of new or worsening of previous neurologic symptoms without fever and lasting ≥48 h, which determines objective change on neurologic examination in patients with stable disease for ≥4 weeks. Sustained progression was defined as an increase of ≥1 point on the Expanded Disability Status Scale (EDSS) (10) score on two consecutive examinations ≥6 months apart.

We also planned to evaluate the percentages of patients who progressed to secondary progressive MS (SPMS). We considered patients entered the secondary-progressive course of the disease when they experienced a gradual progression following an initial pattern of relapses/remissions and a decline in neurologic functions between attacks (11). Another endpoint was to verify the safety of IM IFN-β-1a and SC IFN-β-1b by evaluating the frequency of, need for therapy change because of, and drug discontinuation resulting from side effects.

Patients

From February 1996 to December 1997, 126 consecutive patients with RRMS seen at two MS centers in Italy (Catania and Naples) were consecutively enrolled in the study (Table 1). All patients had been clinically stable for ≥4 weeks before treatment initiation. Previous therapy with immunosuppressive drugs was not allowed. In Italy, we obtained licenses to use IFN-β-1b and IFN-β-1a for patients with RRMS in February 1996 and August 1997, respectively. This study was not randomized. All patients gave the informed consent for the study. Three different neurologists carried out the clinical evaluation, either in the retrospective or in the prospective period. The mean values that were obtained were considered for the analysis.

Table 1 Patient demographics and baseline characteristics

	Group A ($n = 62$)	Group B ($n = 64$)
Female/male	36/26	38/26
Mean age, ± SD	36.81 ± 7.26	36.62 ± 7.69
Mean age at treatment initiation, years	32.42 ± 7.38	31.67 ± 7.68
Mean disease duration, years	5.81 ± 5.97	5.85 ± 6.31
Mean age at diagnosis, years	29.50 ± 7.28	30.00 ± 8.18
Disease duration, years		
<2	10 (19.23)	10 (18.18)
2–10	18 (34.61)	24 (43.63)
>10	24 (46.15)	21 (38.18)
Baseline EDSS		
<1.5	16 (30.77)	16 (29.09)
2.0–2.5	25 (48.08)	24 (43.64)
3.0–3.5	10 (19.23)	10 (18.18)
4	1 (1.92)	5 (9.09)
Relapse rate	1.31	1.31

EDSS, Expanded Disability Status Scale.

MRI

Brain scans of the transverse plane were performed from the level of the foramen magnum to the vertex. Throughout the study, a 1.5-T magnet, precise positioning, and a double-echo spin-echo sequence were used, with echo tomes chosen so that cerebrospinal fluid was of low intensity on the first echo (TR 2400 ms) and of high intensity (TE 25/90 ms) on the second echo. The sequence, a 5-mm slice thickness, and a 256×256 matrix were chosen to maximize lesion detection and facilitate lesion tracing. Analysis of demyelinated areas was performed (with slight modifications) according to Ormerod's criteria by a radiologist unaware of the clinical findings for any patient (12).

We assessed the percentage of patients with stable disease at either T1-Gd evaluation or T2 evaluation after 1 year of therapy and at years 2–6. Moreover, we measured T1-LL and T2-LL 1 month before treatment initiation (baseline) and then at years 1–6.

Neutralizing antibodies

We measured the presence of neutralizing antibodies (NAbs) every 6 months beginning at baseline. Patients who were Nab+ at baseline evaluation were excluded from the study. NAbs were evaluated using the cytopathic effect assay (13, 14). The neutralization titer of a serum sample was

calculated according to Kawade's formula and indicated in laboratory units (LU). A level of ≥20 LU was considered the threshold of positivity.

Statistical analysis

The primary comparison of relapse rate before and after treatment was evaluated by using a paired *t*-test. The comparison of relapse rate and percentage of relapse-free patients between the two groups was determined by using a chi-square test.

Magnetic resonance imaging data (T1-LL, T2-LL, and percentages of patients stable at T1-Gd evaluation and T2 evaluation) were analyzed by using a chi-square test. Disability progression and EDSS variation were analyzed by using a chi-square test with Yate's correction. The percentage of patients whose disease progressed from RRMS to SPMS was evaluated by using either Fisher's exact test or a chi-square test.

Results

In group A, 62 patients were treated with IFN-β-1a (Avonex) 30 μg intramuscularly once weekly. In group B, 64 patients received IFN-β-1b (Betaferon) 250 μg subcutaneously every other day. Patients were well matched for age, sex, disease duration, age at MS diagnosis, and age at IFN-β treatment initiation. Patient demographics and baseline characteristics were similar in the two groups (Table 1). The mean disease duration was 5.81 ± 5.97 years in group A and 5.85 ± 6.31 years in group B. Ten (16.12%) of 62 patients in group A and 10 (15.62%) of 64 in group B had a shorter duration of disease than 2 years at baseline. EDSS scores ranged from 0 to 4 at baseline.

The annual exacerbation rate at baseline was 1.31 in both groups (Table 2). This rate decreased to 0.58 in group A and to 0.65 in group B after 1 year of therapy, 0.56 and 0.44 at year 2, 0.61 and 0.50 at year 3, 0.55 in both the groups at year 4, 0.35 and 0.45 at year 5, 0.32 and 0.41 at year 6. Overall, a statistically significant reduction from baseline was seen in the relapse rate ($P < 0.0001$) in both groups. No significant difference was found between the two groups ($P = 0.43$). The percentage of relapse-free patients was 53.22% in group A and 54.68% in group B after 1 year, 35.71 and 34.48 at year 2, 17.85 and 22.41 at year 3, 14.28 and 15.51 at year 4, 9.43 and 7.4 at year 5, and 7.54 and 7.4 at year 6 (Table 2). Mean times from treatment initiation to first relapse were 17.17 and 13.43 months in the IFN-β-1a and IFN-β-1b groups, respectively ($P = 0.09$).

Disability

After 6 years of therapy, the mean EDSS was 3.22 ± 1.47 (Δ 1.03 ± 1.35) in group A and 3.34 ± 1.47 (Δ 0.97 ± 1.47) in group B ($P = 0.47$) (Table 3). The disease was considered to have 'worsened' if patients had an increase of ≥1 point on EDSS evaluation. In group A, the disease worsened after 6 years of therapy in 38.46% of patients, whereas the disease stabilized or improved in 61.54% of patients. In group B, the disease worsened in 36.36% of patients, whereas it stabilized or improved in 63.64% of patients. No

Table 3 Variation in Expanded Disability Status Scale (EDSS) score

EDSS score	Group A	Group B
At diagnosis	2.13 ± 0.80	2.35 ± 0.9
At IFN-β treatment initiation	2.21 ± 0.87	2.37 ± 1.00
After 6 years of IFN-β therapy	3.22 ± 1.47	3.34 ± 1.47
Variation	1.01 ± 1.35	0.97 ± 1.47

IFN-β, interferon beta. $P = 0.47$.

Table 2 Relapse rate, disease progression and MRI findings

	Exacerbation rate*		Relapse-free patients, %		Patients with stable disease on T1-Gd				Patients with stable disease on T2 evaluation			
	Group A	Group B	Group A	Group B	Group A		Group B		Group A		Group B	
Year					% pts	Lesion load†	% pts	Lesion load‡	% pts	Lesion load¶	% pts	Lesion load¶
1	0.58	0.65	53.22	54.68	75.8	9.1	73.43	9.1	58.06	29.4	59.37	29.4
2	0.56	0.44	35.71	34.48	60.71	9.2	65.51	9.2	48.21	29.8	55.17	30.0
3	0.61	0.50	17.85	22.41	51.78	9.3	55.17	9.4	30.35	30.5	36.20	30.5
4	0.55	0.55	14.28	15.51	41.07	9.5	43.10	9.6	19.64	31.0	24.13	30.8
5	0.35	0.45	9.43	7.40	30.18	9.6	31.48	9.6	16.98	31.6	22.22	31.3
6	0.32	0.41	7.54	7.4	28.3	9.8	29.62	9.7	15.09	31.9	20.37	31.4

*Baseline 1.31.
†Baseline 8.7.
‡Baseline 9.1.
¶Baseline 29.1.

significant differences were found between the two groups on a chi-square test with Yate's correction. Only 20% of patients with lower disease duration scored ≥4 on EDSS evaluation after 6 years of therapy.

Over 24 months, 12 patients switched treatment because of significant disease worsening; two of the 12 switched to mitoxantrone therapy and 10 to a combination regimen, IFN-β-1a plus cyclophosphamide. Cyclophosphamide was administered monthly.

Disease worsening to secondary progressive MS

One patient in group A and one in group B progressed to secondary progressive MS after 1 year of therapy, two in both the groups at year 2, three in the Avonex group and two in the Betaferon group at year 3, three in both the groups at year 4, four in both the groups at year 5, four in group A and five in group B at year 6. At the end of 6 years of therapy, 32.07% ($n = 17$) of patients in the IFN-β-1a group and 31.48% ($n = 17$) in the IFN-β-1b group had disease progression from RRMS to SPMS. Twelve of 17 (70.58%) in group A and 13 of 18 (72.22%) in group B had a disease duration longer than 10 years. The differences between the two groups were not significant when using either the chi-square test or Fisher's exact test.

MRI findings

The percentages of patients with stable disease on T1-Gd were 75.8% in group A and 73.43% in group B after 1 year, 60.71% and 65.51% at year 2, 51.78% and 55.17% at year 3, 41.07% and 43.10% at year 4, 30.18% and 31.48% at year 5, and 28.30% and 26.62% at year 6.

The percentages of patients with stable disease on T2 evaluation were 58.06% in group A and 59.37% in group B at year 1, 48.21% and 55.17% at year 2, 30.35% and 36.20% at year 3, 19.64% and 24.13% at year 4, 16.98% and 22.22% at year 5, and 15.09% and 20.37% at year 6 (Table 2).

At baseline, T1-LL was 8.7 in group A and 9.0 in group B, 9.1 in both groups at year 1, 9.2 in both the groups at year 2, 9.3 in group A and 9.4 in group B at year 3, 9.5 and 9.6 at year 4, 9.6 in both the groups at year 5, and 9.8 and 9.7 at year 6. At baseline, T2-LL was 29.1 in both groups 29.4 in both groups after 1 year, 29.8 and 30.0 at year 2, 30.5 in both the groups at year 3, 31.0 and 30.8 at year 4, 31.6 and 31.3 at year 5, and 31.9 and 31.4 at year 6 (Tables 2 and 4).

Table 4 Variation (Δ) in T1 and T2 lesion load*

	T1 lesion load		T2 lesion load	
Years	Group A	Group B	Group A	Group B
0–1	0.4	0.1	0.3	0.3
1–2	0.1	0.1	0.4	0.6
2–3	0.1	0.2	0.7	0.5
3–4	0.2	0.2	0.5	0.3
4–5	0.1	0.0	0.6	0.5
5–6	0.2	0.1	0.2	0.1

*P = NS.

Adverse events

Treatment with either IFN-β-1a or IFN-β-1b was tolerated throughout the 6-year study in 122 of 126 patients. Four patients in the IFN-β-1b group withdrew from the study, two because of a high incidence of injection site reactions and two because of a significant increase in levels of aspartate aminotransferase and alanine aminotransferase.

The most frequent side effects were flu-like syndrome, fever, headache, injection site reaction, fatigue, myalgia, increased spasticity, and depression. Headache was significantly more frequent in group A, and injection site reaction in group B. No significant differences were seen between the two groups regarding other side effects. Therapy for side effects consisted of nimesulide or paracetamol (acetaminophen).

Initial NAb titers at study entry were negative in all patients. After 6 years of treatment, 4 of 64 patients in the Betaferon group and 1 of 62 in the Avonex group had a level of ≥20 LU. However, none of these patients withdrew from treatment.

Withdrawal

As previously mentioned, 19 of 126 patients withdrew from treatment during the study. Six of 62 in the Avonex group and 6 of 64 in the Betaferon group switched therapy because of significant disability progression and withdrew from the study during the first 2 years. Four patients in the Betaferon group withdrew because of a significant incidence of side effects. Three patients in the Avonex group planned a pregnancy, therefore, it was decided to suspend treatment. Taking into account these considerations, 62 and 64 patients, respectively, in groups A and B were included in the statistical analysis for year 1, 56 and 58 patients for years 2, 3 and 4, and 53 and 54 patients for years 5 and 6.

Discussion

The main objective of our study was to mirror the clinical practice setting in which people affected by MS are daily involved.

All studies, either randomized controlled trials or open-label studies, have demonstrated the effectiveness of IFN-β therapy in reducing exacerbation frequency in patients with RRMS by as much as one-third (1–8).

Regarding the slowing of cumulative disability, studies have been of too short a duration to determine whether IFN-β could be effective in slowing long-term disability progression, as shown by increased EDSS scores. Up to now, however, only a few studies have been carried out with long-term clinical and MRI follow-up.

Paolillo et al. (15) described a sustained effect of IFN-β on the relapse rate over 6 years of therapy in patients with RRMS, suggesting the moderate effect in modifying the disease course over 6 years. Rio et al. (16) reported that the three IFN-βs provide a comparable efficacy in a large non-selected cohort of RRMS patients, followed for 8 years.

Before commenting on the results of our study, the study design and its limitations must be considered. Our study was a non-randomized, controlled, open-label study. Randomized controlled trials are considered the optimal research design (17) because bias can be introduced in open-label, non-randomized studies and cannot be overcome by any statistical method. Nevertheless, randomized controlled trials are not always feasible because of the difficulty of completing long-term studies, expense, and risk of patient withdrawal. Wingerchuk and Noseworthy (17) showed the difficulty in escalating sample size requirements in detecting partial therapeutic benefits. At the same time, however, the role of observational studies should not be underestimated. In a recent review, Benson and Hartz (18) reported that the estimates of the treatment effects from observational studies and randomized controlled trials are similar. In our study, the clinical and demographic aspects of the patient sample were well matched. No significant differences were seen between the two groups at baseline for age, sex, and disease duration. The relapse rate and T2-LL also had the same value at baseline, and mean EDSS and T1-LL values were similar.

Our study results are suggestive of the effectiveness of IM IFN-β-1a 30 μg once weekly and SC IFN-β-1b 250 μg every other day in determining a significant reduction in relapse rate over a 6-year follow-up period. A significant proportion of patients in both groups were exacerbation free during the first 2 years of therapy, even though the percentages of relapse-free patients decreased over the successive 4 years.

Regarding the other primary endpoint, we noted that both IFN-β-1a and IFN-β-1b are effective in slowing disability progression. Unfortunately, not all of the enrolled patients at baseline were included in the analysis after 6 years, because 19 of them suspended the treatment.

More than 50% of patients (54.36% in group A and 54.19% in group B) had disease that remained stable or improved over 6 years, whereas 45.64% in the Avonex group and 45.81% in the Betaferon group had disease that worsened, with an increase of ≥1 point on the EDSS score. The most interesting finding was that only 20% of patients with a disease duration of 6–10 years scored ≥4 on EDSS evaluation after 6 years of treatment. These results may be interpreted as clinically relevant in comparison with the natural history of patients with MS (19).

No significant difference was found between IFN-β-1a and IFN-β-1b in decreasing the relapse rate or in slowing disability progression over the 6-year follow-up period. The percentages of patients progressing to SPMS were similar in both groups. Both IFN-β-1a and IFN-β-1b were well tolerated, despite some side effects. Headache was more frequent in patients receiving IFN-β-1a; injection site reactions were more frequent in patients receiving IFN-β-1b. The differences were statistically significant. Other side effects in both groups were similar, without significant differences. Only four patients (all in group B) had to stop treatment because of side effects.

Our MRI data demonstrated that IFN-β-1a and IFN-β-1b have similar effects in suppressing formation of either Gd+ lesions or T2-hyperintense lesions, which are related to the acute and chronic phases of MS, respectively. IFN-β-1a and IFN-β-1b produced similar effects in preventing the accumulation of T1-LL on MRI.

The results of our observational study are in agreement with those of some recent open-label clinical studies which have shown that immunomodulatory therapies for MS have comparable efficacy (20–26).

The results of these open-label studies suggest that increasing the dose or frequency of administration, or both, does not determine superior clinical efficacy; there are no significant differences between IFN-β-1a and IFN-β-1b therapies.

Instead, Khan et al. (27) found that the reduction in the relapse rate was statistically significant only in the glatiramer acetate and IFN-β-1b groups, in contrast to patients treated with IFN-β-1a.

The results of our study and other open-label clinical trials are in disagreement with those of two recent randomized controlled trials – Independent Comparison of Interferon (INCOMIN) (28) and EVidence of Interferon Dose–response: European North American Comparative Efficacy (EVIDENCE) (29). The results of these two studies should be interpreted with caution because they contradict data obtained in pivotal, controlled, clinical trials designed to satisfy the highest standards required for drug approval.

In summary, the results of our study confirm results obtained during phase III randomized controlled trials, despite the limitations of the design and sample size. In addition, the results of our study do not differ from observations made in larger, more rigorously controlled studies.

The long follow-up may contribute to the assessment of the long-term effectiveness of DMAs in patients with RRMS. Additional comparative studies with larger cohorts and similar or longer follow-up periods are needed.

Conflict of Interest

The study was not supported by a corporate sponsor. None of the authors have or had a financial relationship with the companies who manufactured the drugs.

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