A prospective, open-label treatment trial to compare the effect of IFN β-1a (Avonex), IFNβ-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis

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A prospective, non-randomized, open-label treatment trial was performed in patients with relapsing-remitting multiple sclerosis (RRMS), with follow up for 12 months. Our primary objective was to prospectively compare the effect of IFNβ-1a (Avonex), IFNβ-1b (Betaseron), and glatiramer acetate (GA, Copaxone) on the relapse rate in patients with RRMS. Between August 1996 and September 1999, 156 consecutive patients with clinically definite RRMS with a Kurtzke scale (EDSS) score of 4 or less were followed for 12 months, from the time of initiating therapy or electing to remain untreated. Prior 2-year relapse history and available chart information was carefully reviewed at the time of enrolment. Thirty-three of 156 elected no treatment (mean age 32.5 years; mean EDSS 2.64) at enrolment; 40 elected IFNβ-1a (mean age 32.4 years; mean EDSS 2.69), 41 IFNβ-1b (mean age 32.1 years; mean EDSS 2.56), and 42 chose GA (mean age 31.5 years; mean EDSS 2.57). Annual relapse rate based upon the 2 years prior to enrolment was 1.08 in the untreated group, 1.20 in the AV group, 1.21 in the BE group, and 1.10 in the GA group. There were no statistically significant differences among the four groups at enrolment. After 12 months of treatment, patients in the untreated groups had a relapse rate of 0.97, whereas patients in the IFNβ-1a, IFNβ-1b, and GA groups had relapse rate of 0.85, 0.61, and 0.62, respectively. Compared to the untreated group, reduction in the relapse rate was statistically significant only in the GA ($P = 0.003$) and IFNβ-1b ($P = 0.002$) groups, in contrast to the IFNβ-1a treated patients, who did not show a significant reduction ($P = 0.309$). Compared to the untreated patients, mean EDSS was significantly reduced only in the GA ($P = 0.001$) and IFNβ-1b ($P = 0.01$), in contrast to IFNβ-1a treated patients ($P = 0.51$). In this prospective, controlled, open-label, non-randomized 12-month study, treatment with only GA and IFNβ-1b significantly reduced the relapse rate compared to untreated patients, supporting early treatment in RRMS. Our results are similar to the observations made after 12 months of therapy in phase III studies of IFNβ-1a, IFNβ-1b, and GA. Despite some limitations of the study design, the results provide helpful clinical information regarding the relative efficacy of each therapy in mildly affected treatment-naïve RRMS patients.

Introduction

Three disease-modifying therapies are currently approved in the United States for use in relapsing-remitting multiple sclerosis (RRMS): interferon β-1b (IFNβ-1b, Betaseron), IFNβ-1a (Avonex), and glatiramer actetate (GA, Copaxone). In pivotal trials, all three agents demonstrated a reduction in the relapse rate in relapsing MS (IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al.*, 1995; Jacobs *et al.*, 1996), although IFNβ-1b has also been shown to be effective in secondary progressive MS in one study (European Study Group, 1998). Extended follow-up and posthoc analyses continue to demonstrate the efficacy of each agent in RRMS (IFNB Multiple Sclerosis Study Group and UBC MS/MRI Analysis Group, 1995; Rudick *et al.*, 1997; Johnson *et al.*, 1998). Claims of superiority for each therapy has led to much speculation regarding the relative efficacy of each agent in RRMS. However, no single prospective study has compared the effect of all three therapies on the relapse rate in RRMS. A comparison of the three immunomodulating treatments for RRMS is important to patients and to clinicians concerned about the appropriate use of disease-modifying therapies.

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We report the results of a prospective open-label, non-randomized study comparing the effects of IFNβ-1a, IFNβ-1b and GA to no treatment on the relapse rate in patients with RRMS. The study was conducted by the authors with no commercial funding from any of the manufacturers.

Methods

Patients

The primary objective of the study was to compare the effect of IFNβ-1a (Biogen Inc, Cambridge, MA) IFNβ-1b (Berlex laboratories, Richmond, CA) and GA (Teva Pharmaceuticals, Petah Tiqva, Israel) on the relapse rate in treatment-na RRMS patients after 12 months of therapy. The study was conducted at two university-based MS centres between August 1996 and September 1999. One hundred and fifty-six consecutive patients with clinically definite RRMS (Poser *et al.*, 1983) were enrolled after obtaining informed consent, of which 88 patients were enrolled at one centre and 68 at the other. All patients were between 18 and 60 years of age, with a Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) of ≤ 4, and had had at least one exacerbation in the previous two years. No patient had previously received treatment with IFNβ-1a or IFNβ-1b or GA. All patients had been clinically stable for at least four weeks before treatment initiation and had received no treatment with steroids during this period. No patient had previously received immunosuppressive treatment including cyclophosphamide, methotrexate or azathioprine.

Study design

This was a prospective, non-randomized open-label study. Patients were provided information regarding the three therapies in RRMS. Patients discussed various aspects of each therapy with their neurologist before making a treatment choice or electing to remain untreated. Data from pivotal phase III studies (IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al.*, 1995; Jacobs *et al.*, 1996), as well as information regarding the safety profile of each agent, was presented to patients. At the time of study initiation (August 1996), only IFNβ-1a and IFNβ-1b were available by prescription in the United States. Glatiramer acetate (Copaxone) became available in the US in March of 1997. Thus, pretrial allotted enrolment (35–40 patients per group) in the IFNβ-1a and IFNβ-1b groups was completed several months prior to enrolment in the GA group. No patient was excluded from the study if he or she elected to choose a therapy different from the one recommended by the neurologist. Once enrolment in the IFNβ groups was complete, patients who chose these agents, i.e. IFNβ-1a or IFNβ-1b, were not included in the study. Upon completion of enrolment, patients were followed in one of four groups, i.e. IFNβ-1a, IFNβ-1b, GA or untreated. Common reasons for not taking any of the three therapies included fear of injections, concerns about side-effects, and contemplating conception. All patients had baseline neurological examination and EDSS, and were subsequently seen for scheduled visits at 6 and 12 months after initiating therapy. Some patients were seen more often for scheduled visits at the discretion of the neurologist. The same neurologist followed a patient throughout the duration of the study. All neurologists involved in the study were experienced in rating neurological disability on EDSS and in the care of MS patients.

Relapse

A relapse was defined as appearance of new or worsening of previous neurological symptoms lasting at least 48 h, accompanied by objective change on neurological examination in a patient who had been clinically stable for the previous four weeks. All patients were seen within 10 days of the onset of symptoms and treated with intravenous methylprednisolone (IVMP) at a dose of one gram per day for three to five days, followed by an oral prednisone taper of 12–21 days. All but four relapses were treated with IVMP. Of these, two relapses were in the untreated group and one each in the IFNβ-1a and GA groups.

Study medication

All patients in the treatment groups received either 6 MIU (30 μg) of IFNβ-1a i.m. once a week, 8 MIU (250 μg) of IFNβ-1b subcutaneous (s.c.) on alternate days, or 20 mg of GA s.c. daily. All patients were trained in the injection technique and the first injection was administered in the presence of a nurse either at home or in the clinic.

Statistical analyses

The primary objective of the study was to compare the effect of IFNβ-1a, IFNβ-1b and GA on the relapse rate compared to untreated patients after 12 months of treatment. This was calculated by performing a one-way analysis of variance (ANOVA). Additionally, several secondary endpoints were also examined, including change in mean EDSS and the effect of treatment during the first and second six months of therapy. An evaluation of the proportion of relapse-free patients during the entire study and during each half of the study was also performed.

Results

Baseline demographics

Baseline demographics and disease variables are shown in Table 1. All four groups were well matched for age, sex, duration of disease, mean relapse rate in the prior two years, and EDSS. There were no statistically significant differences.

Patients who switched treatment groups

Ten out of one hundred and fifty-six patients switched groups during the 12-month study (Table 2). Of these ten patients, six were in the untreated group, and two each in the IFNβ-1a and IFNβ-1b groups at the time of study enrolment.

In order to evaluate any possible effect caused by the ten patients switching treatment groups during the study, we performed a one way ANOVA for all end-points in two ways. First, we examined all four patient groups at the end of 12 months based on the treatment (or no treatment) selected at enrolment (intent to treat analysis), which we designated as type 'I' (intent) analysis. In this analysis, relapses (or EDSS depending on the end-point being analysed) were ascribed to the treatment chosen at enrolment even if patients switched treatment groups during the course of the 12 month study.

We also examined patient groups at the end of 12 months based on the treatment patients were on at the end of the study, i.e. taking into account the 10 patients who switched treatment groups. In this analysis, designated as type 'F' (final drug) analysis, relapses (or EDSS depending on the end-point being analysed) were ascribed to the treatment that patients were taking at the end of the study, even if such relapses were recorded prior to the switch.

Primary end-point

Relapse rate

The mean number of relapses at the end of 12 months of treatment was 0.97 in the untreated controls, 0.85 in the IFNβ-1a, 0.61 in the IFNβ-1b, and 0.62 in the GA treatment groups (Table 3). Compared to untreated patients, patients treated with IFNβ-1b and GA had a significant reduction in the relapse rate ($P = 0.002$ and $P = 0.003$, respectively), whereas patients treated with IFNβ-1a showed no significant reduction in the relapse rate ($P = 0.309$). Overall, there was a statistically significant ($P = 0.004$) reduction in the relapse rate with treatment (all three treatment groups combined) compared with no treatment.

Table 1 Baseline demographics (SEM in parenthesis)

	Untreated	IFNβ-1a	IFNβ-1b	GA
No. of patients	33	40	41	42
Sex				
Male	11	14	15	14
Female	22	26	26	28
Mean age	32.5 (1.0)	32.4 (1.1)	32.1 (0.9)	31.5 (0.9)
Mean pre-study disease duration	3.85 (0.38)	4.83 (0.31)	4.05 (0.25)	4.33 (0.29)
Mean annual prior two-year relapse rate	1.08 (0.1)	1.20 (0.1)	1.21 (0.1)	1.10 (0.1)
Mean baseline EDSS	2.64 (0.1)	2.69 (0.1)	2.56 (0.1)	2.57 (0.1)

Table 2 Patients who switched treatment groups during the 12-month treatment period[a]

Patient no.	Treatment group at entry	No. of relapses on initial therapy	Duration of initial therapy (weeks)	Treatment group switched to	No. of relapses after switching
1	Untreated	0	16	IFNβ-1a	1
2	Untreated	1	12	IFNβ-1a	0
3	Untreated	1	10	IFNβ-1a	0
4	Untreated	1	24	GA	0
5	Untreated	1	18	GA	0
6	Untreated	1	22	IFNβ-1b	0
7	IFNβ-1b	0	12	IFNβ-1a	1
8	IFNβ-1b	1	10	GA	1
9	IFNβ-1a	1	28	GA	0
10	IFNβ-1a	1	18	IFNβ-1b	0

[a] No patient in the GA group switched during the study.

Table 3 Observed relapse rate at one year

	Untreated	IFNβ-1a	IFNβ-1b	GA
Type 'I' analysis				
No. of patients	33	40	41	42
Mean no. of relapses	0.97	0.85	0.61	0.62
Type 'F' analysis				
No. of patients	27	42	41	46
Mean no. of relapses	0.96	0.86	0.61	0.65

Type 'I' Analysis: treatment groups at the end of 12 months based on treatment patients chose at entry. Type 'F' analysis: treatment groups at the end of 12 months, based on treatment patients were receiving at the end of 12 months. *P*-values: Type 'I' analysis, overall treatment effect: 0.004, untreated vs., IFNβ-1a: 0.309 (NS), untreated vs. IFNβ-1b: 0.002, untreated vs. GA: 0.003. Type 'F' analysis, overall treatment effect: 0.010, untreated vs. IFNβ-1a: 0.394 (NS), untreated vs. IFNβ-1b: 0.005, untreated vs. GA: 0.012.

Relapse percentage change

The change in the relapse rate was also expressed as a percentage change. This was obtained by calculating the difference between the annual relapse rate reported during the two years prior to enrolment and at the end of 12 months of treatment for each group, expressed as a percentage. The relapse percentage change increased, on average by 2.53% in the untreated group, and decreased by 23.3%, 43% and 37.8% in the IFNβ-1a, IFNβ-1b, and GA groups, respectively (Table 4). Compared to the untreated group the reduction in the relapse percentage change was significant only in the IFNβ-1b ($P = 0.002$) and GA ($P = 0.007$) groups. However, patients receiving IFNβ-1a had a reduction in the relapse percentage change approaching significance ($P = 0.08$). Overall, patients receiving treatment (all three treatment groups combined) had a significant percentage reduction in relapses ($P = 0.01$) compared to untreated patients.

Table 4 Relapse percentage change from pre-treatment to 12-months post-treatment

	Untreated	IFNβ-1a	IFNβ-1b	GA
Type 'I' analysis				
No. of patients	33	40	41	42
Mean percentage change	+2.53	−23.33	−43.09	−37.80
Type 'F' analysis				
No. of patients	27	42	41	46
Mean percentage change	+4.93	−19.84	−43.09	−37.78

P-values: type 'I' analysis, overall treatment effect: 0.013, untreated vs. IFNβ-1a: 0.084 (NS), untreated vs. IFNβ-1b: 0.002, untreated vs. GA: 0.007; type 'F' analysis, overall treatment effect: 0.013, untreated vs. IFNβ-1a: 0.114 (NS), untreated vs. IFNβ-1b: 0.003, untreated vs. GA: 0.006.

Secondary end-points

Change in EDSS

After 12 months of therapy, mean EDSS in the untreated and IFNβ-1a groups increased by 0.21 and 0.11, respectively. In contrast, mean EDSS decreased by 0.18 in the IFNβ-1b and 0.31 in the GA treatment groups (Table 5). Compared to untreated patients, there was a significant reduction in mean EDSS only in the IFNβ-1b ($P = 0.01$) and GA ($P = 0.001$) treatment groups, in contrast to no significant improvement in mean EDSS in the IFNβ-1a treated patients ($P = 0.51$). Overall, there was a significant treatment effect ($P = 0.01$). Additionally, categorical change in EDSS is shown in Fig. 1 for patients who did not show any change or were worse by one or more points on the EDSS.

Relapse rate during each half of the study

Relapse rate was also examined during each half of the study independent of the other half. During the first six months of the study, there was no significant reduction in the relapse rate in any group (Table 6), although IFNβ-1b exhibited a reduction which approached statistical significance ($P = 0.099$). However, during the second six months of the study (Table 6), compared to untreated patients, there was a significant reduction in the relapse rate in only GA-treated patients ($P = 0.004$). Treatment with either IFNβ-1a or IFNβ-1b showed no significant reduction in the relapse rate ($P = 0.459$ and 0.199, respectively). Overall, there was a significant treatment effect ($P = 0.023$).

Proportion of relapse-free patients

The numbers of relapse-free patients during the entire 12 months of the study period were as follows: five (15.2%) in the untreated group, eight (20.0%) in the IFNβ-1a group, sixteen (39.0%) in the IFNβ-1b group and sixteen (38.1%) in the GA group (Table 7).

Table 5 Change in mean EDSS

	Untreated	IFNβ-1a	IFNβ-1b	GA
Type 'I' analysis				
No. of patients	33	40	41	42
Change in mean EDSS	+0.21	+0.11	−0.18	−0.31
Type 'F' analysis				
No. of patients	27	42	41	46
Change in mean EDSS	+0.24	+0.10	−0.20	−0.25

P-values: type 'I' analysis, overall treatment effect: 0.013 untreated vs. IFNβ-1a: 0.512 (NS), untreated vs. IFNβ-1b: 0.010, untreated vs. GA: 0.001; type 'F' analysis, overall treatment effect: 0.004 untreated vs. IFNβ-1a: 0.365 (NS), untreated vs. IFNβ-1b: 0.008, untreated vs. GA: 0.002.

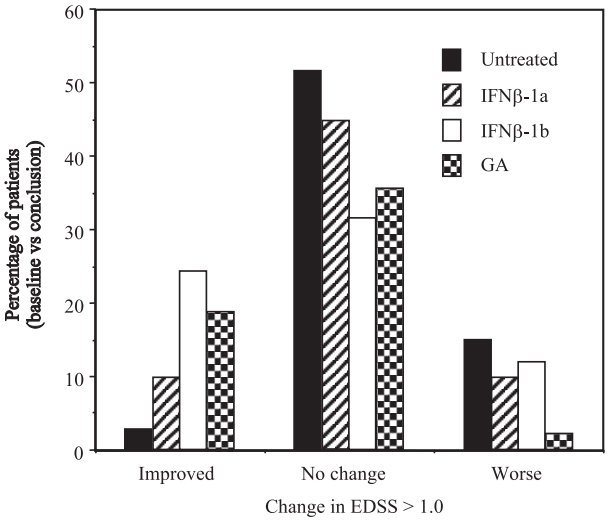

Figure 1 Percentage of patients who were unchanged, improved, or worse by ≥ 1 point on the EDSS after 12 months of therapy. In the untreated group, 3% improved, 51.6% were unchanged, and 15.2% were worse. In the IFNβ-1a group, 10% improved, 45% remained unchanged, and 10% were worse. In the IFNβ-1b, 24.4% improved, 31.7% remained unchanged, and 12.2% were worse. In the GA group, 19% improved, 35.7 remained unchanged, and 2.4% were worse.

Table 6 Observed relapse rate during the first and last six months of treatment

	Untreated	IFNβ-1a	IFNβ-1b	GA
First six months[a]				
Type 'I' analysis				
No. of Patients	33	40	41	42
Relapse rate	0.52	0.48	0.32	0.50
Type 'F' analysis				
No. of patients	27	42	41	46
Relapse rate	0.52	0.52	0.29	0.48
Last six months[b]				
Type 'I' analysis				
No. of patients	33	40	41	42
Relapse rate	0.45	0.38	0.32	0.14
Type 'F' analysis				
No. of patients	27	42	41	46
Relapse rate	0.44	0.36	0.32	0.20

[a] *P*-values: type 'I' analysis, overall treatment effect: 0.286 (NS), untreated vs. IFNβ-1a: 0.738 (NS), untreated vs. IFNβ-1b: 0.099 (NS), untreated vs. GA: 0.898 (NS); type 'F' analysis: overall treatment effect: 0.146 (NS), untreated vs. IFNβ-1a: 0.966 (NS), untreated vs. IFNβ-1b: 0.075 (NS), untreated vs. GA: 0.744 (NS). [b] *P*-values: type 'I' analysis, overall treatment effect: 0.023 untreated vs. IFNβ-1a: 0.459*P*-values: type 'I' analysis, overall treatment effect: untreated vs. IFNβ-1b: 0.199*P*-values: type 'I' analysis, overall treatment effect: untreated vs. GA: 0.004; type 'F' analysis, overall treatment effect: 0.141 (NS), untreated vs. IFNβ-1a: 0.445 (NS), untreated vs. IFNβ-1b: 0.268 (NS), untreated vs. GA: 0.028.

Table 7 Analysis of the proportion of relapse-free patients

	Untreated	IFNβ-1a	IFNβ-1b	GA
Type 'I' analysis				
No. of patients	33	40	41	42
Number (%) of relapse-free patients	5 (15.2)	8 (20.0)	16 (39.0)	16 (38.1)
Type 'F' analysis				
No. of patients	27	42	41	46
Number (%) of relapse-free patients	5 (18.5)	8 (19.1)	16 (39.0)	16 (34.8)

P-values: type 'I' analysis, overall treatment effect: 0.038 untreated vs. IFNβ-1a: 0.761 (NS), untreated vs. IFNβ-1b: 0.037, untreated vs. GA: 0.038; type 'F' analysis: overall treatment effect: 0.106 (NS), untreated vs. IFNβ-1a: > 0.999 (NS), untreated vs. IFNβ-1b: 0.108 (NS), Untreated vs. GA: 0.184 (NS).

Compared to untreated patients, the proportion of relapse-free patients in the IFNβ-1b and GA treatment groups was significantly higher ($P = 0.037$ and 0.038, respectively). The number of relapse-free patients receiving IFNβ-1a was not significantly different from the untreated group ($P = 0.761$). Overall there was a significant treatment effect ($P = 0.038$). However, in the type 'F' analysis, there was no significant treatment effect with any treatment individually or collectively.

Proportion of relapse-free patients during each half of the study

During the first six months of the study period, compared with the untreated patients, none of the treatment groups had a significantly higher proportion of relapse-free patients (Table 8). Furthermore, there was no significant overall treatment effect in the first six months. However, during the second six months, independent of the first six months (Table 8), compared to untreated patients, only GA-treated patients had a significantly higher proportion of relapse-free patients ($P = 0.004$) in contrast to IFNβ-1a ($P = 0.633$) or IFNβ-1b ($P = 0.240$) treated patients.

Discussion

Before discussing the results of this study, it is important to consider the study design and its limitations. This was a prospective, controlled but non-randomized, open-label study. The bias introduced by an open-label and non-randomized design can not be overcome by any statistical method. However, the study was intended to mirror the clinical practice setting in which patients are fully involved in making treatment choices. Thus, randomization was not possible. Furthermore, as seen in Table 1, there were no significant differences among the four groups at baseline. Additionally, there

Table 8 Analysis of the proportion of relapse-free patients during the first and last six months of the study

	Untreated	IFNβ-1a	IFNβ-1b	GA
First six months[a]				
Type 'I' analysis				
No. of patients	33	40	41	42
No. (%) of relapse-free patients	17 (51.5%)	21 (52.5%)	28 (68.3%)	21 (50.0%)
Type 'F' analysis				
No. of patients	27	42	41	46
No. (%) of relapse-free patients	14 (51.9%)	20 (47.6%)	29 (70.7%)	24 (52.2%)
Last six months[b]				
Type 'I' analysis				
No. of patients	33	40	41	42
No. (%) of relapse-free patients	18 (54.6%)	25 (62.5%)	28 (68.3%)	36 (85.7%)
Type 'F' analysis				
No. of patients	27	42	41	46
No. (%) of relapse-free patients	15 (55.6%)	27 (64.3%)	29 (68.3%)	37 (80.4%)

[a] *P*-Values: type 'I' analysis, overall treatment effect: 0.307 (NS), untreated vs. IFNβ-1a: > 0.999 (NS), untreated vs. IFNβ-1b: 0.159 (NS), untreated vs. GA: > 0.999 (NS); type 'F' analysis: overall treatment effect: 0.150 (NS), untreated vs. IFNβ-1a: > 0.808 (NS), untreated vs. IFNβ-1b: 0.131 (NS), untreated vs. GA: > 0.999 (NS). [b] *P*-Values: type 'I' analysis, overall treatment effect: 0.019, untreated vs. IFNβ-1a: 0.633 (NS), untreated vs. IFNβ-1b: 0.240 (NS), untreated vs. GA: 0.004; type 'F', overall treatment effect: 0.132 (NS), untreated vs. IFNβ-1a: 0.614 (NS), untreated vs. IFNβ-1b: 0.315 (NS), untreated vs. GA: 0.033.

were no patients at entry who had an unusually high number of relapses, which could potentially skew the data. The patient population was treatment-naïve with a low EDSS (≤ 4) at entry. The probability of enrolling patients with RRMS instead of SPMS at a low EDSS is relatively high. This was important because patients with SPMS have been reported to have a lower relapse rate (Weinshenker *et al.*, 1989). We also wanted to measure a primary end-point that could be objectively documented while being indicative of the relative efficacy of each therapy compared to no treatment. Thus, the number of relapses after 12 months of treatment was considered an appropriate primary end-point. In addition, because the study was not funded by any pharmaceutical company and because of limited internal funds, it was not possible to obtain brain MRI scans in a standardized protocol for all patients.

The results of this study indicate that treatment with immunomodulating therapy is beneficial compared to no treatment in treatment-naïve RRMS patients. This observation supports the consensus statement issued by the National Multiple Sclerosis Society encouraging treatment-naïve RRMS patients to consider therapy (NMSS, 1998). Clinicians as well as patients should be encouraged by the fact that even in a 'real-life situation' outside the context of placebo-controlled randomized trials, treatment is beneficial.

In this study, treatment with only IFNβ-1b (Betaseron) and GA (Copaxone) led to a significant reduction in the relapse rate after 12 months of treatment, in contrast to patients receiving IFNβ-1a (Avonex), who did not demonstrate a significant reduction in the relapse rate. These results are similar to those observed in pivotal phase III studies involving the three agents after one year of therapy despite the obvious limitations of our study design. In the phase III studies of IFNβ-1b (Berlex Laboratories, 1993; IFNB Multiple Sclerosis Study Group, 1993) and GA (Johnson *et al.*, 1995; Teva Pharmaceutical Industries, 1996), there was a significant reduction in the relapse rate after 12 months of treatment whereas in the phase III study with IFNβ-1a (Biogen, 1995; Jacobs *et al.*, 1996), there was no significant effect on the relapse rate after 12 months of treatment. We also observed that there was a significant reduction in the mean EDSS in patients receiving GA and IFNβ-1b, in contrast to the group receiving IFNβ-1a. Although, there was a significant reduction in the mean EDSS in patients receiving GA in the phase III trial (Johnson *et al.*, 1995), and a favourable trend in mean EDSS reduction in patients receiving IFNβ-1b in the phase III study (IFNB Multiple Sclerosis Study Group, 1993) was observed, neither study was designed to measure disease progression as a primary end-point. In the phase III study with

IFNβ-1a, there was no significant difference in the mean EDSS between patients receiving IFNβ-1a or placebo after 12 months of therapy (Rudick *et al*., 1997).

It is possible that the results seen after 12 months of therapy in this study could change at 24 months, which was the primary study duration in all three pivotal studies (IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al*., 1995; Jacobs *et al*., 1996). However, it is also possible that the relative lack of efficacy seen with IFNβ-1a given at a dose of 6 MIU i.m. once a week may reflect a lower or infrequent dose or both. Beta-interferons have been reported to have a dose-dependent effect (IFNB Multiple Sclerosis Study Group, 1993; Knobler *et al*., 1993; Prisms Study Group, 1998; OWIMS Group, 1999). Recombinant human IFNβ-1a is currently available in two preparations. Avonex or IFNβ-1a is given at a dose of 30 micrograms (μg) i.m. once a week. Rebif (Ares-Serono, Geneva, Switzerland; currently not available in the United States), which is identical to Avonex in structure and amino acid sequence, can be given at two doses of 22 or 44 μg s.c. three times a week. The OWIMS study examined the effect of Rebif on the relapse rate after 12 months of treatment when given at 22 μg and 44 μg s.c. once a week (OWIMS Group, 1999). The authors compared the one-year relapse rate observed with once-a-week dosing regimen of IFNβ-1a (Rebif) at 22 μg and 44 μg s.c. in the OWIMS study with the one-year relapse rates observed with IFNβ-1a (Avonex) given at 30 μg i.m. once a week (Jacobs *et al*., 1996) and IFNβ-1a (Rebif) given s.c. at 22 and 44 μg three times a week (PRISMS Study Group, 1998). It was observed that a once-a-week dose of IFNβ-1a (Rebif) at 22 μg and 44 μg s.c. and IFNβ-1a (Avonex) at 6 MIU i.m. once a week had no significant reduction on the relapse rate after one year, whereas 22 or 44 μg of IFNβ-1a (Rebif) given s.c. three times a week led to a significant reduction in the relapse rate as observed in the PRISMS study (PRISMS Study Group, 1998). Although such comparisons have limitations because of different study designs and patient populations, a dose-dependent effect of IFNβ-1a was suggested. Two doses of IFNβ-1b were used in the initial phase III study (IFNB Multiple Sclerosis Study Group, 1993). In contrast to the higher dose (8 MIU or 250 μg) of IFNβ-1b given s.c. on alternate days, there was no significant effect on the relapse rate in the lower dose (1.8 MIU or 50 μg s.c. on alternate days) group compared to placebo (IFNB Multiple Sclerosis Study Group, 1993). Issues relating to bioequivalence of various recombinant human IFNβ can be problematic because of difference in assay systems and titration standards, among other reasons. Nevertheless, both total dose and dose frequency affect the magnitude and duration of biologic response (Witt *et al*., 1993; Munafo *et al*., 1998; Williams and Witt, 1998). Moreover, in contrast to the serum levels of IFNβ-1b given at 250 μg s.c. on alternate days, which can be detected 24 h after administration (Khan *et al*., 1996), serum levels of IFNβ-1a given at 30 μg i.m. once a week could not be detected at 24 h after administration using the same assay system (Khan and Dhib-Jalbut, 1998). Although the optimal dose and injection frequency of IFNβ are not established, there is reasonable evidence to suggest that a higher total weekly dose and injection frequency is more efficacious (IFNB Multiple Sclerosis Study Group, 1993; Pozzilli *et al*., 1996; PRISMS Study Group, 1998; OWIMS Group, 1999).

We also examined the effect of each treatment in the first and second six months of the study because of an earlier report that treatment with IFNβ-1b led to a surge in IFNγ-secreting cells in the first 90 days of treatment, potentially placing these patients at an increased risk of relapses (Dayal *et al*., 1995). We had previously reported in a retrospective analysis the lack of such a risk in the first 90 days of treatment with IFNβ-1b (Khan and Hebel, 1998). In the current study, there was no significant therapeutic effect on any of the end-points in the first six months of treatment. However, during the second six months of treatment, there was significant reduction in the relapse rate and mean EDSS only in patients receiving GA. This is an interesting observation, because others have also reported a similar delayed and sustained therapeutic effect of GA, both clinically and by MRI-defined parameters of pathology, in a randomized, double-blind, placebo-controlled study (Comi *et al*., 1999).

The past decade has seen the emergence of MS as a treatable disorder. The quest for an ideal drug to treat MS continues concurrently with the efforts to find a cure. For neurologists, having to choose from more than one effective therapy for MS is refreshing and reassuring. However, in clinical practice the decision to select a first-line therapy for an individual patient may be complex, for a variety of reasons. Despite the obvious limitations in its design, we believe our study does provide meaningful and helpful information to the clinician. First, treatment does make a difference and early treatment should be encouraged. Secondly, even in an open-label and non-randomized study, the results do not differ from observations made after one year of treatment in larger and more rigorously controlled studies (IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al*., 1995; Jacobs *et al*., 1996). Thirdly, the results of our study suggest that IFNβ-1b (Betaseron) and GA (Copaxone) may be more optimal choices than IFNβ-1a (Avonex) at the currently available dose in treatment-naïve relatively mild RRMS patients. Additional comparative studies are indicated to provide the

clinician with conclusive information regarding the relative efficacy of each therapy in RRMS.

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