SHORT REPORT

A post-marketing study on interferon β 1b and 1a treatment in relapsing-remitting multiple sclerosis: different response in drop-outs and treated patients

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Background: Interferon β 1b (Betaferon) and 1a (Avonex) were licensed in Italy for treating relapsing-remitting multiple sclerosis in February 1996 and August 1997, respectively.

Objectives: To evaluate the effectiveness of these agents on the basis of clinical experience in northern Italian multiple sclerosis centres.

Design: Clinical data on patients with relapsing-remitting multiple sclerosis were collected on an appropriate form from 65 centres in northern Italy. Intention to treat analysis was not possible, so patients who discontinued treatment (drop-outs) and who continued treatment (treated) were analysed separately. The main outcome measures were annual relapse frequency, number of relapse-free patients, mean change in extended disability status scale score (EDSS), and number of patients who worsened.

Results: 1481 patients were included; 834 were treated with Betaferon and 647 with Avonex for mean periods of 21.4 and 12.0 months, respectively. Basal EDSS was 2.37 and 2.17, respectively, and relapse frequency was 1.62 and 1.45. The annual relapse rate decreased by more than 60% with Betaferon and 55% with Avonex. The proportions of relapse-free, improved, and worsened patients were similar in the two groups. More patients interrupted treatment with Betaferon (41.1%) than with Avonex (15.3%); such patients showed more active disease at baseline and during treatment. The incidence of side effects was higher in Betaferon treated patients.

Conclusions: The effectiveness of Betaferon and Avonex is confirmed. There was a more marked effect than expected from the experimental trial results. This might reflect differences in inclusion criteria, or, more likely, loss of drop-outs, favouring selective retention of responders.

Recombinant interferon β (IFNβ) is currently the treatment of choice for patients with relapsing-remitting multiple sclerosis. Betaferon and Avonex were approved in 1996 and 1997 by the Italian Ministry of Health[1][2] for the treatment of patients with relapsing-remitting multiple sclerosis who have extended disability scale scores (EDSS) of ≤3.5 and had at least two exacerbations in the previous two years. Prescription is limited to selected Italian multiple sclerosis centres, which also monitor clinical efficacy and the safety of the treatment.

The efficacy of a new treatment—shown in an experimental context, such as by controlled randomised clinical trials—needs to be verified in clinical practice (effectiveness), where an unselected patient population is treated. Such a population may differ from that involved in the controlled clinical trials.[3] To evaluate the effectiveness of IFNβ, we analysed clinical data on patients attending multiple sclerosis centres in northern Italy.

METHODS

Of 106 multiple sclerosis centres in northern Italy identified from the published list,[1] 65 contributed to this study (appendix).

Patients were selected and prospectively monitored according to a predefined protocol; those with definite relapsing-remitting multiple sclerosis, disease duration of at least one year, two or more relapses in the previous two years, and a pretreatment EDSS of ≤3.5 were included. A complete neurological examination was done at entry and every three months thereafter: at each visit the number of intercurrent relapses, EDSS, and the type and severity of side effects were recorded; the principal haematological variables were evaluated at the same time. Patients were treated with Betaferon 250 µg subcutaneously every other day, or Avonex 30 µg intramuscularly once a week.

Data were collected and reviewed by the coordinating centre (Neurological Institute C Besta). Each centre completed a predefined form, in which the following data were reported for each patient: clinical and demographic baseline characteristics (sex, age, disease duration, number of relapses in the previous two years, EDSS); duration of treatment; course of the disease during treatment (number of relapses every six months, EDSS at one, two, and three years); side effects (flu-like syndrome, local reaction, haematological abnormalities, psychopathology); and the time of and reasons for treatment withdrawal (treatment failure defined as more than three relapses or progression of disability, no consent, side effects, others).

A relapse was defined as the occurrence or recurrence of symptoms, lasting for more than 24 hours, following a period of stable neurological state of at least 30 days and without fever. Efficacy of treatment was evaluated in terms of annual relapse frequency, number of relapse-free patients, mean EDSS change, and number of patients who worsened or improved by at least one EDSS point. Patients treated with Betaferon and Avonex were analysed separately.

It was not possible to undertake an intention to treat analysis because the data were censored after discontinuation of treatment. In order to verify whether the observed treatment effect might be influenced by the selective loss of patients who discontinued treatment, basal data and clinical outcome of patients who interrupted their treatment during the observational period (drop-outs) and those who continued treatment (treated) were compared. For both groups,

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*Listed in the appendix

follow up data are referred to the actual period of treatment. The results of our analysis refer to the observational period from February 1996 to June 1999.

Statistical analysis

Comparisons based on continuous variables within groups were assessed by using the paired t test, and those between groups by using the unpaired t test. A χ^2 test was used to compare binary data. The log-rank test was used to compare Kaplan-Mayer survival curves. Results with probability (p) values less 0.05 were considered statistically significant.

RESULTS

In all, 1530 patients had been treated with IFNβ (869 with Betaferon and 661 with Avonex); 49 were excluded because data were inconsistent or unavailable. In the remaining 1481 patients (834 on Betaferon, 647 on Avonex), disease duration and age at entry were similar, while relapse frequency (1.60/year and 1.45/year) and EDSS (2.4 and 2.2) were significantly higher in the Betaferon group.

The mean (SD) treatment duration was 21.4 (11.5) months (range 0.5 to 52) for Betaferon, and 12.0 (7.2) months (range 0.5 to 51) for Avonex.

In the Betaferon group, 709 patients had been treated for one year, 503 for two years, and 238 for at least three years; in the Avonex group the corresponding values were 470 patients for one year, 148 for two years, and four for three years.

During the three years of observation, the number of drop-outs was significantly greater in the Betaferon group (total 41.1%: 15.1% within one year, 18% within two years, and 8% within three years) than in the Avonex group (total 15.3%: 10.2%, 4.9%, and 0.15% within one, two, and three years, respectively) (p<0.001). The percentage of patients who discontinued treatment for side effects (15.3% v 3.8%), disability progression (7.7% v 3.2%), and no consent (12.3% v 3.6%) was greater in the Betaferon group, but there was no significant difference in persistence of relapses (4.3% with Betaferon v 4.4% with Avonex).

Compared with pretreatment values, relapse frequency decreased significantly in both groups and this effect persisted over time; the reduction was greater in the Betaferon group than in the Avonex group; however, the number of relapse-free patients was similar in the two groups (table 1). No significant difference was found between Betaferon and Avonex groups in the proportion of improved, stable, or worsened patients or the EDSS changes.

Avonex was usually better tolerated than Betaferon: flu-like syndrome occurred in 58.2% and 62.0%, in the Betaferon and Avonex groups, respectively; local reactions in 33% and

8%; depression in 15% and 11%; and leucopenia in 17% and 6%.

The possibility that our results might be influenced by a selective loss of patients after treatment interruption was investigated by comparing baseline clinical characteristics and response to treatment of drop-outs and treated patients.

Drop-outs had more active disease than treated patients, showing a higher baseline relapse frequency (1.67 v 1.58 in Betaferon; 1.61 v 1.42 in Avonex) and EDSS (2.5 v 2.3 in Betaferon; 2.4 v 2.1 in Avonex) in both treatment groups. During the first two years of follow up, the relapse frequency was significantly higher in drop-outs than in the treated group (0.89 v 0.47 and 0.71 v 0.49 with Betaferon; 1.5 v 0.5 and 1.58 v 0.56 with Avonex, at one and two years, respectively), while the percentage of patients deteriorating was significantly higher in drop-outs at one year (16.2% v 6.4% with Betaferon; 22.7 v 9.9% with Avonex). Furthermore the proportion of relapse-free patients was lower in drop-outs than in treated patients in both groups (fig 1A, 1B).

DISCUSSION

The results of our study confirm the beneficial effect of IFNβ treatment in ambulatory patients with relapsing-remitting multiple sclerosis.[4–7] However, observational post-marketing studies such this have several obvious limitations. First, they cannot be randomised as both neurologists and patients are involved in therapeutic decisions. Second, an analysis by intent to treat cannot be done, as patients who discontinue treatment are not followed according to the same protocol. On the other hand, post-marketing studies mirror the impact of a new treatment in clinical practice better than randomised controlled trials, and may raise new questions that cannot be addressed in the latter.

In spite of the predefined inclusion criteria, the baseline characteristics of our patients were different between the two treatment groups, probably because several of the centres tended to select patients with a more severe course for Betaferon treatment. This selection bias precludes direct comparison between the two drugs. A more marked effect on relapse rate was observed in the Betaferon group. Whether this effect was related to differences in treatment schedule—as suggested by the results of two recent controlled prospective studies[8 9]—or to differences in the patients' baseline characteristics cannot be determined. However, both drugs significantly reduced relapse frequency and showed the same impact on the probability of remaining relapse-free. No effect on progression of disability was observed.

The extent of the decrease in relapse frequency was greater than reported in the pivotal phase III randomised controlled trials, which showing a reduction of 44%[10] and 50%[11 12] in

Table 1 Relapse frequency and numbers of relapse-free patients

	Betaferon			Avonex		
Time	No of patients	RF mean reduction (%)	Relapse-free patients (%)	No of patients	RF mean reduction (%)	Relapse-free patients (%)
0 to 6 months	834	−1.11* (68)	76.01	647	−0.80 (55)	71.4
0 to 12 months	709	−0.97* (60.4)	58.2	470	−0.80 (55)	55.3
0 to 18 months	612	−1* (63.7)	47.9	322	−0.84 (57.1)	44.7
0 to 24 months	503	−1.02* (64)	42.5	148	−0.83 (56)	39.2
0 to 30 months	378	−1.09 (69.7)	40.2	11	−0.69(47.6)	27.3
0 to 36 months	238	−1.10 (69.6)	36.9	4	−1.33 (50)	0

*Relapse frequency reduction was significantly greater in the Betaferon than in the Avonex group at six months (p<0.001), 12 and 18 months (p=0.01), and 24 months (p=0.02). The reduction was calculated on the actual basal relapse frequency in the patient subgroups at each time interval.
No significant difference was found between Betaferon and Avonex groups in the proportion of relapse-free patients.
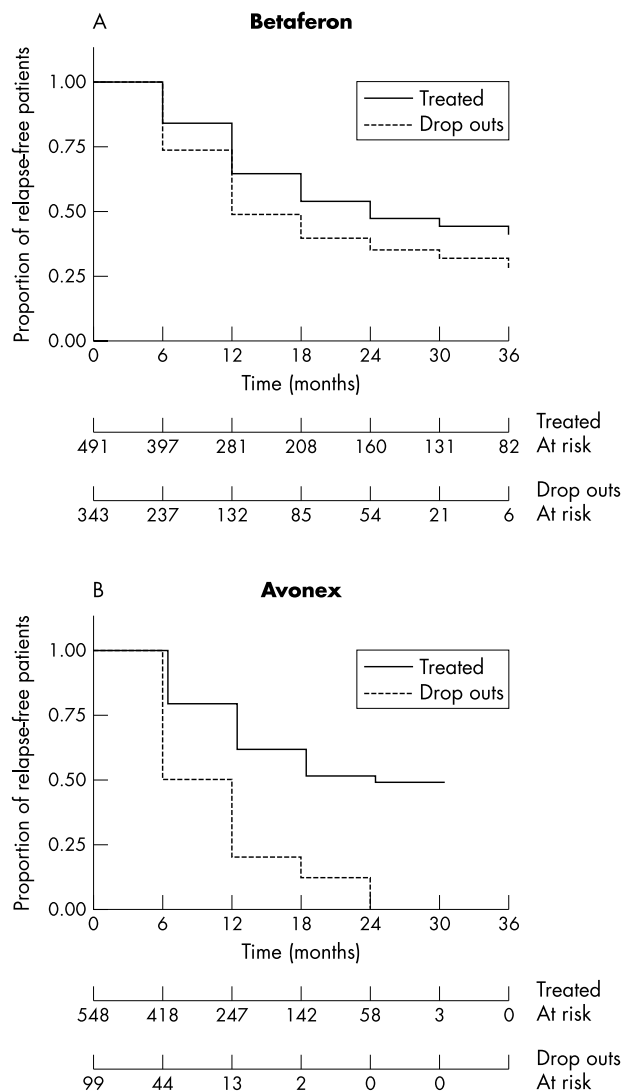RF, relapse frequency.

Figure 1 Kaplan-Meyer survival curve of relapse-free patients in treated v drop-out groups in patients treated with Betaferon (panel A) and Avonex (panel B). The proportion of relapse-free patients was lower in drop-outs than in treated patients (log-rank test, p<0.001 for both Betaferon and Avonex).

comparison with pretreatment values after two years. This may partly be explained by different selection criteria, but more probably by a selective loss of patients who discontinued treatment. Our analysis clearly shows that drop-outs had a worse response to treatment than patients who continued on treatment, thus favouring selective retention of responders to treatment.

The possibility cannot be ruled out that differences in reporting relapse numbers (historically in the last two pretreatment years, and prospectively during treatment)—which this study shares with randomised controlled trials—might have contributed to the observed results.

The drop-out rate was significantly greater in the Betaferon group than in the Avonex group. Differences in baseline disease activity and follow up duration may have contributed to the increased drop-out rate in the Betaferon group.

The problem of selecting patients who are most likely to benefit from this treatment remains an unresolved but important issue. A detailed analysis of the clinical characteristics of responders and non-responders is expected to help

define the criteria for selecting the best candidates to IFNβ treatment.

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APPENDIX
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