Interferon beta-1a in relapsing-remitting multiple sclerosis

Lance Blumhardt

The accumulated results from multiple trials have unequivocally demonstrated beneficial effects of interferon beta-1a on disease activity in relapsing-remitting multiple sclerosis, both for clinical and magnetic resonance endpoints. New data suggest that low doses administered once weekly are relatively ineffective and that higher, more frequent doses are required for optimal benefit.

The first report of the beneficial effects of a recombinant interferon beta in multiple sclerosis (MS) (IFNB Multiple Sclerosis Study Group, 1993) was, perhaps inevitably, followed by controversy and debate. Criticisms were directed at the trial methodology, the apparent lack of effect on disability progression and the clinical usefulness or 'cost-effectiveness' (Broderick and Samaha, 1994; Klapper, 1994; Longstreth and Franklin, 1994; McDonald and McDonald, 1994; Metz et al, 1994; Compston, 1995; Mumford, 1996). The MS Collaborative Research Group (MSCRG) study (Avonex, Biogen; Jacobs et al, 1996) reported a similar (albeit delayed) effect on relapses, a less convincing effect on magnetic resonance imaging (MRI) parameters and, rather surprisingly, an apparent effect on disability progression, despite the enrolment of only mildly impaired patients.

Subsequently, two important trials of recombinant interferon beta-1a (rIFNB-1a) for active relapsing-remitting MS (RRMS) have been reported (Freedman et al, 1998; PRISMS, 1998).

The most recent report, from the PRISMS (Prevention of Relapses and Disability by Interferon-beta 1a Subcutaneously in Multiple Sclerosis) study (1998), addresses many of the concerns raised about the results of previous trials and confirms the significant benefits of rIFNB-1a for patients with active RRMS, at least within the 2 years of a clinical trial. The accumulated evidence for efficacy on relapse reduction and in-trial disability now supports the widespread use of interferons across Europe, Australasia and North America for patients with RRMS of above-average activity. Data from trials with multi-dose regimens have also confirmed the significant dose–response effects of rIFNB-1a which have important practical implications for patient management.

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INTERFERON BETA-1A

rIFNB-1a has the same amino acid sequence and carbohydrate side-chain as human IFNB. After intravenous administration in healthy individuals, rIFNB-1a shows a sharp multi-exponential decline, with serum levels proportional to the time elapsed after the injection. The initial half-life is of the order of minutes and the terminal half-life is several hours. Serum levels, although low, are still measurable 12–24 hours after injection, whether administered subcutaneously or intramuscularly.

Subcutaneous and intramuscular administration of the Rebif® (Ares-Serono, Geneva) preparation of rIFNB-1a produces equivalent exposure to IFNB. After a single dose, intracellular and serum activity of 2-5A synthetase and serum concentrations of β2-microglobulin and neopterin increase within 24 hours and start to decline within 2 days. Intramuscular or subcutaneous administration produces equivalent responses. After repeated subcutaneous administration every 48 hours (or three times weekly), the biological responses remain elevated with no signs of tolerance. IFNB-1a is mainly metabolized and excreted by the liver and the kidneys.

INTERFERON BETA-1A IN RRMS

MSCRG trial

Jacobs et al (1996) enrolled 301 mildly impaired patients (Expanded Disability Status Scale (EDSS) 1.0–3.5) with RRMS who were treated with placebo or low dose rIFNB-1a (30 μg weekly) by once a week intramuscular injection for 1–2 years. Patients with two or more relapses in the previous 3 years were enrolled. Clinical assessments and MRI with and without gadolinium enhancement were carried out at 6-monthly intervals. Of the 301 patients, 287 (95%) completed 1 year, but only 172 (57%) completed 2 years of treatment.

Positive effects on the outcome measure of 1.0 EDSS increase confirmed at 6 months were reported. Compared with placebo-treated patients, IFNB-1a conferred a 9% reduction of relapses at 1 year and an 18% reduction at 2 years. The MRI data were less impressive than for the other interferon trials with a significant improvement in the gadolinium-enhanced lesion volumes for the rIFNB-1a treated group at 1 year, but (inconsistently) not at the end of the trial at 2 years. In contrast to the reported effects of IFNB-1b in the Betaseron trial (IFNB Multiple Sclerosis Study Group, 1993), there was no effect on the lesion load on T2-weighted images.

It has been pointed out that the positive effects in this trial mainly occurred at the impairment end of the EDSS scale (i.e. effectively for non-disabled patients) and could be largely, if not entirely, accounted for by the unexpectedly poor course experienced by the patients allocated to placebo (Noseworthy, 1997). It is indeed difficult to understand why the placebo patients in this trial behaved so eccentrically compared with those in natural history studies and in all other trials (Liu et al, 1999; Noseworthy, 1997).

The PRISMS study

The PRISMS study (1998) was a double-blind, randomized, placebo-controlled study in which 560 patients were enrolled in 22 centres in nine countries. The study included both impaired (EDSS 0–3.5) and truly disabled patients (EDSS > 3.5). Patients were randomized to receive subcutaneous rIFNB-1a (Rebif) or placebo three times weekly for 2 years.

In the light of earlier evidence of a dose effect of beta-interferons from dose-ranging studies (Johnson et al, 1990), relatively intensive regimens of 66 μg and 132 μg weekly were chosen. As the bioavailability of rINFB-1a is comparable after subcutaneous and intramuscular injection, the more convenient subcutaneous route was selected. The primary endpoint was the number of clinical relapses. The study also determined the proportion of patients who remained free of attacks, the time to the first exacerbation, progression by 1.0 EDSS point confirmed at 3 months, change in the area under the disability/time plots, requirement for steroids and hospitalization, ambulation index, disease activity and burden of disease on MRI.

Patients were included if they were aged 18–50 years with a diagnosis of RRMS for at least 12 months and an EDSS of between 0–5. They were required to be mobile without assistance and to have above average relapse rates (at least two relapses in the previous 2 years), but with none in the 2 months before study entry.

Neurological examinations were performed quarterly and all patients underwent MRI scans twice a year. After 2 years, clinical data were available on 533 patients (95%) of the 560 enrolled and 502 (90%) completed 2 years of treatment. Data from 98% of the cohort were available for an intention-to-treat analysis.

Both doses of rIFNB-1a demonstrated significant efficacy for each of the major categories of outcome measures: relapse rate, disability progression, MRI disease activity and burden of disease. The trends invariably favoured the high dose. Both the total number of relapses and moderate and severe relapses were significantly reduced. Patients on placebo had an average of 0.99 moderate or severe relapses during the 2 years compared with 0.71 in patients on 66 μg weekly and 0.62 in those on 132 μg weekly (*Table 1*). At the end of the trial 27% and 32% of patients on active treatment (66 μg and 132 μg respectively) were relapse free compared with 16% of those on placebo.

The mean number of admissions to hospital as a result of MS-related problems was decreased in patients on both doses and significantly for those on 132 μg weekly (0.25 and 0.38 admissions *vs* 0.48 for placebo). Reduced use of steroids was

TABLE 1.
Major clinical endpoints in the PRISMS trial

	Placebo	IFN beta 1a 66 μg weekly	IFN beta 1a 132 μg weekly
Relapses per patient			
Mean	2.56	1.82*	1.73*
% reduction *vs* placebo on observed means		29%	32%
% reduction *vs* placebo (95% CI)		27% (14–39)	33% (21–44)
% patients relapse-free over 1 year	22%	37%*	45%*
% patient relapse-free over 2 years	16%	27%†	32%*
Odds ratio (none *vs* any) compared to placebo (95% CI)	1.0	2.01† (1.21–3.35)	2.57* (1.56–4.25)
Moderate or severe relapses			
Mean	0.99	0.71*	0.62*
% patients with 0	42%	61%	62%
% patients with 1–2	47%	32%	32%
% patients with ≥3	11%	7%	6%
Odds ratio (none *vs* any) compared to placebo (95% CI)	1.0	2.13* (1.41–3.21)	2.23* (1.47–3.37)
Time to confirmed progression in disability			
First quartile, time to progression (months)	11.9	18.5 †	21.3 †
Risk ratio compared to placebo (95% CI)	1.0	0.68† (0.48–0.98)	0.62† (0.43–0.91)
High baseline EDSS (>3.5) cohort (months)	7.3	7.5 (ns)	21.3 *
Risk ratio compared to placebo (95% CI)	1.0	0.75 (ns) (0.35–1.56)	0.42 (0.18–0.99)

CI = confidence interval; EDSS = Expanded Disability Status Scale. From PRISMS (1998).
*P<0.005; †P<0.05; ns = not significant

seen with both doses: patients on placebo received 1.39 pulses compared with 0.97 pulses in 2 years for those on 66 μg weekly (a 30% reduction), and 0.75 pulses for those on 132 μg weekly (46% reduction, $P<0.005$). The 66 μg dose delayed the first in-trial relapse by 3 months and 132 μg by 5 months compared with placebo. The time to sustained progression (an increase of 1.0 EDSS points sustained for 3 months) was prolonged by 6.6 and 9.4 months respectively (first quartile).

For most endpoints, the more disabled patients in the trial (entry EDSS >3.5) responded less well to the low dose and required the high dose to achieve similar benefits to the patients with mainly neurological impairment (i.e. EDSS 3.5 or below). The mean increase in EDSS seen in the placebo arm was halved or more by both active doses. There was a 77% and 86% reduction in the total disability experience (a combination of both transient and permanent disability changes) for the 22 and 44 μg doses respectively, as reflected by the integrated area under the disability (EDSS) time plots (Liu et al, 1999).

Active treatment was also associated with significant decreases in the mean number of active (new or enlarging) lesions on T2-weighted MR images and in the burden of disease (total volume of abnormal tissue on MRI).

The treatment was well tolerated with a safety profile that appeared to be more benign than IFNB-1b, particularly in terms of local injection site reactions, incidence of neutralizing antibodies (NABs) and influenza-like symptoms. The incidence of serious adverse events did not differ between the low and high doses. The presence of NABs on at least one occasion during the 2-year trial occurred in 16–18% of patients (persistently in about 6%), but had no significant effect on efficacy as judged by any primary or secondary endpoint. Furthermore there was a significantly lower incidence of NABs on the 132 μg weekly dose, compared with the 66 μg weekly dose, possibly due to the phenomenon of high zone tolerance. The use of three depression scales showed comparable scores for all three arms of the trial with no evidence to support an increased risk of depression or suicide on active treatment.

Once Weekly Interferon in MS Trial (OWIMS)

This randomized, double-blind, placebo-controlled study recruited 293 patients from 11 centres in five countries (Freedman et al, 1998). Patients were randomized to receive either placebo, IFNB-1a 22 or 44 μg, once weekly for 12 months by subcutaneous injection. Of the 293 patients, 287 (98%) completed 24 weeks of treatment and 269 (92%) completed 48 weeks. Combined active lesions per scan were reduced compared with placebo by both once weekly doses (median 29.6% reduction for 22 μg (not significant; ns) and 53.5% for 44 μg ($P<0.01$). The percentage of scans with active lesions were 50% for placebo, 45% (ns) for 22 μg and 33% for 44 μg ($P<0.05$) once weekly. The reduction of mean exacerbation rates at the 1-year endpoint were 0% for IFNB-1a 22 μg and 19% for IFNB-1a 44 μg once weekly.

DISCUSSION

rIFNB-1a has beneficial effects in the treatment of active RRMS as shown by both the clinical and MRI outcome measures. Active treatment showed consistently significant effects across all primary and secondary outcome measures and invariably favoured the higher dose. The MRI results from the PRISMS study show that this treatment significantly reduces overall disease activity. These benefits are stable and persistent and can be considered strong objective evidence that the positive clinical results have been achieved as a result of direct action against the primary (i.e. inflammatory) disease process.

There is an undoubted improvement in the quality of life of patients on treatment with rIFNB-1a: on the one hand, there are markedly lower hospitalization rates, a reduced need for steroids for exacerbations and more than 75% reduction in on-trial disability, and on the other, a very low incidence of clinically relevant side effects. rIFNB-1a is very well tolerated at both doses.

Although it remains to be confirmed that treatment-related reductions in relapses actually lead to a reduction in long-term disability, we do know from well-conducted epidemiological studies that the relapse frequency early in the disease correlates with long-term disability outcome (Weinshenker et al, 1989). The inflammatory processes which underlie acute episodes of MS are also significantly correlated with pathological evidence of axonal transection and irreversible axonal loss (Trapp et al, 1998). Reductions in axonal density are a feature of plaques in the earliest stages of the disease and can be severe (up to 80% loss) even in 'clinically silent' MS (Mews et al, 1998).

Cerebral and spinal atrophy, which at least in part reflects irreversible axonal loss, are features of the early disease course (Liu et al, 1999). From these observations it could be predicted that a reduction in inflammatory disease activity on MRI, as well as reduced attack frequency and the disability associated with relapses, are likely to translate into reductions of permanent neurological disability in the long term. The recent reconfirmation of irreversible axonal damage in acute inflammatory lesions has lead to the conclusion

that aggressive high-dose treatment with neuroprotective agents (e.g. rIFNB) should be instituted at the earliest opportunity (Trapp et al, 1998), and consensus statements that immunomodulators such as IFNB or copolymer 1 should be started as soon as the diagnosis is made (Scrip, 1998).

Evidence from both PRISMS and OWIMS confirms the dose–response relationship for both clinical and MRI data which has important implications for managing patients. The similarity of the baseline characteristics of MSCRG, PRISMS and OWIMS patients and the pharmacokinetic properties of the two formulations of rIFNB-1a (Munafo et al, 1998) allows a meta-study comparison which clearly shows the size of the effects of different doses for several clinical and MRI outcome measures, including relapse rate reduction (*Figure 1*). The PRISMS results consistently favour the 44 μg dose for all outcome parameters.

As rIFNB-1a has a good safety profile and there is no evidence that adverse effects are more problematic at the doses used in the PRISMS study, the risk–benefit ratio is clearly optimal for 'high' dose, i.e. 66 or 132 μg weekly. For patients at significantly increased risk for disease progression (EDSS>3.5) in the PRISMS trial, optimal treatment was 132 μg weekly. This dose is now licensed and widely prescribed for patients in Canada and many European countries.

The results of early treatment of patients with monosymptomatic syndromes and abnormal MRI (at high risk of developing clinical MS in the next 5 years) will soon be available, but it is likely that treatment with IFNB, introduced as early as possible in the disease course, will have long-term benefits in slowing or reducing the risk of worsening disability associated with high levels of disease activity. The results of two current early treatment trials, as well as long-term follow-up data on disability outcomes, are eagerly awaited. **HM**

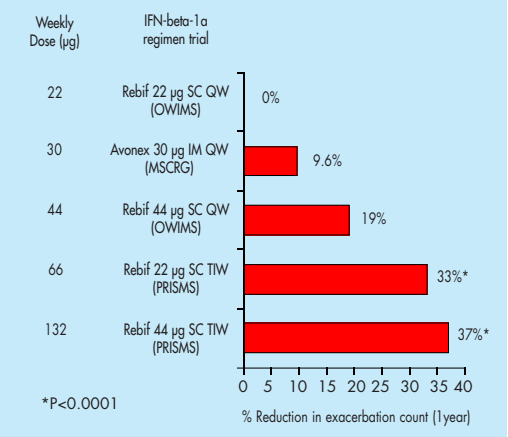

Figure 1. Effect on relapse rate of increasing weekly doses of IFNB-1a in the first year of three different trials.

Conflict of interest: Professor Blumhardt is an investigator in the PRISMS trial and has received hospitality from Biogen and Ares-Serono and fees for lectures and consultancies from Ares-Serono.

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KEY POINTS

- Significant benefits of interferon beta-1a for active relapsing-remitting multiple sclerosis (RRMS) have been shown in the PRISMS study for all major outcome domains (relapses, disability and magnetic resonance imaging).
- Emerging evidence supports important dose–response effects of interferon beta.
- Low weekly doses have less consistent benefits.
- Higher weekly dosese appear optimal for treatment of active RRMS, particularly for patients with an Expanded Disability Status Scale score >3.5.
- The risk–benefit ratio is optimal for the highest available dose of interferon beta-1a.