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## EDITORIAL

# Treatment recommendations for interferon-β in multiple sclerosis

Interferons (IFNs), first recognised because of their antiviral properties,[1] are a key defence mechanism involved in the control of virus infections. They are small proteins separated by nucleated cells in response to viral infection or other appropriate stimuli, and are thought to act principally on other cells in their immediate vicinity. They are divided into two types: type 1 comprises IFN-α and IFN-β, whereas type 2 is IFN-γ.

Initially IFNs were considered for the treatment of multiple sclerosis in the context of presumed viral pathogenesis. Because there was some evidence for a decrease in the concentration of IFN-γ in the CSF of patients with multiple sclerosis, a pilot study was performed to assess its safety and efficacy. This trial was prematurely terminated because of an unexpected increase in relapse rate.[2] This adverse result focused attention on the effects of type 1 IFNs because they were found to have some immunomodulatory effects that were opposite to those of IFN-γ. IFN-α and IFN-β use the same receptor, have comparable effects, and a high degree of homology. Some smaller studies suggested efficacy for intrathecally, subcutaneously, and intramuscularly administered type 1 IFN in decreasing the frequency of exacerbations in relapsing-remitting multiple sclerosis. Therefore, further studies were performed: subsequently the availability of recombinant IFN led to the abandonment of natural IFN.

Research programmes, started over a decade ago, have now resulted in the regulatory approval (in the USA, Europe, or both) of three preparations of IFN-β, these being, in alphabetical order, R/Avonex (IFN-β-1a produced by Biogen), R/Betaseron/Betaferon (IFN-β-1b produced by Berlex/Schering), and R/Rebif (IFN-β-1a produced by Ares Serono).

The clinical evidence that has led to regulatory approval and the scientific debate surrounding it is reviewed here. It is important to realise that it is difficult to compare the various preparations. Their specific activity differs (higher for IFN-β-1a than for IFN-β-1b) and there is considerable controversy about the effects of different routes of administration and different dosage schedules on the biological effects of IFN-β.

### Review of evidence
Currently applied IFN-β products are made by recombinant DNA technology in tissue culture and are highly purified before use. IFN-β-1a is a glycosylated, recombinant mammalian cell product, with an amino acid sequence identical to that of natural IFN-β. IFN-β-1b is a non-glycosylated recombinant bacterial cell product in which serine is substituted for cysteine at position 17.

INTERFERON-β-1a
Two forms of IFN-β-1a were subjected to investigation in large clinical trials: R/Avonex and R/Rebif

R/Avonex was tested in a trial involving 301 patients with relapsing multiple sclerosis and mild to moderate neurological impairment (baseline EDSS 1.0–3.5). Treatment consisted of weekly intramuscular injections (6 MIU (30 µg) or placebo) for up to 2 years. The principal outcome measure was the length of time to progression of disability, defined as a worsening from baseline of at least 1.0 points on the EDSS that persisted for at least 6 months. The study was prematurely terminated when it was recognised that the dropout rate was less than anticipated. At the time the trial was stopped 57% of enrolled patients had completed 2 years, and 77% had been followed up for 18 months. Despite this early cessation, patients treated with IFN-β-1a were significantly less likely to reach the primary outcome, the probability being about 21% in the treatment group and about 33% in the placebo group for those who completed 2 years of therapy.[3] An 18% reduction in exacerbations was seen for the treated group, and those patients who completed 2 years had one third fewer exacerbations. The early termination meant that the difference between the proportions of patients who had progressed in the actively treated group and the placebo group did not reach statistical significance (18/83 on IFN-β and 29/87 on placebo respectively).[4] The treatment effect was supported by a reduction of gadolinium enhancement and new or enlarging T2 lesions on annual MRI; a significant difference between the treatment groups, however, was not found for the total T2 brain lesion load.[5]

The clinical significance of the beneficial effect of IFN-β-1a on progression of disease at the lower EDSS scores has been supported by the findings of a post hoc statistical analysis of data on other disability outcomes obtained in this study.[6] Sensitivity calculations indicated that the primary outcome parameter was robust to changes in definitions of EDSS progression and that the proportion of patients progressing to EDSS milestones of 4.0 and 6.0 was significantly lower in the patients treated with IFN although numbers were small.

R/Rebif was investigated in one large published study, in which 560 patients with active relapsing-remitting disease and mild to moderate disability (EDSS 0.0–5.0) who were randomised to treatment with IFN-β-1a (6 MIU (22 µg) or 12 MIU (44 µg)) or placebo, given subcutaneously three

times a week for 2 years.[7] The primary end point for this study was the relapse rate. At the end of the study 95% of patient data were available for analysis. The results showed that, compared with placebo, IFN-β-1a significantly decreased the number (by 27% and 33% in the 22 µg and 44 µg groups respectively) and severity of exacerbations, increased the time to first and second relapse, and increased the percentage of patients who were relapse free during the study. In addition, IFN-β-1a prolonged the time to confirmed progression as measured by EDSS scores (1.0 point confirmed at 3 months). Furthermore, there was a significant reduction in the disease activity on MRI (gadolinium enhancing lesions, new or enlarging T2 lesions) as well as on total T2 lesion load in patients receiving active treatment compared with those given placebo. Over the 2 years the placebo group showed an accumulation of about 11% in lesion load, whereas there was a decrease of about 1% among patients receiving 22 µg, and a decrease of almost 4% in the 44 µg group.

It was reported that patients with higher disability at baseline (EDSS 3.5 or higher) showed better response to the higher dose of IFN-β-1a, but is unclear how this finding should be interpreted as it is based on post hoc analyses only.[8]

### INTERFERON-β-1b

Interferon-β-1b was initially tested in a multicentre United States trial involving 372 patients with relapsing-remitting multiple sclerosis and mild to moderate disability (EDSS up to 5.5). Treatment consisted of either 8 MIU (250 µg) or 1.6 MIU (50 µg) of IFN-β-1b or placebo given by subcutaneous injection every other day. The primary outcome was the relapse rate. Compared with placebo, treatment with the higher dose reduced the relapse rate by 31%, increased the time to first relapse and the proportion of patients who were relapse free, and reduced by about 50% the number of patients who had moderate and severe relapses.[9] [10] There was, however, no significant difference in changes in EDSS scores between treatment groups. The patients in the placebo group had a mean increase of 17% in the total T2 lesion load on brain MRI at 3 years, compared with a mean decrease of 6% in those on high dose IFN-β-1b.[11] In addition there was a significant reduction in disease activity as measured by the analysis of new or enlarging lesions on serial MRI.

A second multicentre trial of IFN-β-1b was recently completed in Europe, comprising 718 patients with secondary progressive multiple sclerosis (EDSS between 3.0 and 6.5, inclusive) who had been clinically active in the 2 years preceding the study (defined as either two relapses or deterioration of at least 1.0 EDSS point.[12] Treatment consisted of either 8 MIU IFN-β-1b or placebo subcutaneously on alternate days over 3 years. The primary outcome was the time to confirmed neurological deterioration defined as a 1.0 point increase on EDSS present for at least 3 months. In this study for EDSS scores of 6.0 and higher a change of 0.5 point was considered to be equal to 1.0 point for scores lower than 6.0, because changes at these levels are both clinically relevant and easily discernable and because the number of years patients stay at these levels is almost doubled according to natural history data.[13] [14] A prospectively planned interim analysis for efficacy was performed after all patients completed at least 24 months of treatment. An α level of 0.0133 was predetermined for the intention to treat analysis of the primary end point. Based on this interim analysis the independent Advisory Board recommended that the study be stopped because there was a highly significant difference in the primary end point favouring active treatment (p=0.0008). The delay of progression was between 9 and 12 months. Post hoc analyses showed that this effect was seen in both patients with and without superimposed relapses before or during the study and that it was consistent across all baseline EDSS levels studied. Significant reductions in time to becoming wheelchair bound (EDSS 7.0), number of steroid courses given, and number of multiple sclerosis related admissions to hospital were also found. Effects on relapse rate and on MRI were consistent with findings in the relapsing-remitting population. Whereas the mean T2 lesion volume increased by about 8% at 2 years in the placebo group, the mean lesion load in the active treatment group decreased by about 5%. In a subcohort of patients (n=125) a marked and significant reduction of new and enhancing lesions could be demonstrated for the initial 6 months of study and also between months 19 and 24.

It can be concluded that all of these studies were successful in meeting their predefined primary outcome measures as well as additional outcome measures with high levels of significance, but that according to many experts the clinical impact of interferon-β for the individual patient should be classified as modest.

### SIDE EFFECTS ASSOCIATED WITH TREATMENT WITH INTERFERON-β

Treatment with IFN-β is usually reasonably well tolerated. Side effects partially depend on the dosage used and on the route of administration. For all preparations mentioned patients can experience flu-like reactions such as fever, myalgia, chills, and general discomfort for 24 to 48 hours after each injection, especially during the first months of treatment. These symptoms, however, decrease over time, and only a few patients continue to experience them. Management of these symptoms requires simple practical techniques such as dose escalation, bedtime dosing, and use of paracetamol or ibuprofen. The frequency of injection site reactions (redness, tenderness, swelling) is also initially high, almost exclusively in those patients in whom treatment is given by subcutaneous injection. Injection site necrosis occurs in about 5% of patients in this group. Some patients with multiple sclerosis report an initial worsening of symptoms during the first weeks of IFN therapy;[15] in patients with progressive disease an increase in spasticity has been reported.[12] [16] IFN-β can also cause increases in liver enzymes, lymphopenia, or anaemia.

Overall, in these studies, the percentage of patients discontinuing treatment because of serious or untolerable side effects was low.

### WHO SHOULD BE TREATED WITH INTERFERON-β?

In the 1994 report of the Quality Standards Subcommittee of the American Academy of Neurology it was recommended that IFN-β be prescribed for patients with definite multiple sclerosis, who have active relapsing-remitting disease (at least two acute exacerbations during the previous 2 years), are ambulatory (EDSS 5.5 or lower), and are aged between 18 and 50 years.[17] Class I evidence (evidence from randomised, controlled clinical trials) exists for these patients and expert consensus suggests that IFN-β may be helpful. These criteria have subsequently been adopted in many other countries, with minor adaptations especially regarding the age limits, which are judged to be derived from standard clinical trial procedures rather than representing meaningful biological differences. The more recent evidence supporting the efficacy of IFN-β in the relapsing-remitting patient group has somewhat loosened the criterion that requires at least two exacerbations in the past 2 years as in the study with IFN-β-1a (R/Avonex) patients with two exacerbations in 3 years were included.

Recently, class I evidence has also become available for patients with active secondary progressive multiple sclerosis (at least 2 exacerbations superimposed on continuous progression during the previous 2 years or progression of at least 1.0 EDSS point in that time) and EDSS scores up to 6.5 (inclusive). Especially if the results of ongoing clinical trials with IFN-β-1a in this patient category support the recent findings, then there is a very strong case to expand treatment recommendations to include this population of patients wth multiple sclerosis.

It is not known what the effect of IFN-β is on patients with relapsing-remitting or secondary progressive multiple sclerosis and EDSS scores higher than 6.5 (there is no evidence as to whether the likelihood of more pronounced side effects should be considered as a treatment limiting factor in this disabled population) or to patients with primary progressive disease (clinical trials are ongoing in this population that clearly represents one end of the range of multiple sclerosis; for review see Thompson *et al*[18]).

One very important question is how early in the course of the disease should treatment with IFN-β be initiated? For those patients with a single demyelinating episode who, based on MRI findings, have a high likelihood of progressing to definite multiple sclerosis,[19] there will be class I evidence available within the next year or so as two large, multicentre trials are underway to determine whether treatment with IFN-β-1a in these patients is associated with lower conversion rates to clinically definite multiple sclerosis.[20]

Class I evidence, however, will not be available in the near future for the large population of patients who have definite multiple sclerosis but—at this moment—do not show obvious clinical signs of disease activity. On the one hand, about 20% of patients have relatively benign disease and they probably do not require disease modifying therapy.[21] On the other hand, treatment should not be postponed until after persistent neurological deficits have occurred, as none of the currently available therapies for multiple sclerosis reverses fixed deficits.

At this moment, there is no consensus as to whether MRI can play a part in selecting patients for IFN-β treatment. Serial MRI studies have demonstrated disease activity, manifested as new lesions, in the brain in the early clinical stages of multiple sclerosis and during periods when the disease is clinically quiescent. More recently attention has focused on measures of cerebral and spinal cord atrophy which can develop early in the disease course and might correlate more strongly with clinical progression than do enhancing or T2 weighted abnormalities.[22–24] Atrophy seems to be associated with axonal loss, which is increasingly being recognised as the most important feature leading to irreversible deficit.[25–27] The findings of Losseff *et al* have been extended by Rudick *et al* who reported on post hoc analyses of MRI data of a subgroup of the patients in the original IFN-β-1a (R/Avonex) clinical trial.[28] Seventy patients were treated with IFN-β-1a and 70 with placebo, the groups being well balanced for relevant demographic factors. Even though these patients had a mean EDSS score of only 2.3, they showed considerable brain atrophy (significantly reduced brain parenchymal fraction) in comparison with controls. During the trial a drug treatment effect as measured with this brain parenchymal fraction was found: in the second year (though not over the 2 year study period) the treatment group developed significantly less cerebral atrophy than the patients on placebo (p=0.03). Even though these data are very important in that they suggest a treatment effect on a clinically relevant measure in patients with early disease, it should be re-emphasised here that MRI, although providing an objective, sensitive, and quantitative assessment of evolving pathology in multiple sclerosis, has not yet conclusively been demonstrated to be predictive of long term clinical outcome and that treatment with IFN is only of modest clinical benefit for patients, while being associated with extremely high costs.

## Unresolved issues

An important consideration is the propensity for IFN-β preparations to stimulate the formation of neutralising antibodies (NABs), which might depend on several variables—for example, dosage administered, route of administration, frequency of administration, and type of INF-β used. The rate of NAB production seems to be less in the IFN-β-1a trials (about 15–20% compared with about 25%-35% for IFN-β-1b) but the fact that that different assays were used has to be taken into account. Initially there were reports that development of NABs was associated with reduced effectiveness, but concerns regarding the effects of NABs have been somewhat appeased by reanalysis of the initial correlations and recent evidence that they may disappear during long term treatment. Because of the uncertain validity of the assay of NAB and the limited study of their consequences, clinical decisions based on the presence or absence of NAB cannot yet be made with confidence.[29 30]

It is not known whether treatment with IFN-β should be discontinued at some point in time. Evidence so far indicates that there is no diminution of treatment effect during prolonged treatment up to 2–3 years and therefore interrupting treatment is only advocated for those patients who clearly do not respond, have intolerable adverse events, or who wish to become pregnant.

## Conclusion

The goal of therapy in patients with multiple sclerosis is to prevent relapses and progressive worsening of the disease, which should result in more time to participate in social and physical activities, and an improved quality of life. Documentation of therapeutic advances in multiple sclerosis is dependent on large, randomised, controlled clinical trials because of the highly variable and unpredictable course of the disease and the difficulty in precisely measuring neurological disability. Even though it is obvious that IFN-β does not represent a cure for multiple sclerosis, it has been proved capable of reducing the frequency of exacerbations and slowing the accumulation of disability. Therefore, treatment with either IFN-β-1a or IFN-β-1b should now be recommended for ambulant patients with clinically active relapsing-remitting disease, and treatment with IFN-β-1b may now be considered for ambulant patients with clinically active secondary progressive disease. For patients with secondary progressive disease, the recommendation to initiate treatment is currently less strong than that for those with relapsing-remitting disease, because at present it is based on only one clinical trial. The recommendation for secondary progressive disease should be reviewed as the results of further trials become available.

Neurologists are being confronted with a situation in which they have to explain to their patients that efficacy data for IFN-β are quite robust, but that the magnitude of the effect on subclinical measures (MRI) is much more pronounced than is apparent on clinical measures, and that the long term consequences of these findings are largely unknown. It is extemely important that before long term therapy is implemented, counselling about realistic objectives, both regarding efficacy and side effects, takes place as overly optimistic expectations may complicate treatment and that during the first months of treatment education

and support (preferably by multiple sclerosis nurse specialists) is available to guarantee an optimal injection technique and management of side effects.

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## EDITORIAL COMMENTARY

# Prognosis and recovery in ischaemic and traumatic spinal cord injury

The paper by Iseli *et al*[1] (this issue, pp 567–71) reflects the current interest in diagnostic techniques which could supplement the neurological examination in diagnosing a spinal cord injury, monitoring recovery, and predicting the final outcome.

A detailed neurological examination is still the most accurate assessment tool and the best predictor of the final outcome in patients with spinal cord injury.[2][3] The American Spinal Injury Association (ASIA) protocol with its motor and sensory scores is the standardised instrument of this sort, internationally accepted and widely used.[4] Over the past few years there has been an increased interest in developing additional and more objective instruments for assessing the level and severity of the spinal cord lesion. Curt and Dietz, coauthors of this issue's article, have published several interesting papers examining the relevance of somatosensory evoked potentials, motor evoked potentials, and ASIA motor and sensory scores in predicting the functional outcome in patients with spinal cord injury. The same authors gave a very compehensive scientific review of electrophysiological recordings and their predictive value in patients with SCI.[5]

The originality of this issue's paper is that in it the authors are comparing two groups of patients with different aetiology and pathophysiology of the lesion, one ischaemic and the other traumatic. Using ASIA clinical protocol, tibial and pudendal somatosensory evoked potentials (SSEPs), and ambulation capacity they compare the degree of neurological and functional recovery between the two patient groups. Using multiple regression analysis they try to determine the best prognostic factors for the functional recovery for each of the groups.

The results show many similarities between the groups. The authors suggest that the few differences may be due