Abstract Interferon beta (IFN-β) reduces exacerbation rates in patients with relapsing-remitting multiple sclerosis (MS), but some patients do not respond to treatment. Recent studies have shown a clear dose-response effect on the reduction of exacerbation rates, and on burden of disease accumulation and active lesion frequency seen on MRI. During treatment with 8 MIU IFN-β we noticed a 30% rate of treatment failure. We then treated non-responders with 12 MIU IFN-β and observed significant improvement in the clinical signs of disease activity. In order to compare the efficacy of two different doses of IFN-β-1b, a multicenter study for the optimization of interferon for MS (OPTIMS) has been organized. The design of the study is presented here.

Key words Multiple sclerosis • Interferon beta • High-dose IFN treatment • Non-responders

Interferon-beta (IFN-β) reduces exacerbation rate in patients with multiple sclerosis (MS) by 30% when compared to placebo in controlled trials [1] and by over 50% when compared to the rate before starting treatment [2], but some patients do not respond to treatment. A poor response has been ascribed to the production of anti-IFN neutralizing antibodies (NAB), but the relationship between NAB and clinical response is still controversial [3, 4]. Another reason for treatment failure may be inadequate dosage. The standard IFN-β-1b (Betaferon) dose of 8 million international units (MIU) on alternate days is probably not the maximum effective dose. This was shown by the IFN-β-1b dose-finding study [5] in which patients were treated with increasing doses from 0.8 to 16 MIU, and a dose-related trend of therapeutic effect was noted. Exacerbation rate decreased by 20%-30% from placebo in patients treated with 8 MIU, and by 100% (no relapses in 6 months) in those treated with 16 MIU. Unfortunately, such a high dose was not well tolerated.

Several recent clinical-MRI studies have also demonstrated a dose response curve for IFN-β effects [6, 7]. A clear dose-response trend for MRI outcome measures was demonstrated by the PRISMS study [8], which directly compared 6 to 12 MIU IFN-β-1a three-times per week. The extension of the study to a follow-up of 4 years demonstrated that the 12 MIU dose brought about a significantly greater reduction in the active lesion frequency. In the OWIMS study [9], IFN-β-1a was given in a single weekly dose of 22 or 44 µg compared to placebo. In comparison with the PRISMS study in which higher doses of INF-β-1a were used, the OWIMS study found a definite dose-response effect on the MRI burden of disease accumulation, on the frequency of active lesions, and on clinical grounds. With the weekly dose, there was no significant reduction of relapse rate at the first year of study, but when it was given three times per week, or as 8 MIU on alternate days, there was a 30%-40% reduction in the relapse rate.

Larger doses may also be more useful for certain subtypes of patients. For example, the PRISMS study showed that patients with a more severe baseline disability, having an
expanded disability status scale (EDSS) score over 3.0, did not show slower disease progression with doses as high as 22 µg three-times per week, but did so with higher doses. On the other hand, high IFN doses may reduce patients' tolerance and compliance: doses of 16 MIU IFN-β-1b were poorly tolerated by MS patients treated on alternate days for 6 months, and 4 of 6 patients reduced the dose to 8 MIU after the first month, while doses of 12 MIU IFN-β-1a were well tolerated in the PRISMS study. A gradual dose escalation protocol improves tolerance.

During treatment with 8 MIU IFN-β-1b, we noticed a 30% rate of failure. We then decided to treat non-responders to 8 MIU IFN-β-1b with 12 MIU. Patients whose exacerbations persisted at the same rate as before treatment were tested for NAB. NAB-negative, or low-titer positive patients were given the opportunity to be treated with 12 MIU IFN-β-1b on alternate days, this dose being gradually reached in 6 weeks. There were no significant differences in clinical demographic characteristics of responding and non-responding patients except for EDSS score at entry, which was significantly higher in the IFN-β non-responders (p = 0.0003).

NAB frequency was similar in responders (15%) and non-responders (14%). Ten NAB-negative non-responders chose to increase their dosage of IFN-β-1b. At the end of the first treatment period with 8 MIU dose, non-responders had persistent clinical signs of disease activity. All their clinical parameters were significantly worse than those of IFN-β responders (p < 0.001). After the second treatment of non-responders with high INF-β dose, there was significant decline of clinical signs of disease activity. All clinical outcome measures were significantly better than they had been before the increase of INF-β dose (p < 0.01), becoming similar to those of IFN-β responders receiving 8 MIU IFN-β.

After the first treatment period (at 8 MIU IFN-β dose for all patients), there were five withdrawals (10%) for adverse events with no differences between IFN-β responders and non-responders. After the increase of the IFN-β dose, the frequency and severity of adverse events rose in the high-dose group, but abated after the first 3 months. Drop-out occurrence was 3 of 10 in the high dose and 2 of 38 in the standard dose group, with a significant difference (p < 0.01) between them. The reasons for withdrawal were the same in the two groups, i.e. skin necrosis in one patient, and severe fatigue-depression in another patient of both groups. The third drop-out in the high dose group developed autoimmune thyroid dysfunction followed by clinical symptoms and a serological pattern suggestive of systemic lupus erythematosus which improved after stopping IFN-β.

The results of this single center, uncontrolled study prompted us to organize a multicenter trial to compare the efficacy of two different doses of IFN-β-1b. Thus the Optimization of Interferon for MS Study (OPTIMS) has invited 23 MS centers to participate in a phase II trial with an MRI primary endpoint.

INF-β has a dramatic effect on MRI-detected disease activity, demonstrable even after a few weeks of treatment and leading to an 80%-100% decrease in active lesions in most patients. This MRI effect probably has a positive impact on clinical disease activity, since many studies have shown that the risk of relapses is increased in patients with persistent activity noted on MRI. MRI disease activity is defined in the OPTIMS study as the presence of gadolinium (GD)-positive T1 lesions, or of new or enlarging T2 lesions. We defined MRI non-responders as those patients with persistent MRI evidence of activity on serial monthly examinations. In the OPTIMS study design, non-responding patients

---

**Fig. 1** OPTIMS study design. NAB, neutralizing anti-IFN antibody; sImm, serum immunologic monitoring; ImmEx, immunologic experiments.