Efficacy and Safety of Prolonged Immunomodulatory Treatment with Interferon Beta

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Studies of the natural course of multiple sclerosis (MS) are important for analysis of factors determining favorable and unfavorable prognoses for the progress of the disease. Before the introduction of immunomodulatory therapy (IMT) [2, 4–5, 12–14], which can decrease the frequency of exacerbations and slow disease progression, three large trials were conducted, in France [1], Canada [15, 16], and Sweden [10], which addressed the natural course of MS. These showed that about 50% of patients with remitting MS required walking aids by 15 years after the onset of MS, though factors for a favorable course of disease were also identified – female gender, low frequency of exacerbations in the first years of the disease, prolonged first remission, and low levels of disability during the first five years of disease.

The efficacy of contemporary long-term immunomodulatory therapy is assessed using long-term prospective observations of patients with registers of the corresponding groups of patients. Despite the fact that registers of patients have certain advantages, not all the information they yield is optimal, as the required standardization of therapeutic approaches is often absent and the effects of a whole series of unknown factors cannot be excluded. In this regard, prolonged observations of specific patients in specially controlled studies provide more complete clinical data on patients. Such observations of patients for several years are undoubtedly useful in assessing treatment tolerance and safety. Prognostic indicators can be identified during such studies, though they do not always assist in evaluating efficacy, because the patient’s state may not be standardized over prolonged periods, such that control groups at each stage of the study are relative (controls can only serve for two years).

There has as yet been no planned prospective trial with prolonged dynamic observations of patients using clear control criteria for treatment efficacy including the use of brain MRI scans. Nonetheless, virtually all specialized medical centers dealing with MS are able to analyze the tolerance and long-term effects of treatment. We will discuss the few reports in this area.

Jacobs et al. [5] performed a clinical trial of interferon β-1a (IFNβ-1a) (given i.m. at a dose of 6 MIU weekly) in patients with remitting MS for two years; no further observations of the patients was initially proposed. However, about six months after the end of this first (baseline) trial (and eight years after it started), the authors were able to assess long-term treatment effects. They were able to follow 160 patients (93% of the initial cohort). Retrospective analysis, reported by Rudick et al. [11], showed that 13.8% of patients previously randomized to the placebo group had not started immunomodulatory treatment (IMT) during the six years following the end of the previous study; 29% of patients previously in the IFNβ-1a treatment group and 28% of patients in the placebo group had received at least two immunomodulatory agents. Excluding the participation time in the first study, patients from the placebo group had been receiving IMT for 46.6% of the time after the study ended, while patients from the IFNβ-1a group received treatment for 55.8% of the time. Given that the level of disability on the EDSS was no greater than 3.5 points among the patients who took part in the first trial, it is of note that
29.1% of patients of the treatment group and 42.0% of patients of placebo group had scores of ≥6.0 points in the study performed at eight years.

A similar study of the efficacy of i.m. IFNβ-1a treatment was named the CHAMPIONS study [7] and involved patients with newly diagnosed MS (first clinical episodes of demyelination) who had previously completed the baseline CHAMPS study [6] and consented to continue taking part. All patients continued IFNβ-1a treatment. The CHAMPIONS results showed that during the five-year observation period, MS clinically significant on the Poser scale developed in 36% of patients treated with β-interferon and 49% of the placebo group. These results supported the need for the earliest possible initiation of immunomodulatory treatment in MS, particularly in patients with the first episodes of demyelination.

The results of the PRISMS study of patients with remitting MS were published in 1998 [12]. The long-term effects of IFNβ-1a given s.c. three times weekly were assessed. This study compared three groups: patients given placebo, patients given IFNβ-1a at a dose of 22 μg, and patients given IFNβ-1a at a dose of 44 μg. The agent was given three times weekly for two years. Those patients initially in the placebo group were then split into two therapeutic groups and given IFNβ-1a at doses of 22 or 44 μg with prospective observation for a further two years [13]. At the end of this trial, patients were invited to assessments at seven and eight years for analysis of long-term treatment efficacy and safety [9]. A total of 68% of patients were investigated, of whom 72% were still receiving IFNβ-1a. The mean duration of treatment was 7.4 years. The study showed that 20% of patients experienced secondary progression of the disease; 12% of patients reached 6.5 points on the EDSS scale and 6.1% reached 7.0 points. The mean time for progression of the disease by one EDSS point was 5.3 years. Furthermore, the study showed that during the whole eight years, the level of disability, the frequency of exacerbations, and the severity of focal brain lesions (MRI scan data) in patients initially randomized to the IFNβ-1a (44 μg) treatment group were lower than in those patients who started treatment later.

Several studies have addressed the efficacy of long-term use of interferon β-1b (IFNβ-1b) given s.c. at a dose of 250 μg every other day in relapsing MS [4, 14]. At the end of the baseline study, planned for two years, patients completing this phase were included in the following trial, which lasted three years. This, the longest placebo-controlled study – with five years of observation – demonstrated that the study agent produced stable therapeutic effects.

Two further studies of are interest in this regard [2, 8]. One is the three-year European Study of Secondary Progressive MS [2] and its continuation to eight years of observation [8]. The second part of the study included only 340 of the 718 patients in the initial cohort, of whom 112 completed the eight-year observation period. Of these 112 patients, only 58% continued active treatment, only half receiving IFNβ-1b. These results are probably linked with the initial high disease severity as compared with that in remitting MS and the low level of faith in treatment success on the part of the patients.

The results of a 16-year study have recently been published [3]; this was planned not only to evaluate the long-term effects of IFNβ-1b treatment in patients with remitting MS, but also to develop a hypothesis regarding the link between clinical and tomographic (MRI) measures. This study was one of the longest of those performed to assess the efficacy of different methods of treating MS with IFNβ-1b. Of 372 patients taking part in the baseline study, 328 (88.2%) of the patients were subsequently identified, though only 293 of these were alive. A total of 260 (70%) patients agreed to take part in the study, and these underwent neurological investigations with identification of the level of disability on the EDSS scale, studies of cognitive functions, and the quality of life. In addition, the course of the disease was identified at the visit to the center, along with the exacerbation frequency, the MRI features, the side effects of treatment, and immunological parameters. Mean disease duration for all the initially randomized groups was 19 years and the mean duration of IFNβ-1b treatment was 10 years (the longest was 17.1 years). All patients were then divided into three treatment groups – placebo and IFNβ-1b at doses of 50 μg and 250 μg and into groups according to the time on treatment – less than 10% of the time (group 1), 10–80% of the time (group 2), and more than 80% of the time (group 3). By the end of the study period, 78 patients continued on IFNβ-1b treatment. Intragroup analysis showed that the agent was received more than 80% of the time in patients initially treated at the dose of 250 μg. Changes in the type of disease from remitting to secondary progressive occurred in 51% of patients treated with IFNβ-1b for less than 10% of the time, 47.1% of patients treated for 10–80% of the time, and 35.5% of patients treated with IFNβ-1b for more than 80% of the time. The mean times to the change to secondary progression were nine years for group 1 and 16 years for group 3. At the moment of examination, EDSS scores of 6.0 points were seen in 52.2% of patients of group 1, 48% of patients in group 2, and 43.8% of patients in group 3. Disability levels of EDSS = 7.0 points were seen in 44.2% of patients in group 1 and only 29.4% of patients in group 3. The mean times to reaching EDSS = 6.0 points were seven, 10, and 13 years for groups 1, 2, and 3, respectively. Secondary analysis, whose results have yet to be published, will include comparison of these results with those obtained from observation of two cohorts of patients with MS following its natural course (it is presumed that the untreated patients will be recruited in the UK, in accordance with the criteria of the baseline study). Selection of pairs of patients from the American group will be based on gender, age, disease duration, frequency of exacerbations, EDSS scores, and types of disease course.