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10 years of interferon beta-1b (Betaferon®) therapy

Interferon beta-1b (IFNβ-1b 250 μg every other day [eod] by subcutaneous injection [sc]) was the first immunomodulatory therapy to be approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) over 10 years ago (as Betaferon® in Europe and Betaseron® in the US), and is currently the only IFNβ to be licensed for use in patients with secondary progressive MS (SPMS) in Europe. During this time, a large amount of long-term clinical experience, as well as further efficacy and safety data from clinical trials, have accumulated. The papers presented in this supplement, based on the content of a symposium that took place in the historic city of Prague, entitled *"10 Years' Betaferon®"*, aim to highlight the achievements in the field of MS therapy, focusing on issues that are pivotal to optimal therapy, and discuss those challenges that still remain.

The development of disease-modifying therapies for MS has been a challenge but, ultimately, an opportunity to bring optimism to patients. Fred Lublin, New York, describes the history of modern MS therapy from the earliest record of MS in the 14th century to a description of future developments. Although the treatment of MS has progressed significantly, there are patients who still do not respond well to current therapies. As explained by Wolfgang Brück, Göttingen, this variable response to therapy may, in part, be a consequence of disease heterogeneity. For example, immunomodulatory therapy is an effective treatment for RRMS, whereas most studies in SPMS have yielded less convincing results. Our greater understanding of the pathology and pathogenesis of lesions may eventually help to optimise treatment by tailoring it to subtypes of MS.

Our expanding knowledge of prognostic factors will also help provide optimal therapy for clinical subtypes by determining indicators of disease progression and severity. Natural history studies of MS, which are described by George Ebers, Oxford, have already provided important data to more accurately predict the disease course and treatment needs, as well as important information for clinical trials, such as appropriate endpoints and sample sizes based on the choice of endpoints. Pharmacogenetic, pharmacogenomic and proteomic studies will contribute further to our understanding of disease mechanisms and the response to therapeutic agents. In addition, these studies should enable genetic determinants of treatment response to be used for individually tailored therapy, as explained by Ludwig Kappos, Basel.

Over 10 years ago, the decision to conduct a Phase III trial of IFNβ-1b in MS led to a major therapeutic breakthrough. IFNβ-1b 250 μg eod sc was shown to rapidly decrease the frequency and severity of MS attacks, and reduce magnetic resonance imaging- (MRI) measured disease activity. The benefits seen in the original pivotal study are maintained in the long term. Personal experience with IFNβ-1b in the clinic over the past decade is discussed by Barry Arnason, Chicago, including the subsequent use of IFNβ-1b in patients with SPMS. He also reports on positive effects IFNβ-1b has on cognitive outcome measures.

Looking to the need for alternative strategies for those patients who do not respond well to current treatments, Eva Havrdova, Prague, describes the use of intense immunosuppression followed by haematopoietic stem cell transplantation. Recent clinical trials have indicated that some patients may benefit from this procedure, and thus, further research into more intensive

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therapy of patients with a malignant course of MS is justified.

Since the approval of IFNβ-1b a decade ago, clinical studies have continued, with the aim of optimising treatment schedule and dosing. As Luca Durelli, Torino, discusses, it is, therefore, of considerable interest to examine whether it is useful to increase the dose of IFNβ-1b to 375 μg in patients who do not respond satisfactorily to the approved 250 μg dose. This is the rationale for the OPTIMS (OPTimisation of Interferon for MS) study, in which partially responding patients are randomised to IFNβ 250 or 375 μg every other day. Luca Durelli presents the case for the importance of maintaining a high-dose, high-frequency treatment regimen (IFNβ-1b 250 μg eod sc or IFNβ-1a 44 μg three times weekly sc) throughout the course of the disease, as any dose reduction, however temporary, may risk the benefits that the patient may have gained from treatment.

The concept of extending the benefits of IFNβ-1b treatment to even more patients is further elaborated by Hans-Peter Hartung, Düsseldorf, who discusses the use of IFNβ-1b 250 μg eod sc treatment, coupled with initiation of treatment as early in the course of the disease as possible, at the first clinical demyelinating event, to gain maximum therapeutic effect. The BENEFIT (BEtaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment) study aims to provide long-term data on the effect of IFNβ-1b 250 μg eod sc initiated after the first clinical event on the time to a second clinical event, but also on the long-term effects of IFNβ-1b on clinical and MRI measures beyond the second event. It is hoped that this course of management will help prevent permanent neuronal injury that occurs in the early stages of MS, often before clinical signs of disease are evident. Hans-Peter Hartung also discusses whether doses of IFNβ-1b greater than the currently approved IFNβ-1b 250 μg eod sc regimen may produce even better treatment benefits. This question is being addressed by the BEYOND (Betaferon/Betaseron Efficacy Yielding Outcomes of a New Dose) study, which compares a 500 μg dose of IFNβ-1b with the approved 250 μg dose in patients with RRMS. A third arm of this study includes a comparison to glatiramer acetate 20 mg subcutaneously daily.

There have been many great achievements in the MS therapy area during the last 10 years. However, there are more challenges that must be addressed, and ongoing research is striving to clarify unresolved issues and provide the optimal MS therapy to as many patients as possible.