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The Treatment of Multiple Sclerosis with Beta-Interferon

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It is now a generally accepted practice, especially in the USA, to start treatment of multiple sclerosis (MS) immediately upon establishing the diagnosis or after a clinically isolated syndrome. In the current issue, Fromont et al. [1] propose criteria to be used in selecting patients most likely to respond to treatment with β -interferon, and possibly other, immunomodulatory drugs. Perhaps their suggestions may prove to be a brake on the unselective therapeutic frenzy that dominates the management of MS. They make a persuasive argument in favor of delaying the onset of long-term (lifelong) immunomodulatory treatment to observe the course of disease for at least 1 year.

The efficacy of β -interferon for the long-term treatment of MS and, in particular, its initiation as early as possible remain controversial, despite the exhortations of ‘not a moment to lose’ that the ads for Betaseron® shout in neurological journals. The statement ‘with the BENEFIT study 3-year results, only Betaseron has been shown to significantly delay EDSS [Expanded Disability Status Scale] progression in patients with the earliest signs of MS’ is based on the article by Kappos et al. [2]. Nonetheless, few if any physicians, and certainly even fewer patients, will consult it before embarking on the lifelong regimen. The authors note that the annualized relapse rate estimates for the difference between early and delayed treatment over the full 3 years is only a meager $p = 0.029$, varying from $p = 0.011$ for the first year, $p = 0.27$ for the second to $p = 0.87$ for the third. For all the 3 years, including the first, the confidence intervals between the early- and delayed-treatment groups overlap. The difference of reduction of risk for progression (by 1.0 step or more) between the early- and delayed-treatment groups had a p value of 0.022 and an absolute risk reduction of 8%. These statistics are unimpressive since, according to Goodman [3], observations with p values between 0.01 and 0.05 should be considered marginal, not to mention the fact that there is always the risk of misdiagnosis when treating patients after a clinically isolated syndrome [4].

In his critique, Pittock [5] commented: ‘The differences in each of the three stratified groups between patients treated early and those whose treatment was delayed were small (2, 1 and 2.8%, respectively).’

Coles [6] is equally critical of the BENEFIT study: ‘The result is a tortuously complicated trial. Few people accumulated fixed disabilities during the 3 years of the study, 42/292 from the early group and 40/176 in the delayed arm; as a consequence the number needed to treat early to prevent one additional confirmed progression in the DSS over 3 years is high (11.9). We cannot avoid the frightening possibility that secondary progression might occur whether or not we control relapses and relapse-related disability early in the disease course.’ The continued use of the EDSS is puzzling since the scoring is highly subjective, being affected by elevated body and ambient temperature, fatigue and stress; a score of 2 at 8 a.m. may be a 5 at 4 p.m.

Disability in most patients with relapsing-remitting MS accumulates slowly, if at all, and there is no evidence that aggressive early treatment prevents long-term or even short-term disability [7]. Indeed, Confavreux et al. [8] have shown that relapses do not significantly influence the progression of irreversible disability. More recently, an editorial in *Lancet Neurology* bluntly stated ‘no treatment [for MS] can slow [its] progression’ [9].

The problem of the accuracy of the MS diagnosis and the matter of pseudoexacerbations, such as caused by fever, heat or stress, are difficult to evaluate from patient records. Many patients with true MS often report symptoms that are unrelated, such as headaches, various pains, evanescent episodes of numbness and tingling or momentary blurring of vision, which may be counted as exacerbations.

Diagnostic error in the diagnosis of MS is estimated to be approximately 25–30% [4]. Neither the diagnostic criteria of Poser et al. [10], McDonald et al. [11] nor those of Polman et al. [12] differentiate MS from other recurrent neurological diseases, in particular recurrent and multiphasic disseminated encephalomyelitis [4]. Langer-Gould and Steinman [7] pointed out that the revisions of the diagnostic criteria for MS have served only to broaden the definition of MS, rather than improve the specificity of diagnosis. I have personally seen dozens of patients with disseminated encephalomyelitis, migraine-like syndromes, chronic fatigue syndrome etc. who had been told they had MS, some of whom were enrolled in therapeutic trials, and most already taking one of the immunomodulatory drugs. There is no more tragic illustration of the problem than the woman being treated for MS with natalizumab (Tysabri®) who died of progressive multifocal leukoencephalopathy, but whose brain showed no lesions of MS at the postmortem [7].

Probably the most compelling reason for not only delaying treatment until a firm clinical diagnosis of MS can be made, but even withholding it entirely in some cases, is the 50-year-long study by Benediktsson et al. [13]. In 372 Icelandic MS patients with clinical onset between 1950 and 1999, including those with a primary progressive or relapsing-progressive course, after a disease duration of up to 15 years, 70% still have an EDSS of less than 4,

and only 10% have an EDSS of 7 or more. After 30 years of disease, 50% still remain in the benign group (0–3.5), the other 50% being equally divided between the medium (4–6.5) and the severe (>7) groups; of the 280 patients who had a relapsing-remitting course, including all who converted to secondary progression, after 15 years, 80% have remained in the benign groups.

The question regarding the long-term effects of immunomodulatory therapy on the clinical course of MS remains unanswered. To quote an astute and experienced observer of MS for many years, the late George Schumacher: ‘When somebody finds an effective treatment for MS, you’ll know it without the need for sophisticated statistical calculations.’

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