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The Use of Interferon Beta at the Time of Initial Diagnosis of Multiple Sclerosis

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Dr Hodgkinson points out the increasing evidence that damage to axons as well as to myelin can occur early in the clinical course of multiple sclerosis (MS) and accumulates over time. This indicates the need for a safe effective treatment for MS from its onset. The main question here is whether interferon beta meets this need.

Dr Macdonell makes it clear that when considering this therapy one has to take into account the nature of the disease at the time of clinical presentation. Currently it is unclear whether interferon beta is beneficial in secondary progressive MS, and so its initiation at this stage of MS is probably best avoided. Certainly interferon beta should be avoided in primary progressive MS at present, as there is no evidence that it has a beneficial clinical effect and indeed there is one report that it actually worsens the clinical picture by increasing spasticity.[1]

With regard to the first attack of the type seen in relapsing-remitting MS, Jacobs and colleagues [2] have shown that interferon beta can delay the onset of the first relapse of MS. This is perhaps what would have been expected from previous studies on established relapsing–remitting MS. Should interferon beta therefore be used in all patients from the time of the first attack of the type seen in relapsing-remitting MS?

Dr Macdonell makes the important point that such an approach would mean unnecessarily treating a large number of patients who will not develop clinically definite MS anyway. Furthermore, O'Riordan and colleagues[3] have shown that the majority (64%) of those patients who develop definite MS after presenting with a clinically isolated syndrome and 2–3 MRI brain lesions follow a relatively benign course (EDSS greater than or equal to 3 after 10 years) without treatment. Fifty per cent of the patients treated by Jacobs and colleagues[2] with interferon beta from the onset of such a syndrome had 2–4 MRI brain lesions at presentation and would probably have followed a relatively benign course if untreated. Even in the subgroup of patients (>10 MRI brain lesions at presentation) who have a high risk of significant functional impairment after 10 years,[3] it is unknown whether treatment with interferon beta has any significant longer-term benefit, that is after 5–10 years.

Given that interferon beta has partial short-term (2–5 years') efficacy and unknown longer-term efficacy in MS, is its safety profile sufficient to recommend its use in all patients from the time of the first attack of the type seen in relapsing-remitting MS? In view of the long duration of therapy, there are two important considerations regarding the safety of interferon beta. Firstly, interferon beta,[4,5] like interferon alpha (another type 1 interferon),[6] may induce or aggravate autoimmune diseases other than MS. As there is accumulating evidence that MS patients are genetically predisposed to other autoimmune disorders,[7] it is likely that interferon beta treatment will eventually induce or exacerbate conditions such as autoimmune thyroid disease, psoriasis and rheumatoid arthritis in a significant number of MS patients. Secondly, the mechanism of action of interferon beta in MS is unclear. Although it may have a beneficial effect on T-cell-mediated autoimmunity, which may account for its effect of reducing gadolinium-enhancing MRI brain lesions, it would be unwise to assume that its actions in MS are only beneficial. Indeed both

interferon alpha and interferon beta inhibit B cell receptor-mediated apoptosis[8] which is an important mechanism for controlling B cell (antibody) reactivity. There is increasing evidence that antibodies against myelin and axonal antigens have an important pathogenic role in MS, and it should be considered whether interferon beta may aggravate antibody-mediated myelin and axonal damage. Is aggravation of such antibody-mediated damage the explanation for the worsening of spasticity by interferon beta in primary progressive MS?

At present the use of interferon beta from the time of the first attack of the type seen in relapsing-remitting MS should probably be limited to patients with a high risk of developing severely disabling MS, for example those patients with >10 MRI brain lesions at presentation. With regard to patients with an established diagnosis of relapsing-remitting MS and with recent clinical attacks, treatment with interferon beta is clearly indicated. However, in patients with infrequent attacks of relapsing-remitting MS it is unclear whether the potential beneficial effects of commencing interferon beta outweigh the potential harmful effects.

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