Preventing multiple sclerosis?

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A common feature of organ-specific autoimmune disorders is a broad disease spectrum, which ranges from self-limited acute illnesses to relapsing or more chronic and fatal forms. The variation is less in disorders in which a threshold effect must be exceeded to result in symptoms, as in juvenile diabetes. However, a wide spectrum occurs in most autoimmune disorders, including uveitis, non-infectious arthritis, as well as in optic neuritis and other monosymptomatic demyelinating syndromes. In the last group it is now possible to identify with some accuracy those patients at highest risk of recurrence of lesions elsewhere in the nervous system. Well-validated markers of recurrence include the presence of additional lesions on magnetic-resonance imaging, the presence of the MHC allele *DRB 1501*, and oligoclonal bands in the cerebrospinal fluid.[1,2] When the well-used definitions of dissemination in time and space are satisfied (perhaps in 50–60% of cases),[3] the demyelinating syndrome is called relapsing-remitting multiple sclerosis.

Since there is now overwhelming evidence that type 1 interferons reduce exacerbation rates in multiple sclerosis by a third,[4–6] it was inevitable that their potential would be evaluated in patients with their first attack. Appropriately they have been first tested in those with a high risk of new lesions. The driving hypothesis might have been that disease at the first attack is more susceptible to the effects of interferon. Two recent studies, CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study)[7] and ETOMS (Early Treatment of Multiple Sclerosis), which is published in today's *Lancet*, have each shown that the time to the development of a second clinical lesion is prolonged by type 1 interferons.

With relapse suppression of the degree seen in trials of patients with multiple sclerosis (ie, about a third), the prolongation of time to relapse in CHAMPS and ETOMS was to be expected. However, have the findings any implications for everyday clinical practice? Both studies were stopped far too soon to enable definitive answers to the question of treatment value. In neither study was the delay in time to the second exacerbation greater than that seen in the trial of intravenous solumedrol given to patients with optic neuritis around the time of the initial exacerbation.[8] Since two large (unpublished) studies in secondary progressive multiple sclerosis have been negative, the results of CHAMPS and ETOMS may be taken to boost the prospects of interferon therapy. Despite lack of evidence, the notion that early treatment is important has been widely promoted and will continue to be.

In patients with relapsing remitting multiple sclerosis a reduction of a third in exacerbations has been also been found in several trials of interferon and glatiramer acetate, and some reduction may have occurred in earlier trials of immunosuppressive treatment. Hence it is possible that suppression of up to a third of exacerbations is non-specifically achievable, whereas suppression of the next two-thirds may be more difficult. A different issue is whether treatment suppresses long-term disability. Although there are insufficient data to rule out some such effect, it remains to be proven whether interferons have any impact on the progression of the disease apart from their effect on relapses. Since the development of a progressive course dwarfs all other prognostic features, an impact on progression is a more worthy target than reduction in exacerbations but has not been found for any form of therapy. Regrettably this issue will require yet another study. Giancarlo Comi and colleagues argue that the findings of the ETOMS study support the need for early treatment. Although this point needs to be proven, the three large studies of interferons in remitting-relapsing multiple sclerosis could be reanalysed for evidence of significant benefit favouring patients treated early over those treated late.

Comi and colleagues are continuing to track the patients in the ETOMS study, so more useful information might be obtained during the follow-up. The CHAMPS study is, however, probably unlikely to yield further meaningful information on outcomes because all the patients were effectively removed from further study after the positive results were identified.

What then should be done for the types of patients represented in the ETOMS and CHAMPS studies—ie, those with an attack of monosymptomatic demyelination and prognostic features indicating a high likelihood of recurrence. There simply is not enough information to decide. However, the financial implications are enormous. 6 years of treatment would be required to suppress a single relapse, given a one-third reduction of relapses and an average attack rate of 0·5/year. This proposition is even more unattractive than that posed by the results from the pivotal studies of interferons.[4–6] Here entry criteria would have been applicable to 20% or fewer of all patients at any one time point. Since the prevention of a single relapse in individuals with an average attack rate is very costly, pharmaco-economic roads converge on the same question—do interferons influence the long-term course of the disease? If only the US Food and Drug Administration had reasonably demanded that licensing of interferon be tied to complete follow-up of the original cohorts. The cost would have been trivial compared with the finanical implications faced more than a decade after the first large trial began. Unfortunately uncertainty on the key question of long-term effectiveness seems destined to persist for an uncomfortably long time. Oscar Wilde knew what to call those who know the price of everything and the value of nothing.

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