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Multiple Sclerosis: New Therapeutic Concepts or Better Use of Old Drugs?

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In the last few months new exciting advances have been reported in the treatment of multiple sclerosis (MS): **P** interferon decreases the rate of exacerbations in relapsing remitting (RR) MS patients [1,2] and oral tolerization with myelin antigens might be an original procedure of treatment which is under investigation [3]. These two examples emphasize the efficacy of a strict methodological approach in the therapeutic trials and the growing knowledge in the fundamental mechanisms of demyelinating lesions.

Gamma interferon was the first drug used as a therapeutic agent which demonstrated a harmful effect in RR MS patients [4]. After several negative trials with **a** or (3 natural interferons [5], the recombinant **β**3 interferon Beta-seron was the first drug which showed an actual therapeutic effect in RR MS patients. Interferons are a heterogeneous group of cytokines. Alpha and beta interferons are produced by macrophages and fibroblasts under viral activation. Their pharmacological properties are similar because they share the same receptor. Gamma interferon is secreted by activated lymphocytes as an enhancing factor of the immune responses [6]. Experimentally beta interferon suppresses the synthesis of gamma interferon and activates some subpopulations of lymphocytes which down-regulate the immune responses.

From June 1988 to May 1990, 372 patients with RR MS of a disease duration less than 5 years were randomized into three groups: group 1 (123 patients) was treated with placebo, group 2 (125 patients) and group 3 (124 patients) were treated with Betaseron, 1.6 and 8 M**I**U, respectively. Placebo and Betaseron were administered subcutaneously every 2 days. After 2 years the two major end points were significantly different between patients treated with Betaseron compared to placebo controls: annual exacerbation rates were lower and more patients on high-dose Betaseron were exacerbation-free. However there was no difference in the disability scores after 2 years, only a tendency to be less severe in the high-dose group after 3 years. MRI scans of the brain of patients showed significant reduction in disease activity in the high-dose group, measured by total lesion area or appearance of new lesions. The treatment was well tolerated: major side effects, more frequently observed in the high-dose group, a flu-like syndrome and inflammation at the injection site, decreased after 3 months.

The general impression given by these results is a great consistency: beta interferon reduces the activity of the disease without suppressing its evolutivity. Two findings must be outlined. Firstly, in the low-dose group, the therapeutic results were intermediate between placebo and the high-dose group, but the local inflammation at the injection site was identical in the high- and low-dose groups: the beneficial effect appears to be dose-dependent and not related to any placebo effect. Secondly, this is the first trial in which the monitoring of the disease activity by MRI strengthens the clinical data. This monitoring must be included in future therapeutic trials. However reducing the disease activity on MRI cannot yet be considered as a major end point because of the uncertainty about its clinical significance [7].

The main problem raised is the inefficacy of Betaseron to modify the disability score: either follow-up duration can be too short to observe any modification or disability

and exacerbation rate are not correlated, a hypothesis which is less likely [8]. Many questions are unanswered: is a single trial sufficient to confirm the efficacy of a drug? Which patients to treat, at what time, and how long? Is this treatment efficient in the chronic progressive phase of the disease? What is the long-term tolerance?

The small pilot clinical trial of oral myelin conducted by Weiner et al. [3] opened up a new era in an approach to specifically suppress the deleterious immunological reaction against myelin basic protein, supposed to be the main autoantigen. The rationale of this trial was the observation that oral myelin suppressed experimental allergic encephalomyelitis, the laboratory animal disease often used as a model for MS. In this study 30 patients with a RR MS were treated with oral administration of bovine myelin (300 mg per day: 15 patients) or a placebo (15 patients) for 1 year. During this period, 6 of the myelin-treated and 12 placebo-treated patients had one or more relapses. This difference is not significant. Surprisingly, the most significant results were observed in HLA DR2-negative men compared with women or HLA DR2-positive patients. This trial does not demonstrate the efficacy of oral myelin. However it suggests that a larger trial, taking into account the complexity of the previous findings, must be conducted.

There is an obvious interest in this approach: the oral suppression might be due to some cytokines, like TGFβ, which are secreted by suppressor cells activated by the antigen. This suppression is exerted in the microenvironment of the lesions, thus secondarily nonspecific: immune responses against other autoantigens like PLP or MOG can also be inhibited.

The evolution of the immunological concepts allows many other ways for curing autoimmune diseases, like T cell lymphocyte vaccination, blockade of HLA or adhesion molecules ... Some of them are already under investigation in patients. A promising period has undoubtedly begun in the treatment of MS if, as is usually believed, MS is an autoimmune disorder.

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