Statins for the treatment of multiple sclerosis: cautious hope

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During the past decade there has been much progress in the treatment of multiple sclerosis, and therapeutic nihilism can no longer be justified. Immunomodulatory drugs (eg, interferons beta-1a and beta-1b, glatiramer acetate, and mitoxantrone) are now widely used. Nevertheless, the limited effectiveness of these treatments and inconvenience and toxicity associated with their use emphasise the need for new therapies.

Statins are widely used cholesterol-lowering drugs that have immunomodulatory effects by which they might be beneficial in the treatment of inflammatory disease. Statins interfere with mediators of inflammation in the central nervous system, suggesting that statins may prevent the accumulation of leucocytes there;\(^1\)\(^2\) and cause a shift from a proinflammatory to an anti-inflammatory cytokine profile.\(^3\) In addition, statins inhibit in-vitro T-cell proliferation in a dose-dependent manner, especially when combined with interferon beta-1b.\(^4\) Besides strong anti-inflammatory properties, however, statins also have some proinflammatory effects; pre-treatment with simvastatin induced a dose-dependent increase of the proinflammatory cytokines interferon gamma and interleukin 12 in the supernatant of T cells stimulated with anti-CD3 antibody.\(^5\) Lovastatin was effective in Lewis rat and mouse models of experimental autoimmune encephalomyelitis,\(^1\) whereas atorvastatin prevented the development of chronic relapsing paralysis in mice.\(^2\) On the basis of their biological effects, and the fact that statins are generally well tolerated and safe, given orally, and cheap, clinical trials in multiple sclerosis have been eagerly awaited.

In this issue of The Lancet, Timothy Vollmer and colleagues report the results of the first clinical trial with a statin in multiple sclerosis. Their study was multicentre and open label, with a baseline versus treatment comparison. Patients were selected by active disease on MRI at entry. The primary outcome was the mean number of gadolinium-enhancing lesions. 30 patients with relapsing-remitting multiple sclerosis were eligible to receive an 80 mg daily dose of oral simvastatin for 6 months. Two patients dropped out before the end of the study. In the 28 remaining patients, the number and volume of enhancing lesions decreased significantly. The drug was safe and generally well tolerated. Exploratory immunological studies showed no changes in the expression of surface markers on leucocyte cells or in cytokine profiles.

These results provide hope, although they should be interpreted cautiously. The number of patients and the design of the study do not allow for a definitive conclusion on the role of statins in multiple sclerosis. The main concern with Vollmer and colleagues’ study is whether, without a placebo group, the reduction in disease activity as measured with MRI could be due to regression to the mean. The fact that patients were included in the study on the basis of the presence of gadolinium-enhancement might have selected for patients with active disease and who would have subsequently had reduced disease activity anyhow. Additional questions relate to other factors that might have had an effect on the trial’s outcome—eg, steroid use and the way any such use was accounted for, and any potential for unblinding of the readers of the MRI scans. Vollmer and colleagues did not find their exploratory immunological data to be supportive, which might be explained by the limited number of samples tested or might challenge the notion that meaningful anti-inflammatory effects can be achieved at a daily dose of “only” 80 mg simvastatin.

Vollmer and colleagues’ study is a big step forward because it is the first to provide some evidence of an effect with a statin in multiple sclerosis—but it is only an initial step. Additional data are required to more precisely determine the clinical effects of statins, to explore the optimum dose, the therapeutic window, and the differential potency of statins, and to evaluate whether combination therapy might be more effective than monotherapy. Physicians, scientists, drug companies, and regulatory agencies should now work together to design and do randomised studies that have adequate power to address these and other important issues. It is the joint responsibility of all involved to ensure that some of the potential charms of statins (low-hurdle access, convenience, low cost) do not develop into a dangerous boomerang, in case proper studies become jeopardised by widespread off-label use.

We have both worked with companies that market currently approved drugs for multiple sclerosis, but not with any of the companies that market statins.

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