Simvastatin and cognition in multiple sclerosis

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Few treatment options are available for patients with progressive multiple sclerosis,[1] in whom anti-inflammatory drugs have little effect and for whom clinical manifestations, such as cognitive impairment and neuropsychiatric dysfunction, have a dramatic effect on quality of life. Preservation of functional and social independence are perhaps the main therapeutic goals in these patients.

Statins are widely used for the treatment of vascular diseases, and have an excellent safety profile and low cost. In addition to their beneficial effect on hypercholesterolaemia, statins exert immunomodulatory and neurotrophic effects.[2] Studies in patients with relapsing-remitting multiple sclerosis found no clear beneficial effects of statins,[2,3] either as monotherapy or as add-on to interferon beta, at reducing clinical and MRI disease activity; however, in a 2-year double-blind controlled trial[4] of 140 patients with secondary progressive multiple sclerosis (SPMS; MS-STAT), a 43% reduction in annualised brain atrophy rate was reported in patients treated with high-dose simvastatin (n=70) compared with placebo (n=70). Simvastatin-treated patients also experienced a less pronounced accumulation of disability and worsening on the Multiple Sclerosis Impact Scale and, as might be expected, a significant reduction in serum cholesterol concentrations over the trial period. No effect on measures of disease activity (new MRI lesions or clinical relapses) was detected.

In *The Lancet Neurology,* Dennis Chan and colleagues[5] report findings from a cognitive substudy of the previous trial,[4] providing data to further our understanding of the effect of simvastatin in patients with SPMS. At the end of the 2-year period, compared with placebo, simvastatin-treated patients showed better performance in some frontal lobe tests (difference in Frontal Assessment Battery score 1·2 points, 95% CI 0·2–2·3) and improved physical quality of life (difference in physical component summary of the Short-Form 36 2·5 points, 95% CI 0·3–4·8; p=0·028); these differences were not associated with frontal lobe volume changes, which were similar in the two study groups (difference in mean rate 0·0 mL/year, 95% CI –0·7 to 0·7; p=0·97). The discrepancy between the regional and global assessments of brain atrophy in the two analyses were discussed briefly by the investigators. Findings from several volumetric studies have shown that different patterns of regional involvement are associated with cognitive deficits in patients with multiple sclerosis, with a more distributed pattern of atrophy in patients with SPMS than in those with relapsing-remitting multiple sclerosis.[6] As a consequence, one may be tempted to speculate that region-specific involvement might be important in explaining cognitive, and clinical, deficits early in the course of the disease, whereas later on, the global burden of the disease, as reflected by whole brain atrophy, might become more clinically relevant. Disappointingly, since Chan and colleagues'[5] substudy was planned and focused particularly on frontal lobe assessment, the possible association between patients' functional improvement and global volume changes was not investigated. This is one of the main limitations of this study. Although adherence to pre-planned statistical analysis is a major requirement for confirmatory trials aimed at providing firm evidence of efficacy or safety of a drug, exploratory trials, and trial substudies, warrant a more flexible approach, particularly when peculiar aspects or groups of well-characterised patients are under investigation, as is the case in Chan and colleagues'[5] substudy.

From this perspective, despite the limitations, Chan and colleagues' work offers several important take-home messages, which might affect the planning of future clinical trials as well as clinical practice in SPMS. First, treatment trials in patients with SPMS should include not only disability as the clinical outcome measure, but also cognition and quality of life measures. Second, investigating and controlling for comorbidities and their risk factors might help minimise the devastating clinical effect of the disease. Even though the exact mechanism of action of simvastatin has not been established, it is thought to work on vascular function and cell protection.[2] Consistent with the effects of comorbidity in other chronic diseases, vascular comorbidity adversely affected disability in multiple sclerosis,[7] justifying the investigation of the effect of treatment of vascular comorbidities on disease progression. Unfortunately, assessment of comorbidities was not done in the MS-STAT trial, and so establishing whether simvastatin might have a different effect depending on their presence was not possible.

Chan and colleagues' work has further merit in that it extensively characterises the pattern of cognitive

dysfunction, including neuropsychiatric symptoms, and its progression over 2 years in a large cohort of patients with SPMS, assessed with a standardised battery of neuropsychological tests. Even though the data need confirmation in other groups of patients, as acknowledged by the investigators, these assessments could be used to inform the selection of patients with SPMS in future studies in which cognition is one of the outcomes and in studies aimed at treating cognitive impairment.

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