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.

Massimo Filippi, Maria A Rocca
Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, and Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, 20132 Milan, Italy (MF, MAR)
filippi.massimo@hsr.it

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1 Ontaneda D, Thompson AJ, Fox RJ, Cohen JA. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. *Lancet* 2017; **389:** 1357–66.
2 Pihl-Jensen G, Tsakiri A, Frederiksen JL. Statin treatment in multiple sclerosis: a systematic review and meta-analysis. *CNS Drugs* 2015; **29:** 277–91.
3 Sorensen PS, Lycke J, Eralinna JP, et al. Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial. *Lancet Neurol* 2011; **10:** 691–701.
4 Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet* 2014; **383:** 2213–21.
5 Chan D, Binks S, Nicholas JM, et al. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. *Lancet Neurol* 2017; published online June 6. http://dx.doi.org/10.1016/S1474-4422(17)30113-8.
6 Rocca MA, Amato MP, De Stefano N, et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol* 2015; **14:** 302–17.
7 Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology* 2010; **74:** 1041–47.

Potential biomarker breakthrough for Huntington's disease

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Huntington's disease, with a single genetic cause and correlation between age of onset and length of the CAG repeat in the huntingtin gene (*HTT*), has long served as a model for neurodegenerative diseases. Predictive genetic testing has made it possible to define the natural history of the disease and to show that regional brain atrophy, especially of the striatum, begins many years before diagnosable motor onset and progresses steadily through the premanifest and manifest periods.[1–3] Structural neuroimaging enables excellent tracking of progressive atrophy; however, it requires an expensive apparatus and does not provide a direct chemical reflection of brain injury.

Lauren Byrne and colleagues report in *The Lancet Neurology*[4] a remarkable new study of 298 participants enrolled in the TRACK-HD study.[2] It shows that plasma concentrations of neurofilament light (NfL) chain are substantially increased in Huntington's disease and correlate well with age and CAG repeat length.[4] NfL concentrations were as much as 3·6 times greater in patients with manifest Huntington's disease compared with controls, and there was a very clear gradient from controls to early premanifest (far from expected motor onset), late premanifest (close to expected motor onset), and then to manifest Huntington's disease. The NfL increases in manifest Huntington's disease were similar to those in multiple sclerosis relapses,[5] and were at least as great as in other neurodegenerative diseases including progressive supranuclear palsy,[6] multiple system atrophy,[7] and corticobasal syndrome.[7] In Parkinson's disease[7] and Alzheimer's disease,[8] plasma and blood NfL concentrations are not substantially different from those of controls, partly because of the wide range of disease severity and subtypes within those diseases. In Huntington's disease, since patients can be genetically tested and subgrouped by time to expected motor onset, NfL concentrations have the potential to be used to study disease biology directly.