Effect of high-dose simvastatin on cognition (MS-STAT cognitive): a randomised, placebo-controlled, phase 2 trial

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Background: Cognitive impairment is a major contributor to disability and reduced quality of life in secondary progressive MS (SPMS). In the 24 month MS-STAT phase 2 trial we showed that high dose simvastatin significantly reduced the rate of whole brain atrophy, as well demonstrating effects on clinician and patient observed outcome measures. We describe here results of the MS-STAT sub-study, evaluating treatment effect on cognitive and neuropsychiatric outcome measures.

Objectives: 140 patients with SPMS, with Expanded Disability Severity Scales (EDSS) scores between 4 and 6.5, were randomised to receive simvastatin (n=70) or placebo (n=70). Full cognitive and neuropsychiatric testing was undertaken at study entry, 12 and 24 months.

Methods: The following cognitive domains were tested: premorbid IQ; general intellectual functioning; verbal and nonverbal memory; semantic memory; visual perceptual function; attention, speed of information processing, and working memory (PASAT-3); frontal lobe function (frontal assessement battery, FAB). Neuropsychiatric symptoms were assessed using the Hamilton Depression Scale and the Neuropsychiatric Inventory Questionnaire. Linear mixed models were used to examine how cognitive and neuropsychiatric scores changed between baseline, 12 and 24 months and to evaluate the difference in score between the placebo and simvastatin group at 12 and 24 months.

Results: Baseline assessment revealed that nearly half of patients showed impairment on frontal lobe function (45%) and on the PASAT-3 (46%). There were also significant numbers of patients (up to 33%) with impairment on tests of verbal and nonverbal memory. Over the entire trial, the cohort as a whole declined on tests of verbal and non-verbal memory. At 24 months, there was a significant difference in FAB scores between the two treatment groups, with a 0.24 point increase in the mean FAB score observed in the simvastatin-treated group, compared with a decline of 0.92 points in the placebo group: a difference of 1.08 (95% CI 0.09 to 2.14). No significant treatment effect was observed on any other cognitive or neuropsychiatric measures.

Conclusion: This represents the largest SPMS published cohort to have been studied with longitudinal cognitive and neuropsychiatric assessments. Frequent cognitive impairment was observed at study entry, with decline at 24 months observed primarily in episodic memory. Although results must be interpreted carefully because of the many variables examined, we found that high dose simvastatin significantly improves frontal lobe function,

adding to our previous observation of a positive treatment effect on brain atrophy rates. These results highlight the importance of including detailed cognitive outcome measures within progressive MS therapeutic trials.

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