Research letters

Oral simvastatin treatment in relapsing-remitting multiple sclerosis

Timothy Vollmer, Lyndon Key, Valerie Durkalski, William Tyor, John Corboy, Silva Markovic-Plese, Jana Preiningerova, Marco Rizzo, Inderjit Singh

Many drugs have been approved for relapsing forms of multiple sclerosis but are only partly effective, are injected, and are expensive. We aimed to investigate use of of oral simvastatin (80 mg) in 30 individuals with relapsing-remitting multiple sclerosis. The mean number of gadolinium-enhancing lesions at months 4, 5, and 6 of treatment was compared with the mean number of lesions noted on pretreatment brain MRI scans. Number and volume of Gd-enhancing lesions declined by 44%, (p<0·0001) and 41% (p=0·0018), respectively. Treatment was well tolerated. Oral simvastatin might inhibit inflammatory components of multiple sclerosis that lead to neurological disability.

Lancet 2004; **363:** 1607–08
See Commentary page 1570

Since 1993, five disease-modifying drugs have been approved for relapsing forms of multiple sclerosis.[1] All these are only partly effective for most patients, need regular injections, and are expensive. Statins are cholesterol-lowering drugs extensively used in medical practice for primary and secondary prevention of cardiovascular events due to atherosclerosis. In addition to their cholesterol-lowering effect, previously unrecognised immunomodulatory effects have been identified.[2] Statins inhibit lymphocyte function associated antigen 1 (LFA-1)—a ligand for intercellular adhesion molecule (ICAM) that enables inflammatory cells to pass through the blood-brain barrier—and the production of matrix metalloproteinase 9, an enzyme associated with T-cell transmigration across endothelial barriers.[3] Singh and his group (Pahan and colleagues,[4] Stanislaus and colleagues[3]) reported the down-regulation of inflammatory mediators (such as tumour necrosis factor α and inducible nitic oxide synthase) in macrophages and glial cells in culture and experimental autoimmune encephalomyelitis brain, a model for multiple sclerosis.[4] Furthermore, Youssef and co-workers[5] showed that statins induce a shift from production of proinflammatory (T-helper [Th] 1) cytokines to anti-inflammatory (Th2) cytokines in autoaggressive T cells. Thus, statins could be beneficial for multiple sclerosis. We aimed to assess use of oral simvastatin in patients with relapsing-remitting multiple sclerosis.

We designed a multi-centre, open-label, single-arm study to gather information on use of oral simvastatin. Between May, 2001, and February, 2002, we enrolled into a pre-treatment phase individuals who were aged 18–55 years with clinically definite relapsing-remitting multiple sclerosis and no previous treatment with interferons or glatiramer in the previous 3 months or corticosteroids within 30 days of screening. We monitored participants for 3 months, and did monthly brain MRI scans; those with at least one gadolinium-enhancing lesion detected during this phase were eligible to receive 80 mg of simvastatin daily for 6 months. We repeated brain MRI at months 4, 5, and 6 of treatment. All MRI scans were read by two expert masked readers who manually established the location of Gd-enhancing lesions. We measured the volume of lesions with a threshold technique. We identified the number of new Gd-enhancing lesions per scan by comparison of the location of lesions on consecutive scans during pretreatment and treatment phases, with masked order of phase.

The primary outcome measure was mean number of Gd-enhancing lesions on magnetisation transfer enhanced T1 images pretreatment and during treatment. Secondary MRI outcomes were volume of Gd-enhancing lesions, number of new Gd-enhancing lesions, and total T2 lesion volume plus a brain atrophy measure, which were quantified by one operator with semiautomated software (MSClassifier). Secondary clinical outcomes were relapse rate and change in expanded

	Baseline	Treatment	Average mean difference	p
Number of Gd-enhancing lesions*				
Mean (SD)	2·31 (1·39)	1·30 (0·99)	–1·01 (1·08)	<0·0001
Median	2	1	..	
Number of new Gd-enhancing lesions				
Mean (SD)	1·37 (1·53)	0·71 (0·68)	–0·679 (1·54)	0·0295
Median	1	0·50	..	
Volume of Gd-enhancing lesions (mm³)				
Mean (SD)	234 (262)	139 (235)	–98·3 (183·8)	0·0018
Median	172·5	71	..	
T2 lesion volume (mm³)				
Mean (SD)	27 019 (23 871)	27 994 (26 284)	862·5 (4605·5)	0·5634
Median	21 398	20 831		
Brain parenchymal fraction				
Mean (SD)	0·87 (0·041)	0·86 (0·040)	–0·002 (0·005)	0·0467
Median	0·88	0·88	..	
EDSS (mean)	2·80	2·98	..	0·6125
Yearly relapse rate (mean)	0·43	0·38	..	1·0

EDSS=expanded disability status score. *Primary outcome (per-protocol, n=28).

MRI and clinical outcomes of participants

disability status score. We assessed adherence with monthly study drug records. We summarised all MRI outcome measures as the average of the mean values per participant and analysed them with the Wilcoxon signed rank test. We did exploratory immunology studies including serial measurement of cytokine production by in-vitro anti-CD3 plus anti-CD28 monoclonal antibody-stimulated peripheral blood mononuclear cells. We monitored secretion of Th1 (interferon γ, tumour necrosis factor α, interleukin 2, interleukin 12) and Th2 (interleukins 4, 6, and 10) cytokines. Further, we noted surface marker expression in a small cohort. Three-colour staining was done and we analysed results on lymphocyte-gated and monocyte-gated populations with Cell Quest software (version 3.3) (Beckton Dickinson Immunocytometry Systems, San Diego, CA, USA).

Of 45 people screened, 30 were eligible for treatment and two discontinued before completion of the three treatment MRI scans (one withdrew consent and one was lost to follow-up before the month 6 scan). Mean age was 44 years (SD 8), and 21 (70%) were women. Of the 28 per-protocol individuals, the average of the mean number of Gd-enhancing lesions was reduced by 44% during treatment compared with pretreatment ($p<0·0001$; table). Similarly, Gd-enhancing lesion volume fell by 41% after treatment ($p=0·0018$). Pretreatment and treatment phase yearly relapse rates did not differ. No relevant change between pretreatment and treatment expanded disability status scores was detected during the 6 month treatment period (table).

Mean baseline total cholesterol and LDL values were 5·0 mmol/L (SD 1·0) and 3·1 mmol/L (0·7) respectively. By treatment month 6, these amounts had fallen to 3·5 mmol/L (0·6) and 1·8 mmol/L (0·5), respectively ($p<0·0001$). Treatment did not affect relative numbers of monocyte (CD14+) and lymphocyte (CD3+, CD4+, CD8+, CD19+) subsets in the cohort of nine patients. Overall, the findings of the immunology studies did not indicate a change in secretion of representative Th1 and Th2 cytokines. No serious adverse events were reported during the treatment phase. Two of the treated individuals had a clinically important increase in liver function tests during treatment and one had a clinically relevant creatinine phosphokinase concentration at month 1 of treatment that returned to normal for the rest of the treatment period. Three people reported muscle weakness possibly related to study drug.

These findings suggest that an 80 mg daily dose of oral simvastatin over a 6 month period could inhibit the inflammatory components of multiple sclerosis that lead to neurological disability. Since individuals were enrolled on the basis of their disease activity on baseline MRI scans, noted reductions in a baseline versus treatment trial design could represent regression to the mean. However, our results, combined with the published work on the immunological effects of statins, lend support to the case for randomised controlled clinical trials to establish the safety and efficacy of statins in the treatment of relapsing-remitting multiple sclerosis.

Contributors

L Key and I Singh were the study chairmen. V Durkalski was the study statistician and project leader at the Clinical Innovation Group (coordinating center). T Vollmer, S Markovic-Plese, W Tyor, and J Corboy were site investigators. J Preiningerova and M Rizzo worked at the central MRI reading center.

Conflict of interest statement

The Medical University of South Carolina and IS are participants in US patent no 6 511 800, an unlicensed patent about use of statins for treatment of neurodegenerative and inflammatory diseases. If the patent is licensed, financial distribution will be due according to the Medical University of South Carolina's intellectual property policy guidelines. IS is entitled to 25% of the income from this patent. TV, IS, and LK have received honoraria for speaking from Merck.

Acknowledgments

This research was supported by an unrestricted educational grant from Merck to the Medical University of South Carolina. The sponsor had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

1 Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002; **58:** 169–78.

2 Neuhavs O, Strasser-Fuchs S, Fazekas F, et al. Statins as immunomodulators: comparison with interferon-beta 1b in MS. *Neurology* 2002; **59:** 990–97.

3 Stanislaus R, Singh AK, Singh I. Lovastatin treatment decreases mononuclear cell infiltration into the CNS of Lewis rats with experimental allergic encephalomyelitis. *J Neurosci Res* 2001; **66:** 155–62.

4 Pahan K, Sheikh F, Namboodiri A, Singh I. Lovastatin and phenylacetate inhibit the induction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia and macrophages. *J Clin Invest* 1997; **100:** 2671–79.

5 Youssef S, Stuve O, Patarroyo JC, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverse paralysis in central nervous system autoimmune disease. *Nature* 2002; **420:** 78–84.

Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, AZ, USA (T Vollmer MD)**; Medical University of South Carolina, Charleston, SC, USA** (L Key MD, V Durkalski PhD, W Tyor MD, I Singh PhD)**; Clinical Innovation Group, Charleston, SC, USA** (V Durkalski)**; Department of Neurology, University of North Carolina, Chapel Hill, NC, USA** (S Markovic-Plese MD)**; Department of Neurology, Yale School of Medicine, New Haven, CT, USA** (T Vollmer, S Markovic-Plese, J Preiningerova MD, M Rizzo MD)**; University of Colorado Health Sciences Center, Denver, CO, USA** (J Corboy MD)**; Neurology Service, Ralph H Johnson Veterans Affairs Medical Center Charleston, SC, USA** (W Tyor)**; Denver Veterans Affairs Medical Center, Denver, CO, USA** (J Corboy)**; and West Haven Veterans Affairs Medical Center, West Haven, CT, USA** (J Preiningerova)

Correspondence to: Dr Inderjit Singh, Medical University of South Carolina, 316 Clinical Science Building, 171 Ashley Avenue, Charleston, SC 29425, USA
(e-mail: singhi@musc.edu)

Serum lipopolysaccharide-binding protein prediction of severe bacterial infection in cirrhotic patients with ascites

Agustín Albillos, Antonio de-la-Hera, Melchor Alvarez-Mon

Serum lipopolysaccharide-binding protein is increased in a subset of non-infected ascitic cirrhotic patients, a finding previously related to bacterial passage from the gut to the circulation without overt infection. We prospectively analysed the risk factors associated with a first episode of severe bacterial infection in 84 ascitic cirrhotics, followed up for a median of 46 weeks. The cumulative probability of such infection in patients with raised and normal lipopolysaccharide-binding protein was 32·4% and 8·0% ($p=0·004$), respectively. Increased lipopolysaccharide-binding protein was the only factor independently associated with severe bacterial infection in a multivariate analysis (relative risk 4·49, 95% CI 1·42–14·1). Monitoring of serum lipopolysaccharide-binding protein could, therefore, help to target cirrhotic patients with ascites for antibiotic prophylaxis.

Lancet 2004; **363:** 1608–10