

Armando Sena
Rui Pedrosa
M. Graça Morais

Therapeutic potential of lovastatin in multiple sclerosis

Received: 29 October 2002
Received in revised form: 16 January 2003
Accepted: 27 January 2003

Sirs: In the last few years many studies have demonstrated that statins, in addition to their lipid-lowering effects, have anti-inflammatory and immunomodulatory properties [1]. These properties of statins have suggested that they could have beneficial effects in immune mediated neurological disorders [2, 3]. In particular, lovastatin has been shown to inhibit the induction of inducible nitric oxide synthase and proinflammatory cytokines in rat astrocytes, microglia and macrophages [2] and to repress MHC-II mediated T-cell activation [3]. Moreover, lovastatin treatment decreased neuroinflammatory activity and clinical signs in experimental allergic encephalomyelitis, an animal

model for multiple sclerosis (MS) [4]. On the basis of these findings we have begun to investigate whether lovastatin could be a treatment option for MS patients.

We report the results observed on seven patients with the relapsing-remitting MS after 12 months of therapy with lovastatin. The study was designed as a one-center, open-label non placebo-controlled trial. All the subjects were recruited and treated on an outpatient basis, at the MS clinic of the Neurology Service of a general hospital. None of the patients was on any immunosuppressive or immunomodulating therapy and none received these agents during lovastatin treatment. The study was approved by the ethical committee of our Hospital and a written informed consent was provided from all patients. Our cohort consisted in women (age between 24 and 45 years) with a mean disease duration of 4.61 ± 2.16 years and clinical evidence of disease activity as measured by at least two relapses within the previous 2 years. Each subject was treated with 20 mg of lovastatin per day for one month and the dose was increased to 40 mg per day if no adverse effects were noted. A clinical examination and hematology and biochemical

tests (including the plasma lipid profile and creatine kinase) were performed at baseline and every 3 months. Brain MRI was performed at baseline and every 6 months. During the follow-up, all clinical evaluations were done without knowledge of the neuroradiological results.

No adverse events associated with therapy were observed. Our results (Table) show that the Kurtzke Expanded Disability Status Scale (EDSS) score was unchanged in 6 patients and improved one point in another patient after treatment. Three patients were free of relapses during therapy and for the whole group the mean annual relapse rate decreased during this period. In four patients there was a reduction of the inflammatory activity of the disease after treatment in comparison to baseline, as assessed by the number of gadolinium (Gd)-enhanced T1 lesions on MRI. One patient did not have active lesions at baseline and two enhanced lesions were seen at the end of the study. In five patients, the number of lesions on T2-weighted images increased after treatment. Lower post-treatment total cholesterol levels provide evidence of compliance with therapy.

The results from this short pilot

Table 1 Effects of lovastatin therapy on plasma cholesterol and disease activity in patients with multiple sclerosis

Patient n° (age, years)	Before treatment					At 12 months after treatment				
	EDSS*	Annual Relapse Rate ^a	Gd-enhanced lesions (n°)	T2-weighted lesions (n°)	Plasma total cholesterol ^b mg/dl	EDSS	n° of relapses	Gd-enhanced lesions (n°)	New T2-weighted lesions (n°)	Plasma total cholesterol mg/dl
1 (45)	4.0	1.0	1	8	224	4.0	1	0	0	180
2 (34)	2.0	1.0	0	9	183	1.0	1	2	1	143
3 (44)	2.0	1.0	0	6	269	2.0	0	0	0	185
4 (27)	2.0	1.5	2	> 10	174	2.0	0	1	2	125
5 (28)	1.0	2.0	1	> 10	218	1.0	2	0	3	188
6 (24)	2.0	1.0	0	> 10	209	2.0	2	0	3	145
7 (35)	2.0	1.0	3	> 10	259	2.0	0	1	3	207

* Kurtzke Expanded Disability Status Scale

^a Calculated on the basis of the number of relapses during the last 2 years; ^b The value in 30 normal subjects was 191.73 ± 39.06 mg/dl

trial suggest that lovastatin treatment may have favorable clinical effects in patients with relapsing-remitting MS. They support recent data on peripheral blood mononuclear cells from MS patients indicating that statins have immunomodulatory effects in part similar to interferon beta [5]. Now there is experimental evidence suggesting that other statins, particularly simvastatin [5] and atorvastatin [6] could be beneficial in MS. Moreover, our data are in agreement with the results of Pozzilli et al. [7] showing a correlation between the mean number of Gd-enhanced MRI lesions and the mean plasma level of total cholesterol. However, the possible beneficial effects of lowering plasma cholesterol suggested by these data are presently uncertain and deserve further studies. We have observed that the clinical response of MS patients to interferon beta therapy is not associated with alterations in plasma total cholesterol and LDL-cholesterol levels [8]. It should be noted that statins might also suppress inflammatory responses by cholesterol-independent effects and independent of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition [1]. As recently discussed, statins may interact with multiple mechanisms involved in the pathogenesis of MS [9, 10]. Nevertheless, our results also suggest that caution is advisable. In fact, MRI data provide evidence that the majority of patients developed new brain lesions over the time course of this study. In this regard it is important to note that statins also exhibit some potent

proinflammatory effects [5]. In addition, inhibition of cholesterol and nonsterol isoprenoid synthesis by these drugs could possibly interfere with remyelination and neural repair mechanisms in the MS lesion. A recent study revealed that statins in therapeutically relevant dosages indeed affect human cerebral cholesterol metabolism [11]. On the basis of these findings we conclude that further evaluation of statins as therapeutic agents for MS should be addressed in larger controlled clinical trials and longer periods of observation.

■ **Acknowledgements** We thank all patients and nurse Cristina Araújo who participated in this study.

References

1. Takemoto M, Liao JK (2001) Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscl Thromb Vasc Biol* 21:1712–1719
2. Pahan K, Sheikh FG, Namboodiri AMS, Singh I (1997) Lovastatin and phenylacetate inhibit the reduction of nitric oxide synthase and cytokines in rat primary astrocytes, microglia and macrophages. *J Clin Invest* 100: 2671–2679
3. Kwak B, Mulhaupt F, Mytt S, Mach F (2000) Statins as a newly recognized type of immunomodulator. *Nat Med* 6:1399–1402
4. Stanislaus R, Singh AK, Singh I (2001) Lovastatin treatment decreases mononuclear cell infiltration into the CNS of Lewis rats with experimental allergic encephalomyelitis. *J Neurosci Res* 66:155–162
5. Neuhaus O, Strasser-Fuchs S, Fazekas F, Kieseier BC, Niederwieser G, Hartung HP, Archelos JJ (2002) Statins as immunomodulators. Comparison with interferon- β 1b in MS. *Neurology* 59: 990–997
6. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, Bravo M, Mitchell DJ, Sobel RA, Steinman L, Zamvil SS (2002) The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* 420:78–84
7. Pozzilli C, Di Legge S, Sormani MP, Pantano P, Antonini R, Monti MS, Tisei P, Giubilei F (2001) Plasma cholesterol levels in early onset multiple sclerosis. *J Neurol* 248 (suppl 2):II/87 (Abstract)
8. Sena A, Pedrosa R, Ferret-Sena V, Almeida R, Andrade ML, Morais MG, Couderc R (2000) Interferon beta 1a therapy changes lipoprotein metabolism in patients with multiple sclerosis. *Clin Chem Lab Med* 38:209–213
9. Zamvil SS, Steinman L (2002) Cholesterol-lowering statins possess anti-inflammatory activity that might be useful for treatment of MS. *Neurology* 59: 970–971
10. Wekerle H (2002) Tackling multiple sclerosis. *Nature* 420:39–40
11. Fassbender K, Stroick M, Bertsch T, Ragoschke A, Kuehl S, Walter S, Walter J, Brechtel K, Muehlhauser F, von Bergmann K, Lutjohann D (2002) Effects of statins on human cerebral cholesterol metabolism and secretion of Alzheimer amyloid peptide. *Neurology* 59:1257–1258

A. Sena, MD, PhD (✉) R. Pedrosa, MD
Neurology Service
Hospital dos Capuchos
Alameda St^o António dos Capuchos
1169-050 Lisboa, Portugal
Tel.: +21-8 80/30-33 or -82
Fax: +21-8 85/19-20
E-Mail: arsena@fcm.un.pt
M. G. Morais, MD, PhD
Dept. of Biochemistry
Faculty of Medical Sciences, UNL
Lisboa, Portugal

Copyright of Journal of Neurology is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.