RESEARCH LETTER

Atorvastatin Does Not Alter Interferon Beta–Induced Changes of Serum Matrix Metalloproteinase 9 and Tissue Inhibitor of Metalloproteinase 1 in Patients With Multiple Sclerosis

Interferon beta, the current cornerstone of multiple sclerosis (MS) therapy, was shown to reduce the ratio of matrix metalloproteinase 9 (MMP-9)–tissue inhibitor of metalloproteinase 1 (TIMP-1) in order to attenuate overactive proteolysis and inhibit leukocyte migration.[1-3] Matrix metalloproteinases, a family of extracellular matrix–degrading enzymes, are involved in the pathogenesis of MS by facilitating leukocyte migration, disruption of the blood-brain barrier, processing of cytokines and their receptors, and demyelination.[1]

Immunomodulatory properties of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, including atorvastatin, may be beneficial for the treatment of MS. Among the immunomodulatory effects proposed for statins, increased attention is drawn to the modulation of MMPs. In vitro results suggest that statins may increase MMP-9 activity and disrupt the proteolytic balance restored by interferon beta.[1,4]

In this study, we aimed to evaluate the treatment effects of interferon beta alone and in combination with atorvastatin on parameters of proteolysis, ie, serum levels of active MMP-9 and TIMP-1 and the active MMP-9–TIMP-1 ratio in patients with relapsing-remitting MS.

Methods. Sequential serum samples were obtained from 28 patients (mean age, 33.4 years; mean Expanded Disability Status Scale score, 2.0) participating in the Swiss Atorvastatin and Betaferon in Multiple Sclerosis Trial with approval of the Cantonal Ethical Review Board (permit 17/05). In this study, patients with relapsing-remitting MS are treated with interferon beta-1b monotherapy (250 μg every other day, subcutaneous) or with a combination of interferon beta-1b (250 μg every other day, subcutaneous) and atorvastatin calcium (40 mg orally). All of the included patients were treated de novo with interferon beta for 3 months, prior to randomization to a monotreatment or combination treatment (n=12 and n=16, respectively). Patients in the Swiss Atorvastatin and Betaferon in Multiple Sclerosis Trial were diagnosed with MS according to the McDonald criteria: disease duration of 3 months or longer, an Expanded Disability Status Scale score of 0 to 3.5 at baseline, and at least 1 relapse in the past 2 years.[5] A 1-month interval between the last relapse and/or prednisone treatment was mandatory for baseline enrollment of the respective patient. The control group consisted of 10 age-matched healthy control subjects (mean age, 34.7 years) after obtaining informed consent.

Serum samples were collected by standard procedures and stored at –80°C until use. Active MMP-9 and TIMP-1 levels were determined with sandwich-type enzyme-linked immunosorbent assay kits (GE Healthcare, Buckinghamshire, England) that had been proven reliable in MS studies.[6] Special emphasis was paid to identical sample collection and processing conditions to minimize possible interference by preanalytical variations. Samples were diluted 1:40, and the detection limits were 0.5 ng/mL (active MMP-9) and 1.25 ng/mL (TIMP-1). The comparisons between control subjects and patients with MS (baseline) and intergroup treatment effects at 3, 6, and 9 months were performed with a Mann-Whitney U test. Changes over time were evaluated with a Wilcoxon signed rank test. $P < .05$ was considered to be statistically significant.

Results. In patients with MS, significantly higher levels of active MMP-9 ($P < .001$) (**Figure**, A) and a higher active MMP-9–TIMP-1 ratio ($P = .002$) (Figure, E) were detected at baseline as compared with the values found in serum samples from control subjects. Serum levels of TIMP-1 were significantly decreased in patients with MS ($P = .049$) (Figure, C). After a 3-month treatment interval with interferon beta, TIMP-1 levels were increased in comparison with TIMP-1 levels at baseline before initiation of therapy ($P = .003$), whereas active MMP-9 levels and the active MMP-9–TIMP-1 ratio were not altered during this treatment interval. Serum levels of active MMP-9 and TIMP-1 and the active MMP-9–TIMP-1 ratio were not influenced by atorvastatin as an add-on treatment during the study period (Figure, B, D, and F).

Comment. Here, we demonstrated a raised serum ratio of active MMP-9–TIMP-1 (Figure, E) and an interferon beta–induced increase of TIMP-1 levels (Figure, C) in patients with MS. These findings are consistent with previous observations of proteolytic dysregulation in MS and stabilization of the MMP-9–TIMP-1 ratio by interferon beta.[6,7] During a study period of 9 months, no further alterations of the proteolytic balance were observed with interferon beta treatment. Ancillary atorvastatin treatment did not have any additional effect on the interferon beta–induced antiproteolytic state. Hence, our results exclude both a detrimental neutralization and a synergistic effect on proteolysis by adding atorvastatin to interferon beta therapy in patients with relapsing-remitting MS.

Johann Sellner, MD
Isabell Greeve, MD
Stephen L. Leib, MD
Heinrich P. Mattle, MD

Correspondence: Dr Sellner, Department of Neurology, Klinikum rechts der Isar, Technische Universität
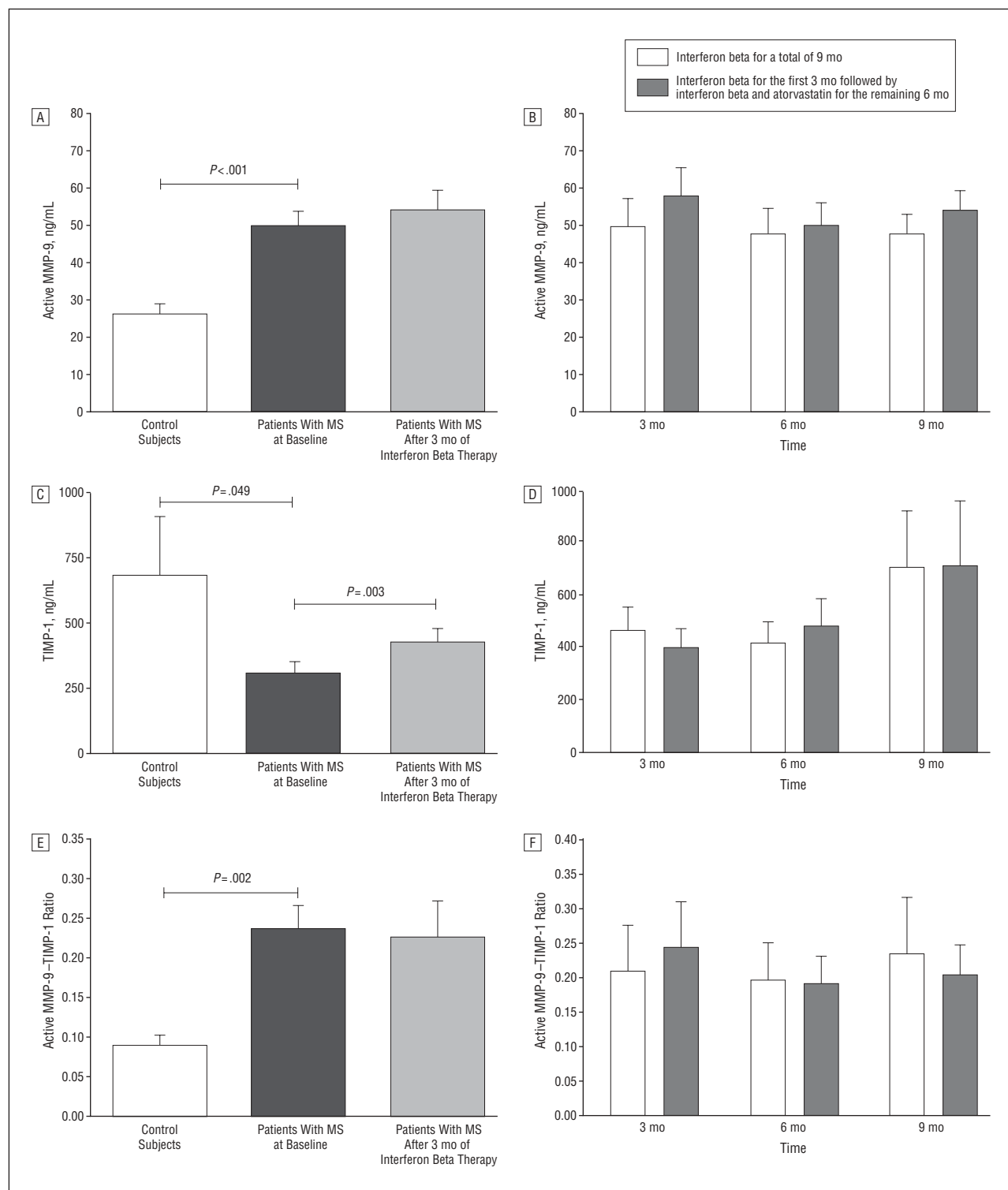
Figure. Mean (SEM) serum levels of active matrix metalloproteinase 9 (MMP-9) (A), tissue inhibitor of metalloproteinase 1 (TIMP-1) (C), and active MMP-9–TIMP-1 ratio (E) in control subjects (n=10) and in patients with relapsing-remitting multiple sclerosis (MS) at baseline (n=28). Mean (SEM) serum levels of active MMP-9 (B), TIMP-1 (D), and active MMP-9–TIMP-1 ratio (F) in patients with relapsing-remitting MS following either a monotherapy of interferon beta for 9 months (n=12) or a monotherapy of interferon beta for 3 months followed by a combination therapy of interferon beta and atorvastatin for 6 months (n=16).

München, Ismaninger Strasse 22, D-81675 München, Germany (sellner@lrz.tum.de).

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COMMENTS AND OPINIONS

Multiple Sclerosis and Recurrent Disseminated Encephalomyelitis Are Different Diseases

The recent article by de Seze et al[1] correctly identifies a set of clinical signs and symptoms that may be useful in differentiating acute disseminated encephalomyelitis (DEM) from the first episode of multiple sclerosis (MS). However, their contention that DEM may evolve or convert to MS implies that the 2 conditions are, if not identical, at least closely related. In fact, they differ in at least 2 ways. Multiple sclerosis occurs in people who are genetically vulnerable, a feature noticeably lacking in DEM. Even more importantly, ever since Robert Carswell and Jean Cruveilhier published their classic illustrations of MS almost 200 years ago, the sharp edges of the typical MS lesion—so aptly described by Ludo van Bogaert as *découpées à l'emporte-pièce*—have been recognized by neuropathologists of the caliber of Ivan Bertrand, Jean Gruner, and François Lhermitte, to name just a few, as pathognomonic for MS; they are never seen in DEM. It is difficult to accept the concept that DEM would morph into a genetically and pathologically dissimilar disease.

The authors seem to rely to a large extent on the series of cases by Schwarz et al,[2] who rather simplistically and inappropriately diagnosed DEM retrospectively based solely on the lack of further episodes of neurological dysfunction. They also ignore the enormous literature describing the qualitative differences between the T2-weighted magnetic resonance imaging lesions of DEM and those of MS,[3-6] relying only on purely quantitative criteria despite their own description of the DEM lesions being widespread, multifocal, and extensive. Surprisingly, they list 2 cases of MS as having spinal cord lesions longer than 2 vertebral bodies despite the admonition in the 2001 diagnostic criteria by McDonald et al[7] that such lesions would strongly militate against the diagnosis of MS. Their use of the term *multiphasic DEM* is confusing: I described multiphasic DEM[6] as the occurrence of new signs or symptoms after an initial episode of acute DEM, in contrast with recurrent DEM in which there is a return of the same signs and symptoms present in the first event. Finally, the cutoff point of 16 years and the exclusion of children seem rather arbitrary because the general consensus is that MS is acquired early in childhood. There is no convincing evidence that MS and DEM in children are different from the adult conditions.

The decision to start a lifelong regimen of immunomodulatory drugs is to be considered with great care; certainly, accuracy of diagnosis should be the principal consideration.

Charles M. Poser, MD, FRCP

Correspondence: Dr Poser, 11 Rutland Sq, Boston, MA 02118 (posercharles11@comcast.net).
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In reply

My coauthors and I thank Dr Poser for the interesting comments. We agree with most of these remarks, but we think that they are not applicable to clinical practice. We agree that acute DEM is a different condition compared with MS; however, as Dr Poser says, the 2 diseases are essentially different concerning genetic susceptibility and neuropathological data. If we consider the question to be a clinical point of view, we are not able to use these parameters to distinguished the 2 diseases.