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Editorial

Cholesterol-lowering statins possess anti-inflammatory activity that might be useful for treatment of MS

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce atherogenesis and cardiovascular morbidity. These effects are attributed to alteration in cholesterol metabolism and reduction in low-density lipoprotein (LDL) formation. Now there is evidence that statins have immunomodulatory activities that could be beneficial in treatment of various inflammatory conditions. In 1995, pravastatin was reported to reduce hemodynamically significant rejection episodes and increase survival in cardiac transplant recipients, independent of its cholesterol-lowering effects.[1] This observation prompted subsequent in vitro studies that demonstrated that statins interfered with production of several important proinflammatory mediators.[2,3] Of relevance to treatment of CNS inflammatory conditions such as MS, lovastatin suppressed production of inducible nitric oxide synthase (iNOS) and secretion of tumor necrosis factor-α (TNFα) by interferon-γ (IFNγ)-activated astrocytes and microglia.[2] iNOS and TNFα may play important roles in the inflammatory process of MS.[4] Lovastatin partially suppressed acute experimental autoimmune encephalomyelitis (EAE) in rats.[5] Central in importance to activation of proinflammatory CD4 T cells, statins inhibited IFNγ-inducible major histocompatibility complex (MHC) class II upregulation on certain antigen-presenting cells via inhibition of IFNγ-inducible transcription of the MHC class II transactivator (CIITA),[6] a protein that directs MHC class II expression. MHC class II genes are associated with susceptibility to MS, and induction of MHC class II in the CNS during the pathogenesis of MS is at the center of a destructive cascade of inflammatory events targeting the white matter and the underlying axon in this disease.

In this issue of *Neurology*, Neuhaus et al.[7] examine how statins influenced in vitro activation of T cells from IFNβ-1b–treated patients with relapsing-remitting MS and healthy controls. Peripheral blood mononuclear cells (PBMC) were activated by mitogen or antibody to the T-cell receptor complex in the presence of lovastatin, simvastatin, or mevastatin. T cells from patients with MS and healthy donors responded in a similar manner. Although all three statins tested inhibited proliferation in a dose-dependent manner, simvastatin, the least hydrophilic, was most potent. In combination with IFNβ-1β, simvastatin suppressed proliferation further, suggesting a potential additive effect. Simvastatin reduced T-cell secretion of matrix metalloprotease (MMP)-9, an enzyme that is important in allowing lymphocytes to breach the Virchow-Robin space and enter the CNS.[4] Simvastatin inhibited upregulation of T-cell surface proinflammatory Th_1 chemokine receptors, important again in the migration of proinflammatory T cells to the white matter, and downregulated intercellular adhesion molecule (ICAM)-1, a key adhesion molecule in the movement of lymphocytes into brain. In addition, similar to a previous report, simvastatin suppressed MHC class II upregulation. Although these results indicated that simvastatin could have anti-inflammatory properties, its effects on secretion of proinflammatory Th_1 and anti-inflammatory Th_2 cytokines were mixed. Interestingly, it was observed that atorvastatin, the currently available statin that is most effective in cholesterol reduction and the most potent statin inhibitor of inducible MHC class II expression, prevented or reversed chronic or relapsing paralysis in three separate murine EAE models.[8] Atorvastatin also promoted the differentiation of Th_0 cells into regulatory Th_2 cells, which could protect recipient mice from EAE induction.

What mechanisms account for the immunomodulatory effects of statins? Mevalonate, which is the product of HMG-CoA reductase and involved in the post-translational modification (isoprenylation) of several proteins involved in cell differentiation and

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signal transduction,[9] can inhibit many of the statin effects described. However, independent of the mevalonate pathway, statins can bind directly to lymphocyte functional antigen (LFA)-1 and inhibit its interaction with ICAM-1,[10] indicating that statins can interact directly with a protein involved in adhesion and T-cell activation. Thus, statins may use multiple mechanisms in altering expression of several targets. Although many of these observations, such as those of Neuhaus et al.,[7] are new, the importance of the mevalonate pathway and its inhibition by statins has been recognized for some time.[9] While interest in testing statins in inflammatory conditions is not an example of rational drug design, the potential use of statins did not result solely from serendipidity. Rather, a growing case can be made that statins are targeting a constellation of critical molecules involved in the pathogenesis of MS.

Current MS treatments are only partially effective, are administered parenterally, and are often limited by side effects or toxicity. In contrast, statins are administered orally, are well tolerated, and are generally safe. They are attractive candidates for MS therapy and their potential use poses important questions: 1) What doses should be tested? A dosage used for cholesterol reduction may not alter immune regulation. 2) At which stage of MS should statins be tested? MS is a multiphasic disease.[4] CNS inflammation and demyelination characterize the early relapsing-remitting phase, whereas neuronal loss and atrophy occur in the secondary progressive phase. EAE data support testing statins in the inflammatory phase. Statins may also have neuroprotective effects, which could be beneficial in the chronic phase. Because statins are safe when given over time, they are attractive candidates for treatment of patients who have experienced one demyelinating attack, a "clinically isolated syndrome," and are at risk to develop clinically definite MS. Since statins have different mechanisms of action from other MS therapies, will they be useful in combination? It is an exciting possibility that oral drugs that are not systemically immunosuppressive could be beneficial in MS. The efficacy of statins should be tested in controlled clinical trials.

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