New Evidence for Beneficial Effects of Statins Unrelated to Lipid Lowering

Wulf Palinski

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) constitute the single most powerful class of hypolipidemic drugs currently available. Their efficacy in reducing coronary morbidity and mortality has been established by several large secondary and primary intervention trials (reviewed in Reference 1). Remarkably, in some of these trials, survival curves began to diverge within a relatively short period, presumably too short to achieve a significant reduction of preexisting atheroma or to prevent progression of lesions to clinically relevant stages. This suggests that effects of statins other than lesion regression contribute to the rapid reduction of coronary symptoms.

During the past several years, numerous additional effects of statins on vascular cells have been identified that could modulate atherogenesis, plaque rupture, or thrombosis. Some of these appear to be independent of the cholesterol-lowering effect. For example, statins upregulate nitric oxide (NO) expression by interfering with the posttranscriptional regulation of endothelial NO synthase (eNOS). Evidence for the importance of this mechanism in vivo was provided by the observation that statins inhibit ischemic cerebral stroke induced by occlusion of the middle cerebral artery in normal but not in eNOS-deficient mice. Other potentially protective effects of statins on endothelial cells include an increased fibrinolytic activity through enhanced expression of tissue plasminogen activator and platelet activator inhibitor-1. In smooth muscle cell cultures, statins inhibit proliferation and stimulate apoptosis. Monocyte recruitment into the vascular intima in response to inflammatory cytokines may also be affected by statins, which inhibit the expression of monocyte chemoattractant protein-1 by stimulated peripheral blood monocytes and endothelial cells.

Such pleiotropic effects of statins are not altogether surprising. In addition to reducing cholesterol synthesis (and plasma cholesterol levels by compensatory upregulation of LDL receptors), HMG-CoA reductase inhibitors decrease formation of isoprenylated and geranylgeranylated proteins through the mevalonate pathway. The role of protein lipida
tion in cell signaling is increasingly recognized, and many of the cholesterol-independent effects referred to above were reversible by addition of geranylgeranyl or farnesyl pyrophosphate. However, it is difficult to estimate the contribution of specific cholesterol-independent effects of statins to the overall reduction of coronary morbidity and mortality because of the marked hypcholesterolemic effects in most human trials and animal studies. Cholesterol lowering—not only by statins but also by dietary means or other drugs—stabilizes plaques via a number of different mechanisms. Conversely, hypercholesterolemia—or the enhanced lipid peroxidation that ensues—activates many of the same pathogenic mechanisms that are attenuated by statins via cholesterol-independent pathways. Classic examples include monocyte chemoattractant protein-1 expression, which is regulated by the oxidation-sensitive nuclear factor κB pathway, and apoptotic signaling. Vascular reactivity, too, may be influenced by the cholesterol-lowering effect of statins. Thus, synergisms of indirect effects resulting from cholesterol lowering and cholesterol-independent cellular effects of statins are likely to exist.

Nevertheless, increasing evidence suggests that the anti-inflammatory effects of statins play an important role in attenuating atherosclerosis and other inflammatory processes. A significant reduction of cardiac rejection, lower incidence of vasculopathies, less intimal thickening, and increased survival were observed in cardiac transplantation patients treated with pravastatin or simvastatin. Neointimal inflammation was also reduced in a rabbit model. Again, this was associated with a significant reduction in plasma cholesterol. Other indications for an anti-inflammatory effect are provided by the reduction of C-reactive protein in a randomly selected subgroup of subjects from the Cholesterol and Recurrent Events (CARE) study. However, neither the mechanism responsible nor the independence of this effect from the cholesterol-lowering effect of statins have been established.

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Sparrow and colleagues provide compelling in vivo evidence for direct, cholesterol-independent inhibition of both acute and chronic inflammatory conditions. Using an established model of acute inflammation characterized by infiltration of polymorphonuclear leukocytes, ie, the plantar injection of a sterile, carrageenan-containing solution, they demonstrated a significant reduction of edema formation in C57BL/6NT mice orally treated with simvastatin 1 hour before carrageenan injection. The effect was dose dependant and comparable to that achieved with indomethacin. Both treated and control mice had normal cholesterol levels, and the short time interval in any case rules out hypocholesterolemic effects. Similar treatment 24 hours before plantar injection of the irritant had no effect. The authors then tested the effect of simvastatin treatment on atherosclerosis in...
apolipoprotein E–deficient (apoE–/) mice. Previous studies had shown that inhibition of HMG-CoA reductase does not significantly lower cholesterol levels in mice, and this was also true in apoE–/– mice fed a diet containing 0.15% cholesterol. In the absence of a significant hypocholesterolemic effect, treatment of 16- to 20-week-old mice with 100 mg simvastatin/kg body weight for only 6 weeks resulted in a significant reduction of the aortic content in total and free cholesterol and cholesteryl esters, compared with controls. In a separate experiment, carrier-treated control animals showed a marked increase in aortic cholesterol, compared with animals killed at baseline, and simvastatin reduced this by 66% to 77%. Given that the aortic cholesterol content is generally correlated with surface or cross-sectional measures of atherosclerosis, these data can be considered to provide the first evidence for a significant reduction of atherosclerosis by statins through a mechanism(s) independent of cholesterol lowering. Most important, this effect was evident in a model with extensive preexisting atherosclerotic lesions and occurred within a remarkably short time.

To date, little is known about the anti-inflammatory effects of statins in vivo. The study by Sparrow and colleagues unfortunately did not investigate the effects of statins on the presence of inflammatory cells or cytokine expression in lesions (with the exception of intimal macrophages) and thus cannot shed light on the mechanism(s) responsible for the reduction of atherosclerosis. Previous in vitro studies, however, have identified a number of candidates. In addition to reducing endothelial leukocyte interactions and protecting against neutrophil-induced ischemic reperfusion injury, at least 1 statin (lovastatin) inhibits expression of inducible NO synthase and the proinflammatory cytokines tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 in macrophages. Similar effects were noted in rat astrocytes and microglial cells, and lovastatin treatment significantly improved survival in a rat model of experimental allergic encephalomyelitis. IL-8 and MCP-1 secretion of Chlamydia pneumoniae–infected human macrophages was also attenuated by statins. In addition, a recent report suggests that lipophilic statins inhibit proinflammatory cytokines IL-1β, IL-6, and cyclooxygenase-2 by upregulating the p53 tumor suppressor protein(s). A marked antiatherogenic effect resulting from the downregulation of several proinflammatory genes induced by synthetic PPAR-γ ligands has recently been demonstrated, but analogous evidence for PPAR-α ligands is still outstanding.

Finally, an important new role for statins in immunosuppression was just reported by the group of Dr François Mach. This elegant study demonstrated that statins inhibit the expression of major histocompatibility class II (MHC II) antigens by primary human macrophages and endothelial cells in response to interferon-γ (IFN-γ). The effect was dose dependent, exerted to various extents by different statins, and limited to cells that express MHC II only in response to IFN-γ stimulation. In contrast, “professional” antigen-presenting cells constitutively expressing MHC II, such as dendritic cells and B lymphocytes, were not inhibited, and neither was MHC I expression. Inhibition of MHC II resulted from reduced activation of the inducible promoter IV of the transactivator CIITA. Because expression of MHC II molecules plays an important role in the activation of T-cell subpopulations (T-helper cells), the immunosuppressive activity of statins may greatly contribute to the beneficial effect of statins in cardiac transplant patients. Although an indication of statins as immunosuppressors for chronic inflammatory conditions will require confirmation by in vivo studies, in vivo evidence for a beneficial role of other forms of specific immunomodulation in atherosclerosis already exists (reviewed in Reference 33). Inhibition of MHC II expression is unlikely to account for the protective role of statins in the acute inflammatory response observed by Sparrow et al. but it would be worth testing its potential involvement in the reduction of atherosclerosis in their model and over longer time periods.

The cholesterol-independent effects of statins appear to be well documented in vitro and a growing number of experimental models. Their relevance to humans, however, remains to be established, particularly in view of the high doses of statins required to achieve some of these effects.

References


**Key Words:** HMG-CoA inhibitors: chronic and acute inflammation atherosclerosis immune system in vivo
New Evidence for Beneficial Effects of Statins Unrelated to Lipid Lowering
Wulf Palinsk

doi: 10.1161/01.ATV.21.1.3

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/1/3

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/