Statin Therapy
Beyond Cholesterol Lowering and Antiinflammatory Effects
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Aggressive cholesterol lowering has gradually been adopted by clinicians as part of a standard treatment regimen for patients with documented coronary artery disease, including those who have had recent bypass surgery and acute coronary syndrome. According to the recently published National Cholesterol Education Program Adult Treatment Panel III (NCEP III) guidelines, those patients who have documented coronary disease should have their LDL cholesterol lowered to less than 100 mg/dL.

The clinical benefit of statin therapy is primarily attributed to its LDL-lowering (and potentially HDL-elevating) effects. A subgroup analysis, however, of large clinical trials indicates that statin-treated individuals have significantly less cardiovascular disease than patients with comparable serum cholesterol levels. Subsequently, intriguing experimental data have shown that statins exhibit pleiotropic effects that can beneficially impact occlusive vascular disease, including inhibition of smooth muscle proliferation and platelet aggregation, enhancement of endothelial function, and antiinflammatory actions. These effects could be due to the fact that mevalonic acid is the precursor of not only cholesterol synthesis but also of many nonsteroidal isoprenoid compounds. These signaling intermediates are thought to be important for the subcellular localization and intracellular trafficking of several membrane-bound proteins. In addition, statins can induce the phosphorylation (and activation) of the serine/threonine protein kinase, Akt. More recently, experimental evidence suggest that statins may also have oncoproteic effects by inducing certain tumor cell types, such as acute myelogenous leukemia, to undergo apoptosis in a sensitive and specific manner. Also of interest clinically is the fact that statin therapy seems to reduce the risk of bone fracture in retrospective analysis of the Scandinavian Simvastatin Survival Study (4S), as well as in a case-control study supported by gathering experimental data. Thus, it is clear that statins have significant non–cholesterol lowering effects, both in the vascular system and in nonvascular systems.

Extensive evidence accumulated over the past 2 decades has demonstrated that the endothelium provides essential vasculoprotective functions. Although the clinical benefits of balloon angioplasty and stent deployment have been well documented, the mechanical nature of the procedures has obvious injurious effects upon the endothelial layer. Thus, it is not surprising that various strategies have been proposed to enhance endothelial regeneration. In the current issue of Circulation, Walter et al. under the direction of the late Jeffrey Isner, demonstrate that simvastatin treatment can accelerate reendothelialization after balloon injury and reduce restenosis in the rat carotid model. They subsequently hypothesized that one of the underlying mechanisms may be the enhancement of the mobilization and recruitment of endothelial progenitor cells from bone marrow to the site of injury by statins.

To test this idea, the authors performed bone marrow transplantation from Tie2/IacZ mice to lethally irradiated nude mice and rats. Animals receiving statin therapy demonstrated an increased number of b-gal positive cells on the carotid luminal surface. Moreover, simvastatin resulted in elevated numbers of circulating cells that were positive for BS-1 lectin and acetyl low-density lipoprotein (acLDL) uptake, suggestive of endothelial precursor cells (EPCs). In vitro experiments with putative human EPCs determined that incubation with simvastatin caused upregulation of integrins, offering a potential mechanism for their increased adhesiveness to fibronectin-rich areas of balloon injury.

Although this provocative study has potential importance for many vasculopathies, there are a few limitations that should be considered. First and foremost is the identification and function of the cells in question. Although it is attractive to think that the lectin/acLDL–positive cells are of bone marrow origin, the possibility that they are endothelial cells that were shed from the vasculature during the isolation procedure cannot be excluded. In addition, because the cells were identified and quantified after 4 days in culture, it may be that simvastatin affects ex vivo EPC proliferation or survival as opposed to mobilization from the bone marrow. It should be noted that the existing literature regarding the effect of statins upon endothelial cell proliferation has been controversial, with studies demonstrating both positive and negative effects. Of course, if it could be shown that endothelial precursors could be mobilized by statins, the underlying mechanisms would be of tremendous scientific and clinical interest. Furthermore, the function of bone marrow–derived cells compared with existing endothelial cells would be important to determine. For example, would the secretion and activity of humoral mediators be equivalent in the 2 cell types? To that end, factors such as nitric oxide...
and tissue-type plasminogen activator would be of particular interest because it has been already been established that statins increase the expression of these products in cultured endothelial cells.\textsuperscript{22–24} Finally, the demonstration of this effect in larger, more clinically relevant models of restenosis is crucial for the eventual translation into clinical medicine. Importantly, it will be necessary to determine whether this effect holds true in the setting of dyslipidemia.

Even with these caveats, however, we can speculate on the potential clinical implications of these findings. It is well known that statin therapy in humans reverses endothelial dysfunction as early as 6 months after therapy. Can this be due to enhanced turnover of “healthier” endothelial cells from the bone marrow? The cholesterol-independent plaque-stabilizing effects of statins may also be due in part to enhanced reendothelialization of injured vascular surfaces. In addition, the potential use of bone marrow stem cells for therapeutic angiogenesis has been discussed at great length in both the scientific and lay press. As suggested by the authors, the use of statins in combination of bone marrow cells may enhance incorporation into ischemic tissue and the initiation of angiogenesis.

There appears to be an ever-growing list of actions that are attributed to statins beyond their ability to reduce serum cholesterol levels. It remains to be determined, however, which, if any, of these effects are actually clinically important at the dose range used. As with many novel scientific endeavors, the current study\textsuperscript{19} seems to invoke more questions than answers. Even after his untimely death, Dr Jeffrey Isner continues to challenge our traditional way of thinking and inspire us to strive for a better understanding of how nature operates.

References


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