Statins as Potent Antiinflammatory Drugs

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Statins have previously been shown to significantly reduce cardiovascular disease events in a number of large clinical trials. As a result, statins are now considered to represent one of the most powerful classes of agents for the treatment of cardiovascular diseases. Statins are rapidly becoming frontline therapy for diabetes mellitus, hypertension, and other known cardiovascular disease risk factors. Originally, reductions in cardiovascular disease events and mortality and overall improved outcomes were attributed to dramatic reductions in circulating serum lipid levels that were mediated by inhibition of liver 3-hydroxy 3-methyl glutaryl coenzyme A (HMG-CoA) reductase. However, more recent experimental and clinical investigations have revealed that statins can exert a number of cholesterol-independent, cardioprotective actions. In this regard, statins are potent modulators of endothelial cell nitric oxide synthase (eNOS) function and have been shown to upregulate eNOS enzyme levels and nitric oxide (NO) synthesis.

Pruefer and colleagues demonstrated in this issue of Circulation powerful antiinflammatory properties of simvastatin in the setting of Staphylococcus aureus α-toxin infection. Endotoxemia represents a potent stimulus for vascular inflammation that is characterized by increased leukocyte recruitment to the microvascular endothelium. The report by Pruefer et al elegantly demonstrates that pretreatment with clinically relevant doses of simvastatin attenuates endotoxin-induced leukocyte rolling and transmigration in the rat mesentery. Simvastatin was administered 18 hours before administration of endotoxin. Simvastatin expression also resulted in a 50% upregulation of eNOS expression in the endothelium and a 50% decrease in endothelial cell P-selectin expression. Circulating cholesterol levels were not reported in this study, but it is unlikely that acute statin therapy would alter lipid levels in rodents. The data presented in this paper are very convincing and provide yet another example of the potent antiinflammatory actions of acute statin therapy. The results of the study by Pruefer et al may have important clinical implications for the treatment of inflammatory disease states with statin therapy.

Previous experimental and clinical studies have also demonstrated that statins can downregulate both acute and chronic inflammatory processes. Early evidence for the direct vascular effects of statins was provided by clinical studies demonstrating improvements in coronary endothelial function in patients as early as 1 month after the initiation of statin therapy. It soon became evident that statins had potent actions on the vascular endothelium that might be mediated by eNOS. Landmark studies by Laufs et al reported that statins upregulate eNOS function under baseline conditions and after hypoxic conditions. Laufs and colleagues reported that simvastatin and lovastatin increased endothelial cell eNOS mRNA half-life from 13 to 38 hours. Furthermore, Laufs and colleagues discovered that statins augmented endothelial NO function via inhibition of biosynthesis of L-mevalonate and the isoprenoid geranylgeranylpyrophosphate (GGPP). GGPP is involved in the posttranslational modification of a variety of proteins, including eNOS, and Ras-like proteins, such as Rho. Inhibition of Rho results in a 3-fold increase in eNOS and nitrite generation, since Rho is an endogenous inhibitor of endothelial NO generation. More recently, Kureishi et al have provided a very elegant demonstration that simvastatin activates the protein kinase Akt resulting in enhanced eNOS phosphorylation and NO generation via eNOS. The results of Kureishi and colleagues demonstrate that statins can produce a very rapid improvement in endothelial function that is independent of changes in eNOS mRNA levels. Kureishi et al also reported for the first time that simvastatin treatment can attenuate endothelial cell apoptosis and augment angiogenesis in the ischemic rabbit hind limb model system. Since eNOS-derived NO represents a highly potent antiinflammatory signaling pathway, the investigation of statins as antiinflammatory agents is very logical.

After the landmark discovery that statins upregulate eNOS function, a number of studies have reported very powerful antiinflammatory actions of statins that are largely eNOS-dependent. Lefer et al were among the first to report antiinflammatory actions of statins in an in vitro model of acute myocardial ischemia-reperfusion. Subsequently, Pruefer et al utilized intravital microscopy to demonstrate that statin therapy very significantly inhibits leukocyte–endothelial cell interactions independently of any lipid lowering actions in normocholesterolemic rats. More recently, rosuvastatin has been shown to exhibit similar antiinflammatory properties in the microvasculature. Since these initial studies of statin therapy in acute myocardial infarction in vitro, there have been a number of in vivo reports demonstrating highly potent antiinflammatory and cardioprotective actions of statins in the setting of acute myocardial infarction in vitro.
normcholesterolemic,13 hypercholesterolemic,13 and diabetic14 animal models. The cardioprotective actions of statin therapy are not transient in nature and have been shown to be present at 6 months of reperfusion after statin therapy before the onset of acute myocardial infarction.15 Statin therapy has been shown to inhibit leukocyte accumulation in the ischemic-reperfused myocardium and to be highly dependent on eNOS, since eNOS deficient mice are completely resistant to statin-mediated cardioprotection.

Clinical evidence supporting the potent antiinflammatory and cardioprotective actions is beginning to emerge. It is now well appreciated that atherogenesis is primarily an inflammatory process mediated in large part by the recruitment of blood monocytes to the vessel wall.16 Statin therapy has been shown to attenuate vascular inflammation in patients, as evidenced by significant reductions in inflammatory markers such as high sensitivity C-reactive protein (hsCRP)17 and soluble CD40 ligand.18 Furthermore, it has been reported very recently that statin therapy in patients is associated with a significant reduction in mortality very early after percutaneous coronary interventions.19 It is possible that these acute effects of statin therapy may be related to attenuation of inflammatory processes. In addition, results from the Platelet Receptor Inhibition in ischemic Syndrome Management (PRISM) study20 clearly demonstrated that withdrawal of statin therapy very significantly increases event rates in patients with acute coronary syndromes. Interestingly, the increased event rate occurred during the first week after the onset of symptoms and was independent of cholesterol levels.

In summary, statins are now becoming recognized as powerful antiinflammatory agents that exert beneficial effects beyond low-density lipoprotein cholesterol reduction. Up-regulation of endothelial function (ie, eNOS enzyme activity) is thought to be a primary mechanism responsible for these antiinflammatory properties. Pruefer et al6 now provide additional evidence that statin therapy attenuates inflammation and further extend our understanding of this very exciting class of cardiovascular agents.

References

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