Editors

Should Treatment of Sepsis Include Statins?

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During the past decade, HMG-CoA reductase inhibitors (statins) have been shown to improve survival in patients with cardiovascular disease. Initially, the beneficial effects of statins were attributed simply to lipid reduction; however, more recent data suggest that “pleiotropic” properties such as improvement of endothelial dysfunction, increased nitric oxide bioavailability, and antioxidative and antiinflammatory properties may contribute to the improvement of prognosis in patients with coronary artery disease. Many of these pleiotropic effects of statins are mediated by the ability to block the synthesis of important isoprenoid intermediates, which have been shown to serve as lipid attachments for a variety of intracellular signaling molecules. In particular, the inhibition of the small guanosine triphosphate–binding proteins rho, ras, and rac, the membrane localization of which depends on isoprenylation, may play an important role in mediating the direct effects of statins on the vascular wall. Thus, the characteristics of this class of drugs may explain the dramatic effects on the progression of atherosclerosis and therefore on survival in patients with established coronary artery disease.

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Chronic inflammation and activation of the coagulation system is thought to contribute significantly to the progression of atherosclerosis and to the induction of acute cardiovascular events. Although inflammatory markers such as C-reactive protein (CRP) have been demonstrated to be predictive of clinical atherosclerosis, the exact pathogenetic role of inflammation in the atherosclerotic process is not yet fully understood. One possible proinflammatory mechanism may be chronic exposure to endotoxin, also known as lipopolysaccharide (LPS). In a prospective epidemiological study, Wiedermann et al demonstrated a strong association of endotoxemia with carotid atherosclerosis and cardiovascular disease. Endotoxin is known to be one of the strongest inducers of tumor necrosis factor-α and other proinflammatory mediators (eg, monocyte chemotactic protein [MCP-1]). CD14 is an important recognition receptor for LPS. On the surface of monocytes and granulocytes, CD14 exists as a glycosylphosphatidyl-inositol–linked protein, whereas in the serum it is found in its soluble form (sCD14). The interaction of Gram-negative bacterial LPS and CD14 results in signal transduction through Toll-like receptor-4 leading to cellular activation (via the nuclear transcription factor-kB [NF-kB]), production of inflammatory cytokines (including tumor necrosis factor-α and interleukin-6), chemokines, and the activation and increase in expression of inducible nitric oxide synthase (iNOS). Furthermore, endotoxin stimulates the expression of tissue factor on the surface of monocytes and endothelial cells and thus activates the coagulation cascade.

If endotoxin plays an important role in the pathophysiology of the atherosclerotic process and because statins improve prognosis in patients with coronary artery disease, then it may be hypothesized that statin therapy could help in the setting of endotoxemia as well. In addition, increased levels of LDL are associated with higher mortality in animals challenged with endotoxin, suggesting that lowering LDL levels may be beneficial in patients with endotoxemia. On the other hand, serum lipoproteins are believed to play a major role in the clearance of circulating endotoxin. Endotoxin bound to lipoproteins is preferentially shunted to hepatocytes rather than hepatic macrophages for clearance, and is ultimately excreted in the bile. Therefore, at first glance, it seems to be detrimental to lower cholesterol levels in the setting of endotoxemia; however, LDL in contrast to HDL is much less effective in clearing endotoxin, and the relative importance of LDL in endotoxemia is probably outweighed by the proatherogenic contributions of its oxidized lipids and other LDL components.

Several clinical studies seem to support the concept that statin therapy may be beneficial in patients with endotoxemia. In a prospective observational cohort study in patients with acute bacterial infections, previous treatment with statins substantially reduced the rate of severe sepsis and intensive care unit admissions. Of the 361 patients enrolled, 22.7% were treated with statins at least 4 weeks before their admission. Severe sepsis developed in 19% of patients with no-statin therapy as compared with 2.4% with previous statin treatment. In a retrospective analysis, Liappis et al reported a decreased mortality rate among patients with bacteremia undergoing statin therapy as compared with patients having no statin treatment.

Numerous studies with different cell culture models and in vitro statin treatment as well as ex vivo studies on monocytes after in vivo statin treatment have demonstrated an inhibitory effect on tissue factor expression and thrombin generation. These ex vivo effects were at least in part independent of cholesterol reduction, indicating that additional pleiotropic anticoagulatory effects of statins may come into play (see Krysiak et al for reference).

In this issue of Circulation, Steiner et al provide evidence that statin treatment exerts a beneficial influence on inflammatory as well as procoagulatory processes in the setting of...
acute LPS challenge. In a double-blind placebo-controlled parallel group study, 20 healthy men were treated with high-dose simvastatin (80 mg/d) for 4 days before intravenous LPS challenge (20 IU/kg Escherichia coli, equivalent to 2 ng/kg). Both 4 and 8 hours after LPS administration, venous blood was drawn and stored until final assessment. The authors analyzed hsCRP, MCP-1, sCD40 and sCD40 ligand, and the prothrombin fragment F1.2 by ELISA. Monocyte tissue factor and monocyte-platelet aggregates were measured by flow cytometric analyses.

Treatment of 20 healthy volunteers with 80 mg simvastatin over the course of 4 days resulted in a significant reduction in serum cholesterol levels (4.4±0.3 mmol/L versus 3.6±0.3 mmol/L, P<0.05). Apart from that, no further changes were detectable. Four hours after LPS challenge, there was a 2-fold increase in leukocyte count and a remarkable drop in monocytes of 82%. LPS treatment resulted in a significant increase in tissue factor–positive cells (%CD14+/TF+) after 4 and 8 hours, a phenomenon that was completely blunted by simvastatin pretreatment. This finding was accompanied by a significant increase in prothrombin fragment F1.2 that was also inhibited by pretreatment with simvastatin. The antiinflammatory effects of statin therapy also were indicated by the inhibition of LPS-induced elevation of serum hsCRP and MCP-1 in the simvastatin group. In contrast, LPS administration did not result in a relevant increase in monocyte-platelet aggregates in either group. Collectively, these data demonstrate a substantial inhibition of in vivo LPS-induced inflammatory and procoagulatory responses.

What are the mechanisms underlying the positive effects of statin therapy? In vitro studies have demonstrated that statins are able to decrease the activation of NF-κB by increasing the expression of the NF-κB inhibitory protein IκB, resulting in reduced cytokine production12 and therefore, for example, reduced iNOS expression and iNOS-mediated NO production.13 In vitro experiments with isolated human vessels such as the vena saphena magna indicate that low levels of endotoxin are able to stimulate the release of interleukin-8 and MCP-1 from human vascular tissue as well as monocyte adherence to the endothelium, all of which are inhibited by atorvastatin pretreatment.14 Studies with cultured endothelial cells indicated that these mechanisms are more likely related to the inhibition of isoprenylation (eg, geranylgeranylation) rather than the result of a reduction in cholesterol.14 Furthermore, it has been shown that statins act through an upregulation of endothelial NOS (eNOS) by inhibition of rho geranylgeranylation to stabilize mRNA for eNOS and increase NO production by the endothelium.15 Antioxidant properties of statins via inhibition of superoxide-producing enzymes such as the NADPH oxidase in vascular tissue16 and in neutrophils17 also may contribute to the protective effects seen in response to acute LPS challenges such as reversal of LPS-induced endothelial dysfunction.17

Some critical aspects of the study need to be addressed, however. First, the 80-mg dose of simvastatin is high as compared with the dose used in other studies (10 to 40 mg/d) to reduce the rate of severe sepsis in patients, and the authors do not explain their choice of this high-dose approach. Furthermore, in the Scandinavian simvastatin survival study, a dose of 20 to 40 mg/d was used and showed a significant improvement in survival in patients with coronary artery disease.1 Thus, it would be important to know whether lower concentrations of simvastatin would have the same effect on coagulation and inflammation following LPS challenge. Thus, a simple dose-response relationship is needed.

Second, because inflammatory and procoagulant markers were assessed only after 4 and 8 hours, it cannot be excluded that statin therapy only delays but does not completely blunt LPS-induced inflammation and coagulation.

Finally, to investigate the degree of inflammation, plasma endotoxin levels should be obtained at all time points. LPS administration resulted in an 82% decrease in monocyte and a 17% drop in platelet count after 4 hours. These changes may explain why increased levels of monocyte-platelet aggregates, as a marker of platelet activation, could not be observed after 4 and 8 hours.

In conclusion, the article by Steiner et al11 describes appealing properties of statins on coagulation and inflammation following LPS challenge. Still, the immunomodulatory and antiinflammatory properties of statins need to be further elucidated; this holds true for the dose as well as the timing of statin treatment. Large clinical randomized trials are needed to investigate further whether the indication of statin use should be extended to patients with bacteremia and severe sepsis.

References


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