Statins: the next anti-endotoxin

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ABSTRACT

Sepsis continues to be a major cause of morbidity and mortality. Evidence is emerging from observational studies and basic science research that statins (3-hydroxy, 3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) might be associated with reduced mortality in sepsis. Statins have become the most widely used drugs for lowering serum cholesterol levels, being used by at least 15% of patients requiring admission to hospital, and this number is growing each year. Current prescribing information suggests withholding statin therapy in acutely ill patients for fear of serious side effects. However, statins have been postulated to have beneficial effects independent of their lipid-lowering effects, including anti-inflammatory and immunomodulatory roles. This review discusses the basis of these observations and the current place of statin therapy in patients with sepsis. This is a rapidly growing field of fascinating experimental biology. It suggests an urgent need to investigate the pharmacology of these drugs and reappraise their therapeutic indications in critically ill patients. This may provide new insights into the role of lipids and the endothelium in sepsis. Statins are significantly cheaper than other therapies that have been shown to improve outcome in sepsis, and the demonstration of a mortality benefit would have enormous cost–benefit implications.

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Sepsis is a systemic response to infection characterised by the triggering of many inflammatory pathways. Much of the organ dysfunction seen in sepsis is thought to result from the effects of inflammatory cytokines, the generation of reactive oxygen species, the production of nitric oxide, and the depletion of antithrombin III. Sepsis continues to be a major cause of morbidity and carries a 20%–50% mortality rate.[1-3] Fluid resuscitation, vasopressor therapy, antibiotics and source control remain the mainstays of treatment. Activated protein C and glucocorticoids have been shown to improve outcome in randomised trials.[4,5] However, there have been few other recent advances in the treatment of sepsis. It is intriguing that a widely used class of drugs — the statins — may provide serendipitous benefits to patients with sepsis.

The statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) were introduced into clinical practice in the 1980s. Recent Australian prescribing data (2001) rank statin drugs first and second among prescription medicines for number of prescriptions used and cost.[6] In fact, at least 15% of patients requiring admission to hospital each year take established statin therapy, and the number is growing each year. A similar trend is seen worldwide.

Statins have been shown to have benefits in many groups, including patients with coronary artery disease, those with stroke, high-risk elderly patients, patients having major surgery, and even those with normal lipid levels.[7-10] Some beneficial effects of statins seem to be independent of their lipid-lowering ability, including effects on endothelial function, apoptosis and plaque stabilisation, and are mainly due to anti-inflammatory, anti-oxidant and immunomodulatory roles.[11,12]

Could statin therapy affect outcomes in sepsis?

Two observational studies of patients with bacteraemia have shown that pre-existing statin therapy was associated with a significant reduction in mortality. In a retrospective study of 388 patients with bacteraemia, Liappis and colleagues reported that overall mortality was reduced from 28% to 6% ($P = 0.002$).[13] Similarly, Kruger et al found that all-cause hospital mortality was reduced from 23.1% to 10.6% in 438 patients with documented bacteraemia.[14] This difference was more pronounced in patients who continued to receive statin therapy after the onset of bacteraemia (18.3% versus 1.8%). These findings raise the possibility that ceasing pre-existing statin therapy in sepsis, as recommended by current prescribing guidelines, may be associated with increased mortality.[14] A recent prospective observational cohort study also concluded that prior statin therapy is associated with a decreased rate of severe sepsis and may reduce intensive care unit admissions.[15] The largest study to date assessed more than 90 000 patients discharged from hospital with cardiovascular disease.[16] Statin therapy was associated with a reduction in the subsequent risk of developing sepsis in all patient subgroups.

The findings of all these studies have the inherent limitations of observational studies. In particular, they cannot fully account for the effect of greater illness severity leading to cessation of statin therapy, thus biasing study outcomes. Not all studies support a potential benefit associated with statin therapy. Fernandez et al recently

reported an increase in mortality for ICU patients who continued statin therapy.[17]

Are there animal data supporting benefits in sepsis?

The potential beneficial effects of statins in sepsis have been tested in several animal models. In a murine model of caecal ligation and perforation, Merx et al demonstrated that mice pre-treated with statins had a fourfold increase in mean survival compared with control mice.[18] The same investigators subsequently found that statin therapy commenced after induction of sepsis also significantly improved survival time, from 23 (SEM, 1.2) hours for placebo-treated mice to 37 (SEM, 3.6) hours for simvastatin-treated, 40 (SD, 4.2) hours for atorvastatin-treated, and 39 (SD, 3.9) hours for pravastatin-treated mice.[19] The improvement was based on the preservation of cardiac function and haemodynamic status, improved responsiveness to dobutamine, and reduction in the inflammatory response. Interestingly, the benefits extended to several, but not all, of the statins tested.

Is there a biological rationale?

In addition to their main effect on low-density lipoprotein (LDL) cholesterol, statins exhibit a wide range of other biological effects. These effects are often termed pleiotropic (Greek for "many turnings"), and include actions on cell proliferation and endothelial function, immunomodulatory effects, antioxidant effects and effects on coagulation. As all statins lower LDL cholesterol levels, and LDL plays an important role in many of these functions, it is difficult to show that the effects of statins are not related to LDL-lowering.

Several authors have recently reviewed the biology of statins in sepsis.[20,21] Emerging research on these pleiotropic effects provides a potential scientific basis for an outcome benefit with statin therapy in sepsis.

What are the potential mechanisms?

Increase or alterations in high-density lipoprotein cholesterol

Significant changes in lipid metabolism occur in sepsis. Total cholesterol and high-density lipoprotein (HDL) cholesterol levels are decreased in sepsis, and the magnitude of the changes seems to reflect the severity of inflammation.[22,23] Both the amount and composition of HDL change in sepsis,[24] potentially affecting the inflammatory cascade and outcome.[22] Bacterial endotoxin (lipopolysaccharide) elicits dramatic responses in the host, including elevated plasma lipid levels due to the increased synthesis and secretion of triglyceride-rich lipoproteins by the liver, and the inhibition of lipoprotein lipase. This cytokine-induced hyperlipoproteinaemia, clinically termed the "lipaemia of sepsis", was customarily thought to represent the mobilisation of lipid stores to fuel the host response to infection. However, as lipoproteins can also bind and neutralise lipopolysaccharide, it is postulated that triglyceride-rich lipoproteins (very low-density lipoprotein [VLDL] and chylomicrons) are also components of an innate, non-adaptive host immune response to infection.[25] In general, statin therapy increases HDL levels, in addition to its LDL-lowering effects.[26,27] The effect of statin therapy on the lipid profile in sepsis remains unclear, but it may be that alterations in the lipoprotein balance have profound effects on inflammation.

Direct antioxidant mechanisms

Oxygen free radicals are involved in the pathogenesis and manifestations of sepsis, as they react with various biological substrates, especially polyunsaturated fatty acids, to induce membrane dysfunction, tissue damage and organ injury.[28] Some pleiotropic effects of statins could be attributed to their ability to suppress the synthesis of isoprenoid intermediates, thereby possibly decreasing oxidative stress.[29] Statins reduce the production of reactive oxygen species by vascular NAD(P)H oxidase, and inhibit the respiratory burst of phagocytes.[30]

Immunomodulatory effects of statins

It appears that statins are able to influence inflammatory processes at several levels. They have been shown to reduce the adhesiveness of monocytes to the vascular endothelium,[31,32] and to directly inhibit the main β_2-integrin leukocyte function antigen-1.[33] Statins deplete isoprenoids, which, via membrane G proteins, play a pivotal role in the signal transduction pathways that regulate cellular migration and proliferation.[34] Several studies have shown that statin therapy either lowers circulating concentrations of C-reactive protein or reduces the risk associated with systemic inflammation, in some cases independently of the reduction in cholesterol level.[35]

Statins have been shown to inhibit elements of the inflammatory cascade induced by *Escherichia coli* endotoxin[36] and *Staphylococcus aureus* α-toxin.[37] They have also been shown to reduce complement activation in vitro and in animal models.[38]

Improvement in vascular function: the role of nitric oxide

Endothelial cells play an important role in the control of vascular tone, permeability, blood flow, coagulation, thrombolysis, inflammation, tissue repair and growth.[39] It is thought that endothelial activation, dysfunction and apoptosis play a crucial role in the pathogenesis of sepsis and subsequent multiple organ dysfunction. Considerable research has focused on the mechanisms by which statins

enhance endothelial anticoagulant and fibrinolytic properties. These studies show that statins increase expression and enhance activity of endothelial nitric oxide synthase,[40] up-regulate prostacyclin[41] and tissue-type plasminogen activator,[42] and down-regulate tissue factor, endothelin-1 and plasminogen-activator inhibitor-1.[43] Statins have been shown to affect serum levels of anti-thrombin III in patients with heart failure.[44]

What is not known?

There is a paucity of data on the use of statins in critically ill patients. While a detailed discussion of the pharmacology of statins is beyond the scope of this article, several gaps in current knowledge are worth highlighting.

How do statins work in sepsis?

It is not known which, if any, of the biological mechanisms discussed above are important in determining outcome in patients with sepsis. It therefore follows that no dose–effect relationship has been described.

When should they be administered?

It is possible that part of the protective effect of statin therapy in sepsis is due to its pre-existing effects, perhaps through its stabilising vascular endothelium and so limiting subsequent organ dysfunction. It is not known whether continuing statin therapy confers additional benefit, whether cessation of pre-existing therapy is detrimental, or whether commencing de-novo statin therapy is an effective adjunct in managing patients with sepsis.

What dose should be given?

The plasma concentration of statins needed for a beneficial effect in sepsis is unknown. However, the pharmacokinetics of these agents are well described in the general population, with most agents having a high first-pass metabolism in the liver, and absorption being affected by food in the stomach. This suggests that changes in splanchnic perfusion associated with sepsis, or the timing of drug administration with enteral feeding might affect plasma levels. Most statin drugs are metabolised by hepatic cytochromes, and interactions with these enzyme systems are ubiquitous in clinical practice, particularly given the range of medications used in critically ill patients. Newer agents are metabolised to a lesser extent, with only 10% of rosuvastatin and pitavastatin being metabolised. This has the potential benefit of limiting the impact of drug interactions that alter serum levels. The impact of organ dysfunction, co-administration of drugs known to affect cytochrome function, and gastric dysmotility on the absorption, pharmacokinetics and pharmacodynamics of statin therapy in patients with sepsis is unknown.

Are statins safe for critically ill patients?

Current prescribing guidelines recommend that statin therapy be discontinued in patients with acute illness, such as severe infection, major surgery, trauma, or severe electrolyte, metabolic or endocrine disorders, for fear of increased risk of toxicity.[45] There are limited data on the safety of statins in patients with sepsis, although rhabdomyolysis and liver dysfunction are well described in high-risk patients.[45-47] While recent publications support the benefits of continued statin therapy in acute coronary syndromes,[48,49] it is not known what should be done with statin therapy when patients are admitted to hospital with sepsis. HMG-CoA reductase inhibition results in inhibition of ubiquinone or coenzyme Q10. It has been reported that this can, rarely, predispose to the development of lactic acidosis caused by paralysis of mitochondrial metabolism.[50] The true relevance of this interaction may become apparent as these agents are increasingly investigated in critically ill patients.

Which drug — are all statins equivalent?

All statins except pravastatin and rosuvastatin are lipophilic. Whether this has any impact on differences in pleiotropic effects remains to be established. While statins as a drug class share many properties, they are not always therapeutically interchangeable.[51] Individual statins have different effects on lipid profiles and possibly also inflammation and pleiotropic effects. They also clearly differ in their propensity to cause rhabdomyolysis, as illustrated by the withdrawal of cerivastatin from the market in 2001, because of a cluster of fatal cases of rhabdomyolysis.[52]

How should they be administered?

The safety, efficacy and place of parenteral administration are unclear, and no intravenous preparations of these agents are marketed.

Conclusions

Emerging evidence suggests that statins have a potentially beneficial role in patients with sepsis, but much remains unknown. Statins are significantly cheaper than other therapies that have been shown to improve outcome in sepsis. Therefore, demonstration of a mortality benefit with statins would have enormous cost–benefit implications for society. Further investigation of the biology of statins in sepsis is warranted.

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References

1 Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29: 1303-10.
2 Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med* 2004; 30: 589-96.
3 Vincent JL, Abraham E, Annane D, et al. Reducing mortality in sepsis: new directions. *Crit Care* 2002; 6 Suppl 3: S1-18.
4 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.
5 Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862-71.
6 Australian Institute of Health and Welfare. Statistics on drug use in Australia 2002. Canberra: Australian Government Department of Health and Ageing, AIHW, 2003: 23-6.
7 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349-57.
8 Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA* 2004; 291: 1864-70.
9 Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003; 107: 1848-51.
10 Lindenauer PK, Pekow P, Wang K, et al. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004; 291: 2092-9.
11 Kwak BR, Mach F. Statins inhibit leukocyte recruitment: new evidence for their anti-inflammatory properties. *Arterioscler Thromb Vasc Biol* 2001; 21: 1256-8.
12 Almog Y. Statins, inflammation, and sepsis: hypothesis. *Chest* 2003; 124: 740-3.
13 Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. *Clin Infect Dis* 2001; 33: 1352-7.
14 Kruger P, Fitzsimmons K, Cook D, et al. Statin therapy is associated with fewer deaths in patients with bacteraemia. *Intensive Care Med* 2006; 32: 75-9.
15 Almog Y, Shefer A, Novack V, et al. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* 2004; 110: 880-5.
16 Hackam DG, Mamdani M, Li P, Redelmeier DA. Statins and sepsis in patients with cardiovascular disease: a population-based cohort analysis. *Lancet* 2006; 367: 413-8.
17 Fernandez R, De Pedro VJ, Artigas A. Statin therapy before intensive care unit admission: protection against infection or a severity marker? *Intensive Care Med* 2006; 32: 160-4.
18 Merx MW, Liehn EA, Janssens U, et al. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. *Circulation* 2004; 109: 2560-5.
19 Merx MW, Liehn EA, Graf J, et al. Statin treatment after onset of sepsis in a murine model improves survival. *Circulation* 2005; 112: 117-24.
20 Terblanche M, Almog Y, Rosenson RS, et al. Statins: panacea for sepsis? *Lancet Infect Dis* 2006; 6: 242-8.
21 Kruger PS, Kostner K, Venkatesh B. Statins in critical illness. In: Vincent JL, editor. Yearbook of intensive care and emergency medicine. Berlin: Springer Verlag, 2005: 477-87.
22 Bonville DA, Parker TS, Levine DM, et al. The relationships of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. *Surg Infect (Larchmt)* 2004; 5: 39-49.
23 Gui D, Spada PL, De Gaetano A, Pacelli F. Hypocholesterolemia and risk of death in the critically ill surgical patient. *Intensive Care Med* 1996; 22: 790-4.
24 van Leeuwen HJ, Heezius EC, Dallinga GM, et al. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med* 2003; 31: 1359-66.
25 Harris HW, Gosnell JE, Kumwenda ZL. The lipemia of sepsis: triglyceride-rich lipoproteins as agents of innate immunity. *J Endotoxin Res* 2000; 6: 421-30.
26 Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999; 341: 498-511.
27 Vaughan CJ, Gotto AM Jr. Update on statins: 2003. *Circulation* 2004; 110: 886-92.
28 Yu BP. Cellular defenses against damage from reactive oxygen species. *Physiol Rev* 1994; 74: 139-62.
29 Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990; 343: 425-30.
30 Beltowski J. Statins and modulation of oxidative stress. *Toxicol Mech Meth* 2005; 15: 61-92.
31 Weber C, Erl W, Weber KS, Weber PC. HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with hypercholesterolemia. *J Am Coll Cardiol* 1997; 30: 1212-7.
32 Crisby M. Modulation of the inflammatory process by statins. *Drugs Today (Barc)* 2003; 39: 137-43.
33 Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med* 2001; 7: 687-92.
34 Frenette PS. Locking a leukocyte integrin with statins. *N Engl J Med* 2001; 345: 1419-21.
35 Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344: 1959-65.
36 Rice JB, Stoll LL, Li WG, et al. Low-level endotoxin induces potent inflammatory activation of human blood vessels: inhibition by statins. *Arterioscler Thromb Vasc Biol* 2003; 23: 1576-82.
37 Pruefer D, Makowski J, Schnell M, et al. Simvastatin inhibits inflammatory properties of *Staphylococcus aureus* alpha-toxin. *Circulation* 2002; 106: 2104-10.
38 Mason JC, Ahmed Z, Mankoff R, et al. Statin-induced expression of decay-accelerating factor protects vascular endothelium against complement-mediated injury. *Circ Res* 2002; 91: 696-703.
39 Cines DB, Pollak ES, Buck CA, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood* 1998; 91: 3527-61.
40 Laufs U, Gertz K, Huang P, et al. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. *Stroke* 2000; 31: 2442-9.
41 Seeger H, Mueck AO, Lippert TH. Fluvastatin increases prostacyclin and decreases endothelin production by human umbilical vein endothelial cells. *Int J Clin Pharmacol Ther* 2000; 38: 270-2.
42 Essig M, Nguyen G, Prie D, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors increase fibrinolytic activity in rat aortic endothelial cells. Role of geranylgeranylation and Rho proteins. *Circ Res* 1998; 83: 683-90.
43 Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. *J Clin Invest* 1998; 101: 2711-9.
44 Tousoulis D, Antoniades C, Bosinakou E, et al. Effects of atorvastatin on reactive hyperaemia and the thrombosis-fibrinolysis system in patients with heart failure. *Heart* 2005; 91: 27-31.
45 MIMS online. Prescribing information. Atorvastatin, simvastatin. MIMS Online Australia, 2004. Available at: http://www.mims.hcn.net.au (accessed Aug 2004).
46 Adverse Drug Reactions Advisory Committee. Risk factors for myopathy and rhabdomyolysis with the statins. *Aust Adv Drug Reactions Bull* 2004; 23: 2.
47 Bellosta S, Paoletti R, Corsini A. Safety of statins: focus on clinical pharmacokinetics and drug interactions. *Circulation* 2004; 109 (23 Suppl 1): III50-7.
48 Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495-504.
49 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; 285: 1711-8.
50 Goli AK, Goli SA, Byrd RP Jr, Roy TM. Simvastatin-induced lactic acidosis: a rare adverse reaction? *Clin Pharmacol Ther* 2002; 72: 461-4.
51 Chong PH. Lack of therapeutic interchangeability of HMG-CoA reductase inhibitors. *Ann Pharmacother* 2002; 36: 1907-17.
52 Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am Heart J* 2004; 147: 956-65. ❑