Statins and Sepsis: Good Bullet, Disappearing Target

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Despite several decades of research and phenomenal advances in technology and therapeutics, sepsis remains a catastrophic enigma. As a frequent cause of death, sepsis now rivals acute myocardial infarction. The longstanding therapeutic principles of early antibiotics use and supportive care have been difficult to improve upon. The authors conducted a concise review of pertinent literature on the pathophysiologic mechanisms of sepsis and the pharmacologic effects of statins. They conclude that, though statins possess anti-inflammatory and lipid-lowering properties, these effects may not be advantageous throughout the changing immunoresponse that can occur in sepsis syndrome. Based on the available information, statin therapy seems advantageous before the onset of sepsis and during sepsis resolution—but not during the compensatory anti-inflammatory response that may occur. Thus, the authors recommend that, until the status of a patient’s changing immune response can be clearly determined, the uninterrupted use of statin therapy throughout the full spectrum of sepsis should be avoided.

In the United States, there were an estimated 750,000 cases of severe sepsis in 1995, resulting in 215,000 deaths, and there was an annualized increase in the incidence of sepsis of 8.7% between 1979 and 2000. Sepsis now rivals acute myocardial infarction as a frequent cause of death. It is the leading cause of death in noncoronary intensive care units (ICUs).

The early use of antibiotics and supportive care are longstanding therapeutic principles for patients with sepsis and have been difficult to improve upon. In large clinical trials of patients with sepsis, hemodynamic optimization, low-volume ventilation, low-dose glucocorticoid therapy for patients with a suboptimal response to adrenocorticotropin, and “tight” glucose control for patients who have had surgery have each demonstrated significant, albeit small, reductions in mortality. Recombinant human-activated protein C has been found to produce favorable results in the most severely ill patients, but it may actually be detrimental to patients whose illnesses are less severe.

When seeking easy solutions to complex medical problems, we sometimes find “silver bullets.” Examples include aspirin for reducing cardiovascular risk, angiotensin-converting enzyme (ACE) inhibitors for managing left ventricular systolic dysfunction, and glucocorticoids for managing reactive airway disease. However, just as a villain must exist before a hero can arise, a clear pathologic target must be known before an effective silver bullet can emerge. In the case of sepsis, the “clear target” remains elusive.

There has been much interest in using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) for sepsis. Therefore, we conducted a concise review of pertinent literature on the pathophysiologic mechanisms of sepsis and the pharmacologic effects of statins using the National Library of Medicine’s PubMed database and other sources. Keywords included compensatory anti-inflammatory syndrome, HMG-CoA reductase inhibitors, sepsis, septic shock, and statins. This review allowed us to speculate on the effectiveness of statin therapy as an adjunct to sepsis management.

Statins: Good Anti-Inflammatory Bullet

In addition to lowering serum lipids and decreasing cardiovascular risk, statins have been shown to have anti-inflammatory effects. Subsequently, speculation has increased as to the beneficial effects of statins in managing sepsis.

In animal studies, improvement in mortality has been demonstrated in sepsis models with administration of the statin simvastatin. In humans with atherosclerotic disease, administration of a statin significantly reduced the risk of subsequent septic events, including severe and fatal sepsis, according to Hackam et al. A list of these and other pharmacologic effects of statins in individuals with sepsis, as indicated by the pertinent literature, is presented in Figure 1.

Published studies on patients with infections—though limited in design, number, and scope—have suggested a net positive effect of prior or concomitant statin prescription.
Almog et al\textsuperscript{15} reported on 361 consecutive patients admitted to a medical service with acute bacterial infection. Within this group, 82 patients (23\%) were treated with a statin before admission.\textsuperscript{15} Severe sepsis occurred in 3\% of statin-treated patients, compared with 19\% of patients not receiving prior statin therapy.\textsuperscript{15}

For patients with documented bacteremia, Liappis et al\textsuperscript{16} and Kruger et al\textsuperscript{17} found a notable decrease in mortality in patients taking statins before hospitalization, compared with patients not taking statins before hospitalization. It should be noted, however, that the number of critically ill patients in each report was small. Within the statin groups, only 6 patients in the Liappis et al\textsuperscript{16} report and 10 patients in the Kruger et al\textsuperscript{17} report required ICU admission.

Fernandez et al\textsuperscript{18} reported on 438 patients who required ICU admission and mechanical ventilatory support. These patients were at high risk of ICU-acquired infections. Within this group, 38 patients (9\%) received statin therapy before ICU admission and continued with this regimen throughout hospitalization.\textsuperscript{18} Statin-treated patients had 61\% mortality versus 42\% mortality for patients not receiving statins.\textsuperscript{18}

In the only long-term study of patients with bacteremia who were receiving concomitant statin therapy, Thomsen et al\textsuperscript{19} found no short-term (0-30 d) advantage—but significantly improved long-term (30-180 d) survival—in patients using statins before, during, and after hospitalization, compared with patients not using statins (8.4\% mortality in statin users vs 17.5\% mortality in nonusers; adjusted mortality rate ratio, 0.44; 95\% confidence interval, 0.24-0.80).\textsuperscript{19} The beneficial effects of statin therapy in this group may have been related to a decrease in cardiovascular events after inflammatory episodes. An association between acute infection and a transient increase in cardiovascular ischemic events was documented by Smeeth et al,\textsuperscript{20} who reported that statins may exert a protective effect in patients with these conditions by decreasing inflammation and blood thrombogenic properties.

Although in vitro studies do not always translate into beneficial in vivo effects,\textsuperscript{21} an extensive accumulation of data has resulted from in vitro studies as to possible physiological mechanisms of statins’ anti-inflammatory effects. This research has found that statins reduce the elevations of cytokine tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) after a lipopolysaccharide challenge.\textsuperscript{22}

Statin also inhibit leukocyte function antigen-1 (LEA-1; also known as CD11a/CD18), which is involved in T-cell activation and leukocyte recirculation and migration to inflammatory sites.\textsuperscript{23} Other research has shown that lipopolysaccharide inhibition of acetylcholine,\textsuperscript{24} norepinephrine,\textsuperscript{24} and phenylephrine\textsuperscript{13} is blocked in the presence of a statin, allowing these agents to result in vasoconstriction. Antioxidant properties of statins include the inhibition of superoxide production via the nicotinamide adenine dinucleotide phosphate oxidase system in monocytes,\textsuperscript{25} neutrophils,\textsuperscript{26} and endothelial cells.\textsuperscript{27} Statin administration has also been found to inhibit the production of nitric oxide, a potent endothelial cell–derived vasodilator that may cause vasopressor-resistant vasodilatation.\textsuperscript{28}

**Other Anti-Inflammatory Bullets**

From the 1970s through the early 1990s, the prevailing concept of sepsis was one of a runaway inflammatory cascade that culminated in multiorgan failure and death.\textsuperscript{29-32} Subsequent research endeavors focused on inflammatory targets.

Several pharmacologic agents were developed based on this concept, but these agents have failed to demonstrate clear, beneficial clinical responses.\textsuperscript{32-35} Among these anti-inflammatory agents are antiprostacyclins,\textsuperscript{36} antiendotoxin antibodies,\textsuperscript{37} bradykinin antagonists,\textsuperscript{38} glucocorticoids,\textsuperscript{39} interleukin receptor antagonists,\textsuperscript{40} monoclonal antibodies to LEA-1 (CD11a/CD18),\textsuperscript{41} nitric oxide synthase inhibitors,\textsuperscript{42} platelet-activating factor antagonists,\textsuperscript{43} soluble TNF receptors,\textsuperscript{44} and TNF antagonists.\textsuperscript{45,46} In addition, some of these agents have even been found to have detrimental effects in patients with sepsis.\textsuperscript{34,44}

**Disappearing Target**

The inability to develop an anti-inflammatory agent with clear clinical benefit for patients with sepsis has led to the concept that sepsis is much more complex and variable than previously believed, making for a very elusive target. Natanson et al\textsuperscript{35} wrote in 1994, “Perhaps our therapeutic premise has been flawed: Attempting to block the harmful effects of inflammatory mediators may not produce a net benefi-
eit [in patients with sepsis] because it may also compromise host defense and ultimately worsen outcome.” Natanson et al\textsuperscript{35} suggested that there is variability in the host response to infection, such as an excessive inflammatory response, immunocompetence, or immunocompromise. The concept of a compensatory anti-inflammatory response syndrome was developed by Bone et al\textsuperscript{39,47} who suggested that an initial intense inflammatory reaction occurs in individuals with sepsis, followed by an immunosuppressed state or downregulation of the immune response. This decrease in immune response, if not recovered, may result in death.\textsuperscript{39,47} The findings of Natanson et al\textsuperscript{35} Bone et al\textsuperscript{39,47} and others demonstrate the complex, variable nature of sepsis. Sometimes it is referred to as the “sepsis syndrome” (Figure 2).

Several mechanisms of immunosuppression in sepsis have been investigated. Among the research findings related to these mechanisms are the following:

- Activated CD4+ T cells can proceed toward distinctly diverging forms of cytokine expression. Type 1 helper T cells produce the inflammatory cytokines TNF-\textalpha, IFN-\gamma, and IL-2. Type 2 helper T cells produce anti-inflammatory IL-4 and IL-10. Patient survival is improved when an exaggerated response by type 2 helper T cells is normalized.\textsuperscript{48,49} Elevated levels of IL-10 can indicate patient mortality.\textsuperscript{39,50}
- Apoptosis via intrinsic proteases occurs at a markedly accelerated rate in patients with sepsis.\textsuperscript{51} Apoptotic cells induce an anergic state in surviving lymphocytes, furthering the anti-inflammatory condition.\textsuperscript{52}
- Monocyte anergy also occurs in patients with sepsis, including down modulation of monocyte human leukocyte antigen-DR\textsuperscript{33} and granulocyte-macrophage colony-stimulating factor.\textsuperscript{54}

Good Bullet, Wrong Target

Statins are effective at lowering lipid levels, but lipids are the wrong target in sepsis. Higher lipid levels are desirable in these patients.

Lipid levels decrease markedly in patients with sepsis and critical illness, with lipoprotein concentrations falling to 50\% of recovery values in most cases.\textsuperscript{55,56} Concentrations of low-density lipoprotein cholesterol are at a nadir at the time of diagnosis of severe sepsis, and concentrations of high-density lipoprotein cholesterol reach nadir by day 3 after diagnosis.\textsuperscript{57} Low lipid levels associated with sepsis—or related to surgery or trauma—may be caused by increased use of the cholesterol substrate for new cell synthesis and repair, according to Engelberg.\textsuperscript{58} Exogenous cholesterol is required for cell development and growth because intrinsic synthesis of cellular cholesterol cannot meet these needs.\textsuperscript{58} Exogenous cholesterol is also required to maintain the fluidity and microviscosity of cell walls.\textsuperscript{58} These cholesterol functions affect the linkage of membrane transport with receptor and enzymatic activities.

Characteristics of Sepsis Syndrome

- fluctuations and variability in immune response (eg, excessive inflammatory response, immunocompetence, immunocompromise)\textsuperscript{35}
- initial inflammatory reaction that may be followed by an immunosuppressed state or downregulation of immune response, which, if not recovered, may result in death (also called compensatory anti-inflammatory response syndrome)\textsuperscript{39,47}

Research has shown that hypcholesterolemia in critical illness and multisystem organ failure correlates with decreased patient survival rates.\textsuperscript{56,59} Lipoproteins have been found to bind with and neutralize bacterial endotoxins.\textsuperscript{60-62} The binding of lipopolysaccharides on the CD14 receptors of monocytes and macrophages results in the production and release of cytokines.\textsuperscript{63,64} Competition for lipopolysaccharide binding between CD14 receptors and lipoproteins is dependent on lipoprotein availability, as noted by Netea et al.\textsuperscript{65} As increasing levels of lipoproteins become available, lipopolysaccharide-lipoprotein interaction and neutralization predominates, resulting in an attenuated release of cytokines.\textsuperscript{65} These data\textsuperscript{60-65} suggest that serum lipoproteins bind lipopolysaccharides, neutralizing them in a concentration-dependent manner.

These and other observations have led to investigations of the effects of lipid-infusion therapy in patients with sepsis.\textsuperscript{66,67} Favorable results of lipid-infusion therapy have been noted in some animal studies.\textsuperscript{66,67} Results from human studies on lipid-infusion therapy were not available at the time the present study was prepared.

When to Shoot

A review of the literature indicates that sepsis is a condition of dynamic response with great variability. Statins clearly possess anti-inflammatory and lipid-lowering properties, but these effects may not remain relevant within the variable continuum of sepsis syndrome. Anti-inflammatory therapies may prove advantageous in cases of excessive inflammatory response, but such therapies may be counterproductive in situations where immunosuppression predominates. Serum lipids also provide essential cellular substrates in times of tremendous demand and dwindling reserves of cholesterol, which is reduced by statins. Furthermore, any process that neutralizes bacterial endotoxins would seem favorable. Thus, based on the
available information, statin therapy seems advantageous in patients before the onset of sepsis and during sepsis resolution, but perhaps not when patients are critically ill.

Ongoing research efforts to develop a means of identifying excessive and potentially detrimental fluctuations in the immune response—whether inflammatory or immune suppressive in nature—may direct statin therapy toward its most effective use. If an excessive inflammatory response is detected, anti-inflammatory agents, including statins, could prove advantageous at that point in the etiologic process. If a transition toward an immunosuppressive state is detected during continued patient monitoring, a change in pharmacologic therapy may be warranted, with deletion of the anti-inflammatory agents.

Until the status of a patient’s changing immune response can be clearly determined, an uninterrupted use of statin therapy throughout the spectrum of sepsis syndrome should be avoided. In summation, we have good pharmacologic “bullets” for sepsis. We just need to know when to “shoot” them.

References

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