EDITORIAL

Statins in patients with sepsis and ARDS: is it over? Yes

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Introduction

Sepsis is associated with significant morbidity and mortality despite advances in treatment, technology and research. Therefore, multiple studies have focused on understanding the pathophysiology of sepsis to improve therapeutic options. We now know that infection triggers an inflammatory response and a compensatory anti-inflammatory response that is intended to minimize the damage from infection. In some patients, this inflammatory response could lead to further tissue damage and, subsequently, to multi-organ failure and acute respiratory distress syndrome (ARDS) [1]. Therefore, various immunomodulating and anti-inflammatory agents have been studied in the sepsis population.

Statins: how do they work?

Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), and have been used as a lipid-lowering agent for many years. However, recent studies have shown that statins have immunomodulation properties that are independent of the lipid-lowering effect.

A randomized trial that enrolled 20 healthy subjects showed that the use of 80 mg of simvastatin for 4 days suppresses the production of high-sensitive C-reactive protein (hsCRP), monocyte chemoattractant protein (MCP-1) and tissue factor (TF), compared to placebo. In addition, simvastatin blunted the increase of monocyte TF expression in response to lipopolysaccharides [2]. Other studies have suggested that statins can inhibit the production of proinflammatory cytokines [3]. An animal

study showed that simvastatin attenuated the inflammatory response and vascular leak in murine models with sepsis-induced acute lung injury (ALI) [4], which formed the basis for subsequent human trials.

Statins and mortality in sepsis

Multiple studies have examined the effect of statins on mortality in patients with varying severities of sepsis. Initial observational studies showed promising results, and a meta-analysis of adjusted estimates from 26 observational studies (336,245 patients) showed a significant reduction in mortality with statin use [relative risk (RR) 0.65; 95 % CI 0.57, 0.75] [5]. However, randomized clinical trials (RCTs) failed to show mortality benefit with statins use. A systematic review and a meta-analysis of five RCTs (650 patients) compared statins to placebo in septic patients. Studies used atorvastatin or simvastatin at doses between 10 and 40 mg daily, for varying durations of therapy. Mortality did not differ significantly between the two groups (RR 0.95; 95 % CI 0.74, 1.21) [6]. However, these results are limited by imprecise estimates and clinical heterogeneity between studies. Subsequently, the largest trial to date (SAILS) randomized patients with sepsis-induced ARDS to receive either rosuvastatin or placebo [7]. The trial was stopped early for futility; 60-day mortality did not differ between the two groups (28.5 vs. 24.9 %; rosuvastatin and placebo, respectively). Some authors argue that hydrophilic statins, like rosuvastatin, have a reduced mitotoxic effect, and the mitotoxic effect may be paradoxically beneficial in septic patients [8]. However, other RCTs, using lipophilic statins, have failed to show mortality benefit of statin use in patients with ventilator-associated pneumonia, ALI, or ARDS [9–11]. Pooled estimates from RCTs in patients with ARDS showed no mortality benefit of statins (Fig. 1). A more robust individual patient data meta-analysis by Gordon et al. (personal communication) revealed no benefit of statins in ARDS, even

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Fig. 1 Meta-analysis using random-effects model to pool the estimates from three RCTs that examined the effect of statin compared to placebo on 28-day mortality in patients with ARDS

when stratified by dosage or lipo/hydrophilic properties. The collective body of evidence from RCTs failed to show mortality benefit of statin therapy in sepsis.

Statins and cognitive impairment in sepsis

A prospective observational study showed that statin use was associated with reduction in the odds of developing delirium in septic patients [12]. This profound treatment effect was not reproducible in a subsequent higher quality study. The SAILS investigator did not find a significant reduction in delirium risk with statin use [13]. This discrepancy in the results could be explained by differences in study design, use of rosuvastatin which has lower penetration to the central nervous system, or differences in the duration of exposure to the intervention or ineffectiveness of statins in preventing delirium. It remains unclear whether statins can lower the risk of delirium in septic patients.

Statins and long-term outcomes in sepsis

Several studies have investigated the impact of statins on cognitive and physical functions in septic patients. Recently, two sub-studies of the SAILS Trial reported long-term outcomes in a subset of patients. Rosuvastatin and placebo groups did not differ in the risk of 6- and 12-month cognitive impairment [13]. Furthermore, 1-year survival, physical function, and mental health did not differ between the two groups [14]. Therefore, it appears that statins do not have an important effect on long-term outcomes in this population.

Statins and adverse events

Statin use can lead to hepatic and skeletal muscle toxicity, the incidence of side effects depending on the type and dose of statin. In the SAILS Trial, the rosuvastatin group was associated with a small but significant reduction in liver and kidney failure-free days (i.e. resulted in more organ dysfunction) [7]. Another RCT in critically ill patients with ARDS showed significantly higher hepatic transaminases and creatine kinase (CK) levels in the simvastatin group; however, serious adverse events did not differ between the groups [11].

Conclusion

There is a clear discrepancy between the results of observational studies and RCTs, and it is likely that observational studies resulted in inflated and biased estimates. Even with robust statistical methods, confounders remain a limitation of observational studies [15]; therefore, observational data should be considered hypothesis-generating and not practice-changing. The current RCTs failed to show significant benefit. In addition, the pharmacokinetics of statins is altered in critically ill patients, which may potentiate adverse events.

It is possible that a subset of patients may benefit from the pleiotropic effect of statins, or that higher dosing maybe more effective (at the expense of potential side effects). Future studies could focus on identifying the target population, the most effective agent, and appropriate dosing. However, such studies would be diverting resources away from other promising therapies. Until more evidence is available, the routine use of statins to treat sepsis or ARDS is not justified.

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Compliance with ethical standards

Conflicts of interest

None.

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