

Statins and Sepsis Literature Review

Alicia Hernández Torres¹, Ana Belén Hernández Cascales², Pedro Pujante Alarcón²,
Alfonso López Ruiz³, María Ángeles Ibáñez Gil⁴, María Dolores Hellín Gil²

¹Hospital University Virgen de la Arrixaca de Murcia, Murcia, Spain; ²Hospital University Virgen de la Arrixaca de Murcia, Murcia, Spain; ³Pharmaceutical Care Research at the University of Granada, Granada, Spain; ⁴Health Center Mariano Yago, Murcia, Spain.
Email: lablilly@gmail.com

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ABSTRACT

Recent data suggest that, in addition to improving dyslipidemia, statin may reduce the risk of infections and infection-related complications. The aim of this study is to make a review of the literature about the effects of statins on clinically relevant outcomes of patients admitted to the hospital and having an infection and/or sepsis, principally in terms of intensive care unit admissions and related death.

Keywords: Statins; Pravastatin; Simvastatin; Sepsis; Bacteremia; Mortality

1. Introduction

The hallmark of sepsis syndrome is an intense inflammatory response, which reflects a delicate interaction between the extensive activation of host defense mechanisms and direct and indirect effects of the invading microorganisms and their toxins. As a result, a number of important abnormalities occur during sepsis, including endothelial dysfunction and apoptosis, activation and increased production of cytokines and other proinflammatory mediators, activation and extravascular transmigration of leukocytes, and activation of platelets and coagulation and complement systems [1-3]. For this reason, because numerous cascades are triggered during sepsis, selective blocking of inflammatory mediators may be insufficient to arrest this process [4].

Recent studies have demonstrated a wide variety of statin properties independent of their lipid-lowering ability [5-8]. Statins inhibit 3-hydroxy-3 methylglutaryl coenzyme A (HMG CoA) reductase, were developed as lipid level-lowering agents, and have been studied extensively in relation to atherosclerosis. However, statins not only reduce cholesterol level but also decrease the levels of intermediate products of cholesterol synthesis, principally mevalonate, precursor of a lot of isoprenoids which play a crucial role in several intracellular signaling pathways in inflammatory response. Apparently, this effect is the major explanation for the observed pleiotropic effects of statins, which include the modulation of both innate

and adaptative immune system, antiinflammatory effects, the direct activation of heme oxygenase, direct interference in leucocyte-endothelial interactions, with limitations of the activation of endothelial cells and improvement of endothelial function, up-regulation of endothelial nitric oxide synthase and direct inhibition of major histocompatibility complex class II (MHCII), counteraction of the deleterious effects of sepsis on the coagulation system by inhibiting tissue factor expression and reducing prothrombin fragment levels and by strongly increasing the expression of thrombomodulin [9-12]. Moreover, they have direct effects on pathogenic microorganisms, such as *Salmonella typhimurium*, HIV, CMV and different fungi species [13-15]. Such anti-inflammatory, antioxidant, immunomodulatory, and antiapoptotic features have been collectively referred to as pleiotropic effects [4].

2. Effects of the Use of Statins in Sepsis Markers

All of us known the effect of the statins in the reduction of pro-inflammatory cytoquines, as have been demonstrated in a randomized and prospective study comparing simvastatin to placebo, where there was a significant reduction in tumor necrosis factor alpha (TNF- α) and interleukin 6 (IL-6) in the statin group [16]. The same effect was demonstrated with atorvastatin in a study with septic rats; it showed that atorvastatin improves survival in septic rats, decreases circulating inflammatory cyto-

kines, attenuating higher levels of IL-6 and TNF- α , and improves insulin resistance. If we take into account that, in septic patients, insulin resistance is accompanied by a reduction in the insulin-induced Akt (proteína kinase B) phosphorylation in liver, muscle and adipose tissue, and that this protein plays an important role in the protection against apoptosis, it is possible that the reduced insulin signaling through this pathway, in sepsis, may contribute to multiorgan failure by preventing or delaying apoptosis [17]. It seems that statins can have a protector activity in yeast sepsis; we know that yeast use the same HMG CoA reductase as humans, however, their end-product is ergosterol rather than cholesterol [18]; probably, this is the explanation of why simvastatin inhibit the growth of different species of *Candida* [19], independently of the effect in the reduction of pro-inflammatory cytokines. The population-based cohort study performed by Thomsen *et al.* C-reactive protein levels at admisión tended to be lower in statin users than in non users, perhaps because of the antiinflammatory effects of statins [20].

3. Clinical Effects of Statins in Sepsis

Many, but not all studies, have demonstrated the benefits of statins in patients with sepsis [21]. Liappis *et al.* demonstrated that patients on statins had greater than 7 times greater chance of survival with sepsis [22]. Almog *et al.* showed in an ICU that only 2.4% of patients on a statin developed bacterial sepsis compared with 19% ($p < 0.001$) who were not on a statin [23]. Gupta *et al.* also found that hemodialysis patients taking statins were also significantly less likely to be hospitalized for severe sepsis [24], and Van de Garde *et al.* showed a significant reduction of the risk of pneumonia among patients with diabetes mellitus [25]. Kruger *et al.* studied a cohort of bacteremic patients and found a significantly lower incidence of mortality and bacteraemia-related mortality with statin therapy [26]. There have been several other retrospective observational studies with similar findings with bacteremia. Also, statins reduce the risk of nosocomial sepsis among patients hospitalized for acute coronary syndrome, ischemic stroke, or revascularization [27], and the risk of infection-related mortality among patients with atherosclerotic disease [28]. Furthermore, in patients with sepsis [29], bacteremia [30] or community-acquired pneumonia [31] and in patients admitted to the intensive care unit with Acute Physiology and Chronic Health Evaluation II scores of ≥ 20 [32], statins prevented sepsis from becoming severe or decreased 28-day, 30-day, or 31 - 180-day mortality, hospital mortality, or bacteremia-related mortality. Al Harbi *et al.* found that statin therapy in critically ill patients (specially those elderly, diabetics, patient with higher severity of illness, with a low GCS, with several sepsis or with simvastatin) had a lower hospital mortality [33]. Statins also improved

mortality among patients with angiographically defined coronary artery stenosis $>70\%$ and with concurrent cytomegalovirus seropositivity and high C-reactive protein levels. Patients who received statins had a lower risk of death due to influenza, pneumonia, or chronic obstructive pulmonary disease in one study [34] and a lower risk of fatal pneumonia in another study [35]. In another hand, in a study which compared the outcomes of immunocompromised patients who received or not statins, the prior use of them was not associated with an increase of the survival [36]. Other investigations haven't demonstrated benefits with statins in patients with sepsis, as Fernandez *et al.*, who found that the hospital mortality was even higher in patients receiving statins and mechanical ventilation [37], or Yang *et al.* [38] who conducted a retrospective study and found no differences in mortality between the two groups. However, Kopterides *et al.*, in a critical review of 22 studies with 177,260 patients (7 prospective cohorts, 12 retrospective cohorts and 1 aleatorized clinic assay), concluded that the majority of studies show that statins have a beneficial effect over the result of the infection; nevertheless, its observational design don't let us to get firm conclusions [39].

Similar effects have been demonstrated with candidiasis. The beneficial effect in the reduction of mortality in patients admitted to an ICU with candidemia associated to a systemic inflammatory response syndrome, was demonstrated in the study performed by Forrest *et al.* [40], although the reduction in mortality wasn't statistically significant in the multivariant analysis. In this study, the reduction of the inflammatory response in comparison with the control group, is probably due to the effects of statins in the production of cytokines and ergosterol.

Evaluating the effects of statins in sepsis caused by concrete microorganisms, we can observe how, in a clinical study, patients who received statins had significantly lower overall and attributable mortality associated with bacteremic infections caused by gram-negative bacilli and *S. aureus* than did those not receiving statins. Simvastatin demonstrated a statistically significant antimicrobial effect against methicillin-susceptible *S. aureus* and, to a lesser extent, against methicillin-resistant *S. aureus*. Fluvastatin also showed a statistically significant but less marked antimicrobial effect, compared with that of simvastatin. Moreover, fluvastatin might have a potential role in the treatment of tuberculosis as a result of the enhancement of the host T-helper response against *M. tuberculosis*. In relation to fungi, we can see that statins show antifungal activity against *Candida* species; they inhibit the growth of *Candida* by decreasing the ergosterol levels. It seems that lovastatin with fluconazole and fluvastatin with fluconazole or itraconazole had synergistic effects on *Candida* species, whereas pravastatin or fluvastatin with fluconazole haven't demonstrated these

effects. The combination of amphotericin B and fluvastatin had additive effects, too. Different statins have demonstrated activity against zygomycetes, *Aspergillus*, *C. neoformans*, or viruses as *cytomegalovirus*, *Epstein-Barr* virus or HIV [41].

4. Are Statins Indicated in the Treatment of Septic Patients?

The timing of initiation of statins with regards to the onset of sepsis is still being determined. This is because it takes several days for statins to achieve desirable concentrations [42]. Moreover, the majority of patients who are statin-users don't receive statins after the admission, because of the lack of intravenous formulation, although recent data suggest that this method may lead to elevated plasma levels of the statins [43]. Pre-admission use of a statin has shown relative risk reductions in large cohort studies evaluating community acquired pneumonia and ICU admission [20,44]. Thomsen *et al.* showed that the use of preadmission statin up to 180 days prior to admission demonstrated a 25% - 30% mortality rate reduction at 90 days [20]. Also, Christensen *et al.* showed about a 20% mortality rate reduction between statin users and non users [44]. However, Majumdar *et al.* showed in a prospective cohort study for pneumonia that the benefit of statins disappeared after adjustment for confounders [45]. We will need, because of all these reasons, more exhaustive studies to be able to make conclusions.

5. Conclusion

Our review suggests that statin use is associated with a beneficial effect in treating and preventing different infections. Further studies are warranted to define the optimal dose of statin and timing of therapy in a prospective manner.

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