Statins and Sepsis: Possible Connections and Therapeutic Implications

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ABSTRACT

Sepsis is a complex inflammatory syndrome induced by infection triggering the activation of multiple humoral cascades. A number of therapeutic interventions aimed at blocking these pathways have been carried out. However, merely blocking one component of inflammation is insufficient to arrest the multiple activated inflammatory cascades. The 3-HMG-CoA reductase inhibitors (statins) exhibit pleiotropic effects independent of lipid lowering, encompassing antiinflammatory, immunomodulatory, antiapoptic and antithrombotic properties. Evidence from experimental models of sepsis and randomized clinical trials suggest that statins have potential and promising prospects in ameliorating the consequences and reducing the mortality and morbidity associated with severe sepsis. Notwithstanding, the crucial role of statins in the prevention and treatment of sepsis, there is need for caution among clinicians, in the use of statins, considering the adverse effects associated with statin use in critically ill patients who may be on other medications.

Key words: Experimental model, Inflammatory syndrome, Pleiotropic effect, Sepsis, Statins and Therapeutic implication.

INTRODUCTION

Sepsis is generally defined as the systemic inflammatory response syndrome that is induced by infection and may eventually lead to organ dysfunction\(^1\). A number of therapeutic interventions such as low dose corticosteroids and activated protein C, have been employed with a view of improving outcome and survival in sepsis\(^2\), yet mortality continues to increase. A delicate balance exists between widespread triggering of defence mechanism by invading micro-organisms and both direct/indirect effects of the micro-organisms and their products. It has been revealed in a retrospective study, that patients with bacteremia concomitantly treated with HMG-CoA reductase inhibitors (statins) showed decreased overall mortality compared to control not treated with statins\(^3\). Sepsis activates multiple complex steps in the inflammatory cascade and a number of experimental and clinical trials have focused on agents aimed at blocking these steps\(^4-7\). It should be noted that in severe sepsis syndrome, blockade of single component of the inflammatory cascade is insufficient and may not have any impact.

The pleiotropic effects of statins independent of lipid lowering encompasses antiinflammatory, immunomodulatory, antiapoptic, antioxidant, antiproliferetive, antithrombotic and endothelium protective features\(^8\). There is substantial evidence in favour of the fact that statin therapy may be beneficial in prevention and treatment of sepsis\(^9,10\). This review paper explores the pathophysiology of sepsis, the impact of statin therapy on outcome of sepsis and the mechanisms involved.
Pathophysiology of Sepsis

The localization and control of bacterial invasion, while initiating tissue repair is the normal response to infection. However, the generalisation of response to infection and involvement of normal tissues distant from original site of infection, invariably leads to sepsis. Innate immune cells recognize and bind to microbial components thereby initiating host response to infection. This may occur by recognition and binding of pattern recognition receptors (PRRs) on the surface of host immune cells to the pathogen associated molecular patterns (PAMPs) of the invading microorganism\(^1\). Sepsis can be regarded as a complex syndrome involving activation of a variety of systems. The outcome in the case of sepsis is dependent on the delicate balance between the pro-inflammatory and anti-inflammatory mediators\(^2\). It has been reported that significant changes occur at multiple levels within both the coagulation system and the cellular regulators during sepsis\(^3\). The inflammatory response represents an important component of sepsis as elements of this response drive the physiological processes which translate into systemic inflammatory response syndrome (SIRS). The concept of SIRS recognizes that lethally altered pathophysiology could exist without necessarily, presence of positive blood culture\(^4\). Sepsis is assumed to be driven by hyper-inflammatory response. This concept is driven by the fact that septic patients at increased risk for death have increased levels of tumour necrosis factor (TNF)\(^5\). Tissue injury and widespread inflammatory alterations similar to observation in septic patients occur following injection of TNF into laboratory animals\(^6,7\). Similar observations have led to institution of clinical trials with a view of blocking TNF\(^8,9\). The above individual trials did not show significant improvement in sepsis survival. Notwithstanding, a meta-analysis of all the TNF inhibitors revealed improvement in overall outcome\(^10\). Inflammatory response in sepsis is heterogeneous and not clearly defined as some patients may benefit from enhancing the inflammation whereas others will be better served by diminishing the inflammatory response. Individualized therapy in sepsis is critical, as evidence from preclinical model of sepsis indicate that diminishing inflammatory responses may be beneficial in animals at high risk of morbidity\(^11\).

Cellular dysfunction in sepsis may manifest as either depressed function or excessive activation. Excessive activation occurs as a result of damage to

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Fig. 1: Pathways to sepsis denoting various components of the inflammatory cascade and indicating sites in which the action of statins may be beneficial. (Adapted and modified from-Novack V., Terblanche M. and Almog Y. Do statins have a role in preventing or treating sepsis Crit Care. 10(1): 113 (2006)
nearby cells by neutrophils generating excess toxic products\textsuperscript{22}. Neutrophil failure to phagocytize and clear invading pathogens is an example of depressed cellular function. Endothelial cells are dysfunctional in sepsis, due to increased expression of adhesion molecules on the endothelial cells, resulting in white blood cells being attached. Endothelial cells elaborate anticoagulant molecules such as protein C. The remarkable relationship between the inflammatory and coagulation systems in sepsis has become increasingly evident\textsuperscript{23}. A state of net immune suppression known as compensatory anti-inflammatory response syndrome (CARS) is attained as sepsis and inflammation progress\textsuperscript{24}.

**Role of Statins in Sepsis**

A number of therapeutic approach has been employed to modulate immunological response and the delicate balance between pro-inflammatory and anti-inflammatory responses in sepsis. The 3-HMG-CoA reductase inhibitors, known as statins, a class of cholesterol lowering drugs reputed for their pleiotropic effects independent of cholesterol lowering are reported to play a crucial role in prevention and treatment of sepsis. Recent report from clinical trials provide new data on the use of statins for treating sepsis\textsuperscript{25}. Evidence from animal models of sepsis indicate that statin use may prevent and modulate sepsis severity\textsuperscript{26,27}. Reducing rates of sepsis-related mortality among patients on statins and a decrease in the severity and incidence of sepsis among patients treated with statins have been noted in two observational human studies\textsuperscript{3,28}. A decrease in the incidence of sepsis among patients treated with statins hospitalized for a cardiovascular event was reported in a population based cohort study\textsuperscript{29}. Another study reported that reduction in the risk of hospitalization for sepsis in patients with severe kidney disease receiving dialysis was strongly and independently associated with statin use\textsuperscript{30}. Immune response to infection is modulated by statins, decreasing the risk of sepsis in infected patients. The outcome of studies on the effects of statins on human immunodeficiency virus, yeast and salmonella suggests that statins may also have antimicrobial effects\textsuperscript{31-34}. Sepsis induced coagulopathy may be blunted by the antithrombotic effects of statins\textsuperscript{35,36}. Data from experimental models of sepsis suggest that statins markedly decreased nitric oxide (NO) production\textsuperscript{3,26}. Simvastatin reduced nitric oxide production and reverted the impaired vascular responsiveness in a pre-treatment rat model\textsuperscript{26}. The inducible heat shock and cytoprotective protein, hemeoxygenase (HO-1) is involved in attenuating endothelial dysfunction consequent on sepsis. It has been shown that the anti-proliferative, anti-inflammatory and antioxidant properties of simvastatin may be largely attributed to hemeoxygenase (HO-1) induction\textsuperscript{37,38}. Statins attenuate hemodynamic perturbation due to myocardial dysfunction in sepsis. Report from an experimental model, revealed mean survival time close to four times that in untreated control mice pretreated with simvastatin\textsuperscript{39}. Same study also confirmed complete preservation of hemodynamic status and cardiac function\textsuperscript{39}. A similar study noted that survival time was markedly improved with statin treatment initiated 6 hours after induction of sepsis\textsuperscript{40}. A study recommended the conduct of large scale clinical trials aimed at evaluating the precise role of statins in the primary prevention and therapy of sepsis\textsuperscript{41}.

**CONCLUSION**

Statins have a crucial role to play in the prevention and treatment of sepsis as a result of their well known pleiotropic effects independent of lipid lowering. However, there is still need for caution among clinicians in translating these outstanding research findings into routine clinical practice; considering the adverse effects, particularly rhabdomyolysis and hepatic toxicity associated with the use of statins, moreso, in critically ill patients who may be receiving other medications.

**REFERENCES**


