Pharmacological Research 88 (2014) 31–40

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Statins role in the prevention and treatment of sepsis

Paul P. Dobesh*, Keith M. Olsen

Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, 986045 Nebraska Medical Center, Omaha, NE 68198-6045, USA

ARTICLE INFO

Article history:
Received 20 December 2013
Received in revised form 21 April 2014
Accepted 22 April 2014
Available online 2 May 2014

Keywords:
Statins
Sepsis
Inflammation
Critical care
Intensive care

ABSTRACT

Sepsis is a complex disease with typically poor outcomes. While the onset of sepsis is typically infectious, the detrimental consequences follow pathogen toxin release that produces activation of numerous cytokines and a pro-inflammatory response. These same cytokines also stimulate activation of coagulation and inhibit natural fibrinolysis. Despite decades of research targeted against these pathways the development of sepsis and mortality in patients with sepsis remains high. While statins were developed for reducing cholesterol in patients with atherosclerotic disease, we now know they have a number of other properties which may be helpful in the prevention and treatment of sepsis. Statins have demonstrated the ability to reduce a number of pro-inflammatory cytokines known to be detrimental in the development and progression of sepsis. Statins have also demonstrated the ability to limit the coagulation response and promote fibrinolysis in the setting of sepsis. Based on these encouraging pharmacologic properties of statins a number of trials have been conducted evaluating the impact of statins on the prevention and treatment of sepsis. Most of the trials to date have been retrospective cohort trials, with very few prospective randomized trials. While some trials fail to demonstrate a benefit of statins, most trials suggest a reduction in the development of sepsis and/or other important sepsis related outcomes. While the laboratory and early clinical experience with statins are encouraging, randomized controlled trials will be need to fully define the role of statins in the prevention and treatment of sepsis.

Contents

Abbreviations: ICU, intensive care units; EGDT, early goal directed therapy; HMG-CoA, 3-hydroxy-3 methyglutaryl coenzyme A; NFκB, nuclear kactor-kappa-B; LDL, low-density lipoprotein; SVR, systemic vascular resistance; LPS, lipopolysaccharide; TLRs, toll-like receptors; IL, interleukins; MODS, multi-organ dysfunction syndrome; TNF, tumor necrosis factor; SIRS, systemic inflammatory response syndrome; TF, tissue factor; PAI-1, plasminogen activator inhibitor-1; NO, nitric oxide; NOS, nitric oxide synthase; OR, odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; HR, hazard ratio; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

* Corresponding author. Tel.: +1 402 559 3982; fax: +1 402 559 5673.
E-mail addresses: pdobesh@unmc.edu (P.P. Dobesh), kolsen@unmc.edu (K.M. Olsen).

http://dx.doi.org/10.1016/j.phrs.2014.04.010
1043-6618/

1. Introduction

Sepsis is a multifactorial disease beginning as an infectious event followed by a cascading sequence of inflammatory and thrombotic responses. Sepsis is the leading cause of death in non-coronary intensive care units (ICU) in the United States and the 10th leading cause of death. Approximately 750,000 new cases of sepsis are diagnosed each year with the resulting mortality rate of 20–80% depending upon a number of host factors [1–3]. The mortality of sepsis is higher than the incidence associated with stroke, cancer and human immunodeficiency virus [3]. The range of mortality varies widely due to host co-morbidities and age. Most cases of adult sepsis result in the patient being admitted into the ICU with a mean length of stay approaching 15 days and an estimated annual cost of $17 billion (USD) [1,4]. The management of sepsis, severe sepsis, and septic shock consists of aggressive fluid replacement therapy and targeted central venous pressure, antibiotics, and other ancillary care that are well described by early goal directed therapy (EGDT) and the Surviving Sepsis Campaign, an international guideline for the management of sepsis and septic shock [5,6].

The use of EGDT has been studied in over 18,000 patients and the resulting publications demonstrate and equal or greater survival rate to that found in the original trial published in 2001 [7]. The Surviving Sepsis Campaign had a similar impact with survival by outlining best practices for the treatment of sepsis, standardization of terminology, and adoption of treatment algorithms and pathways in most medical centers [8]. Despite these improvements in clinical management of sepsis, mortality remains a significant consequence. However, it is not the infection that drives mortality but rather the host autoimmune response in response to the microorganism [4,9] The cellular response to microbial products that include endotoxin-lipopolysaccharide in gram-negative bacteria and exotoxin-peptidoglycan in gram-positive bacteria results in an inflammatory cellular process. Following exposure to microorganism, a number of cytokines, coagulation factors, and tissue factors are released that result in capillary leak, microvascular thrombosis, cell adhesion, tissue hypoxia, apoptosis, and impaired vascular tone [10–12]. These host responses lead to sepsis and severe sepsis, multiple organ dysfunction or failure, and ultimately death if not corrected [13,14]. Numerous investigational pharmaceutical compounds have been developed that targeted specific parts of the inflammatory cascade and coagulation cycle, but the results of multiple clinical trials have been largely disappointing.

New therapies that target the inflammatory cascade and coagulation pathway continue to be sought. Statins, by inhibition of 3-hydroxy-3 methyglutaryl coenzyme A (HMG-CoA) reductase produce powerful effects that are valuable in the prevention and treatment of cardiovascular diseases [15]. Independent of these events, statins possess significant reactions to vascular endothelial inflammatory response that have led to the study in immune related diseases including cancer, pneumonia, acute respiratory distress syndrome, and sepsis [16–19]. Statins have several effects which may protect vascular endothelium and reduce inflammatory damage associated with sepsis. The mechanism by which statins modulate the immune response is multifaceted but they are believed to be low-density lipoprotein (LD) independent. Although the exact mechanisms and timeline for statin interventions in sepsis are not well understood; it is thought the protective effect include down-regulation of tlr-4, inhibition of nuclear factor-kappa-B (NFκB) and protection against endothelial cell apoptosis [20,21]. The pleiotropic effects of statins may also explain a recent meta-analysis which reported improved survival associated with statin usage in sepsis [22]. This review intends to exam the failure of previous immunomodulator therapy clinical trials, the anti-flammatory properties of statins, and the potential role of statins in the treatment of sepsis and severe sepsis.

Table 1
Systemic inflammatory response syndrome (SIRS), sepsis criteria and definitions [29].

SIRS: two or more of the following:
Core body temperature >38 °C or <36 °C
Heart rate > 90 beats/min
Respiratory rate > 20 breaths/min or (arterial $PaCO_2$ < 32 mmHg)
White blood cell count < 4×10^9/L (<4000/mm^3), >12×10^9/L (>12,000/mm^3), or 10% bands
Sepsis = infections + SIRS
Severe Sepsis = infection + SIRS + evidence of organ dysfunction
MODS = multiple organ dysfunction syndrome

2. Current understanding of sepsis

2.1. Host response

Sepsis often presents with fever, shortness of breath, tachycardia, hypotension, shock, respiratory failure, dramatic decrease in systemic vascular resistance (SVR), and subsequent circulatory collapse secondary to capillary leak [23]. However, it is not the infection that results in the high patient mortality but rather the host immune response and subsequent organ failures [24]. The prevailing understanding of sepsis is an uncontrolled hyperinflammatory response and hypercoagulable state followed by a state of hypocytokine secretion. The origins of understanding the inflammatory and coagulaopathy pathways of sepsis was the immune response to endotoxin, a lipopolysaccharide (LPS) found in the outer cell wall of Gram-negative bateria [25]. When bacteria enter the blood stream, endotoxin and other bacterial substances interact with toll-like receptors (TLRs) and lectin receptors on the cell surface of the macrophage. At least ten TLRs have been identified that interact with various microogranism products that in turn stimulate cytokine production by the macrophage. Ten's of other cytokines and extracellular proteins [e.g. interleukins (IL) 1,12, 18, transforming growth factor, lipopolysaccharide-binding protein, cell surface receptors (e.g. IL-1 receptor, platelet activiating factor receptor, CD1 1a receptor)], signal tranduction molecules (e.g. cyclo-oxygenase-II, Inducible nitric oxide sythase, caspase-3) and miscellaneous products (e.g. platelet-activating factor) play important roles in the inflammation cascade and subsequent multi-organ dysfunction syndrome (MODS) [26]. Although very complexed and intertwined within the inflammation cascade, three cytokines have emerged tumor necrosis factor (TNF), IL-1 and IL-10 that triger the sepsis events. For example, administration of small doses of endotoxin to healthy volunteers have resulted in a similar cytokine storm and symptoms closely resembling the systemic inflammatory response syndrome (SIRS) (Table 1) [27–29]. However, this hypothesis of a cytokine storm is not devoid of controversy as other investigators have documented a reduction in pro-inflammatory mediators following the initial cytokine elevation (Fig. 1) [24,30–32].

2.2. Tumor necrosis factor (TNF)

The interaction of a single microbiological product, endotoxin or exotoxin with TLRs on the macrophage surfaces results in an array of inflammatory pathway activation. The cytokine TNF is released from the macrophage in response to the TLRs interaction [32]. In turn, TNF stimulates two receptors p55 and p75 on endothelial cell surfaces that also stimulate gene expression and apoptosis [33]. The multiple inflammatory pathway stimulation precipitates the down regulation of anticoagulant proteins and ehances procoagulants while disrupting the tight junctions between endothelial cells [13]. The latter disruption of tight junctions and stimulation of nitric oxide synthetase in endothelial cells results in a capillary leak with substantial vascular volume loss leading to many of the systemic