Role of Statins in Treatment of Sepsis

Essay

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By

Emad El-Din Mohamed M. Salem
(M. B., B. Ch)

Supervised by

Prof. Dr.
Bassel M. Essam Noor El-Din
Professor of anesthesiology and intensive care medicine
Faculty of medicine , Ain Shams University

Dr.
Aml Mahmoud Badr El-Din Zaki
Ass. Professor of anesthesiology and intensive care medicine
Faculty of medicine, Ain Shams University

Dr.
Amr Maher Mahmoud Yousif
Lecturer of anesthesiology and intensive care medicine
Faculty of medicine, Ain Shams University

Faculty of Medicine
Aim shams University
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تحت إشراف

الأستاذ الدكتور

باسل محمد عصام نورالدين
أستاذ التخدير والعناية المركزة
كلية الطب- جامعة عين شمس

الدكتورة

أمل محمود بدرالدين زكى
أستاذ مساعد التخدير والعناية المركزة
كلية الطب- جامعة عين شمس

الدكتور

عمرو ماهر محمود يوسف
مدرس التخدير والعناية المركزة
كلية الطب- جامعة عين شمس

كلية الطب
جامعة عين شمس
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List of Abbreviation

(AKIN)	Acute Kidny Injury Network.
(ALI)	Acute Lung Injury.
(APACHE)	Acute Physiologic And Chronic Health Evaluation.
(ARDS)	Acute Respiratory Distress Syndrome.
(CIITA)	Class II Transactivator.
(CK)	Creatine Kinase.
(COPD)	Chronic Obstructive Pulmonary Disease.
(COX-2)	Cyclooxygenase-2.
(DIC)	Disseminated Intravascular Coagulation.
(DO_2)	Oxygen Delivery.
(ERK)	Extracellular Signal-Regulated Kinases.
(HPS)	Heart Protection Study
(ICAM)	Intercellular Adhesion Molecule.
(JNK)	**c**-Jun N-terminal
(KIF6)	Gene Variant Is Said to Be Linked To Heart Attack and Prevention.
(LDL).	Low Density Lipoprotien
(LFA)	Lymphocyte Function-Associated Antigen.
(MAPK)	Mitogen-Activated Protein Kinase.
(MCP)	Monocytic Chemoattractant Protein.

(MIP)	Macrophage Inflammatory Protein.
(NF-IκB)	Inhibitor for NFκB.
(NFκB)	Nuclear Factor Kappa B.
(NOS)	Nitric Oxide Synthase .
(NR)	Not Reported.
(PAI-1)	Plasminogen Activator Inhibitor 1.
(PDGF)	Platelet-Derived Growth Factor.
(PI3K)	Phosphatidyinositol-3 Kinases .
(PPARs)	Peroxisome Proliferator-Activated Receptors.
(RANTES)	Regulated Upon Activation, Normal T Cells Expressed And Secreted.
(RIFLE)	The Risk/Injury/Failure/Loss/End-Stage Renal Disease.
(SAPK)	Stress-Activated Protein Kinase.
(SIRS)	Systemic Inflammatory Response Syndrome.
(SOFA)	System and Sequential Organ Failure.
(SVR)	The Systemic Vascular Resistance.
(TAFI)	Thrombin Activatable Fibrinolysis Inhibitor.
(TGF)	Transforming Growth Factor.
(TNF)	Tumor Necrosis Factor.
(TSST-1)	Staphylococcal Toxic Shock Syndrome Toxin 1.
(VLDL).	Very Low Density Lipoprotien

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Introduction

Severe sepsis and septic shock are common and frequently fatal. A future challenge may be to test both the efficacy and the safety of statins when administered at the onset of sepsis and in patients with severe sepsis or septic shock admitted into intensive care unit. **(Remick, 2007).**

The pathophysiological process, signs and symptoms of sepsis are important to be discussed for understanding the role of statins. Infection, sepsis, severe sepsis, and multi-organ dysfunction have internationally recognized definitions. **(Cohen, 2002).**

Hospital mortality rate of severe sepsis remains between 30% and 50%, or 500000 deaths per year (1400 each day) worldwide, with as many deaths annually as those from acute myocardial infarction and the number is projected to grow. **(Annane et al., 2002).**

As the mortality of severe sepsis remains unacceptable, much research for therapeutic interventions is done to improve outcomes.

Considerable amount of research have been targeted to clarify the mechanisms of sepsis. With the exception of activated protein C, no therapy targeting the inflammatory cascade has been shown to alter mortality in sepsis.

The ideal agent would be cheap, have a clearly established and minimal side effect profile, multiple modes of delivery, and have a pleiotropic effect upon the inflammatory cascade. **(Bernard et al., 2001).**

How close statins come to this ideal is the target. Statins therapy may be the next logical step in the search of adjuvant therapy. **(Almog et al., 2004).**

Aim of the work

This work aims to assess the evidence of whether future treatment of sepsis would benefit from including statins therapy.

Sepsis syndrome results from a host reaction to infection, which includes a systemic inflammatory response, enhanced coagulation, and impaired fibrinolysis. The systemic inflammatory response syndrome (SIRS) is defined by fever or hypothermia, tachycardia, tachypnea, and leukocytosis, leukopenia, or the presence of immature neutrophil. **(Hotchkiss, 2003).**

SIRS can result from numerous conditions but only becomes “sepsis” when infection is etiologic. When sepsis causes at least one organ dysfunction, the syndrome is termed “severe sepsis,” and sepsis-induced hypotension that is refractory to fluid challenge defines “septic shock.” **(Bone, 1992).**

Definitions related to sepsis:

Table(1).

Term	Definition and Criteria
Infection	Microorganism invasion of a normally sterile site
Bacteremia	Presence of viable microorganisms in the blood
Systemic Inflammatory Response Syndrome (SIRS)	A systemic inflammatory response to a pathologic insult, such as a burn, trauma, pancreatitis, or infection. SIRS requires two or more of the following conditions: · Temperature >38°C or <36°C · Heart rate >90 beats/min · Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg · WBC >12,000/mm^3, <4000 cells/mm^3, or >10% immature (band) forms
Sepsis (= 1 + 3)	The syndrome caused by a systemic inflammatory response secondary to infection
Severe sepsis	Sepsis associated with organ dysfunction. Specific organ dysfunctions include, but are not limited to, hypotension, renal dysfunction, respiratory failure, and altered mental status.
Septic shock (= 5 + 7)	Sepsis with hypotension or hypoperfusion despite adequate fluid resuscitation.
sepsis-induced Hypotension,	A decrease in systolic blood pressure <90 mm Hg, a mean arterial pressure <60 mm Hg, or a reduction of >40 mm Hg from baseline

(Cohen, 2002)

While the SIRS criteria are sensitive for septic patients, they are criticized for lacking specificity. Many, if not most, ICU patients have tachypnea and tachycardia, raising doubt as to the diagnostic utility of the SIRS criteria. **(Vincent**, **1997).**

Although the specificity of SIRS is increased by requiring three of the criteria, or by mandating that one of two required criteria be abnormal temperature or white blood cell count, even two criteria maintain prognostic importance. **(Brun-Buisson , 2000).**

Importance of sepsis

Large epidemiologic studies report an incidence of 1 to 3 cases per 1000 population per year resulting in approximately 750,000 cases annually in the United States. The average sepsis survivor requires 7 to 14 days of intensive care unit (ICU) support with much of this time spent on a ventilator. After ICU discharge, an additional 10- to 14-day hospital stay is typical. Thus, the average hospital length of stay for survivors is 3 to 5 weeks. **(Martin et al., 2003).**

Hospital charges in excess of tens of thousands of dollars are common for individual patients, resulting in

annual US expenditures of nearly $17 billion. Today hospital mortality rates remain unacceptably high; 30% to 40% of patients die despite prompt, comprehensive treatment**(Angus et al., 2001).**

Predictors of worse outcomes include advanced age, cancer, and a hypothermic presentation. Historically, it was believed specific characteristics of the invading pathogen determined prognosis, but recent investigations have undermined this long-held belief. The identity of the infecting organism is of lesser consequence than physiologic derangements provided appropriate, prompt antimicrobial therapy is administered **(Martin et al., 2006).**

At the bedside, the best practical predictor of outcome is simply the number of organ systems with sepsis-induced dysfunction. Each new organ system failure adds roughly 15% to 20% risk of death to the baseline 10% to 15% mortality rate seen among ICU patients.

On average, patients have two or three failing organ systems at the time of diagnosis. **(Levy et al., 2005).**

Septic patients present typically in their sixth or seventh decade of life, and the average age of afflicted patients has