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Review

Targeting cytokines as a treatment for patients with sepsis: A lost cause or a strategy still worthy of pursuit?

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ABSTRACT

Despite often knowing the aetiology of sepsis and its clinical course there has not been the anticipated advances in treatment strategies. Cytokines are influential mediators of immune/inflammatory reactions and in patients with sepsis high circulating levels are implicated in the onset and perpetuation of organ failure. Antagonising the activities of pro-inflammatory cytokines enhances survival in animal models of sepsis but, so far, such a therapeutic strategy has not improved patient outcome. This article addresses the questions of why encouraging laboratory findings have failed to be translated into successful treatments of critically ill patients and whether modifying cytokine activity still remains a promising avenue for therapeutic advance in severe sepsis. In pursuing this task we have selected reports that we believe provide an incisive, critical and balanced view of the topic.

Contents

1. Introduction

Sepsis, which is organ failure induced by infections, remains the prominent cause of death amongst patients admitted into the intensive care unit (ICU) [1]. Nearly 90% infections are due to common bacteria infecting the lungs, gut urinary tract, blood and soft tissue. In accordance with the guidelines of the Surviving Sepsis Campaign most patients with a suspicion of sepsis are given broad spectrum antibiotics within a few hours of entry into the ICU as every pending hour is coupled with a 7% decrease in mortality rate [2,3]. The incidence of severe sepsis is increasing at a rate of 1.5% per annum due to increases in antibiotic resistance, to the number of immunocompromised patients and to an aging population [4]. Mortality levels in severe sepsis are directly related to the number of organs failing [5] and contributory factors include components of immune and inflammatory pathways, disseminated intravascular coagulation, and derangements of energy metabolism and endocrine systems [6,7]. It is reasoned that modifying one or other of these manifestations will lead to patient benefit. Such expectations were encouraged when recombinant activated protein C was reported to reduce mortality in patients with severe sepsis [8] but the withdrawal of this drug following the failure of the PROWESS-SHOCK study has led to a therapeutic vacuum in sepsis [9]. The need for new treatments in sepsis is as important now as ever.

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2. Cytokines and organ failure

Cytokines are powerful instigators of tissue injury and the generation of a pro-cytokine storm is believed to be responsible for the early phase of sepsis [10] The efficacy of the pro-inflammatory cytokines is aptly illustrated by their effect on endothelium. Upon stimulation by TNFα or IL-1 the luminal surfaces of endothelial cells change from a non-thrombogenic to a pro-thrombotic state that favours the initiation of disseminated intravascular coagulation and the formation of microvascular thrombi [11]. Dysregulation of endothelial cells by cytokines produces an increase in permeability with subsequent macromolecular extravasation and oedema [12]. The endothelial cells may also release nitric oxide, the vasoactive mediator responsible for the fall in systemic vascular resistance that underlies the hypotension of septic shock and which may contribute to mitochondrial shutdown, tissue hypoxia and lactic acidosis [13]. Cytokine activation of endothelial cells also upregulates surface molecules that augment the attachment of neutrophils so as to enable these cells to respond to chemotactic factors generated at underlying infective/inflammatory lesions [14]. In the acute respiratory distress syndrome (ARDS) it seems that the large numbers of infiltrating neutrophils enter the lung in response to IL-8 and promote direct damage by the extracellular release of proteolytic enzymes and oxygen radicals [15] In other organs, such as the kidney, neutrophils may compromise function by binding so firmly to the endothelium that they induce microvascular occlusions that promote tissue hypoxia and hypoperfusion [16]. Should sequestered neutrophils succumb to stimulation by circulating cytokines then their release of lytic factors will further compromise the microvasculature by disrupting endothelial junctions, increasing vascular permeability and thereby promoting tissue oedema and organ failure.

Table 1 shows that levels of circulating cytokines are frequently raised in sepsis [17–33]. High concentrations of TNFα and IL-6 are predictive of organ failure and increased mortality [28.33] but poor patient outcome is also associated with increased blood levels of the anti-inflammatory cytokine IL-10 [30]. This apparent paradox is explained by the proposal, based mainly on animal models, that infection induces an initial stage of systemic inflammation, with elevated blood levels of pro-inflammatory cytokines (e.g. TNFα and IL-1), that is followed by a compensatory anti-inflammatory response (CARS) defined by high circulating levels of anti-inflammatory cytokines (e.g. IL-10 and IL-13) [34,35]. These latter cytokines are believed to generate immunosuppression (immunoparalysis) by reducing the number and function of circulating lymphocytes and monocytes [36,37] with the result that many patients will succumb to hospital-acquired infections [38]. Whether such a sequential expression of pro- and anti-inflammatory cytokines occurs in patients with sepsis is difficult to ascertain because of the variability in circulating levels of cytokines and the difficulty in establishing the precise time of the onset of infection [39]. Support for the contribution of anti-inflammatory cytokines to organ dysfunction comes from the study of families whose members died from meningococcal sepsis. It was noted that when whole blood samples were stimulated with endotoxin those individuals with low TNFα production had a ten-fold increased risk for fatal outcome whereas high IL-10 production increased the risk 20-fold: the highest risk was found in families with both characteristics [40].

As outlined in Fig. 1 injection of TNFα into animals produces several of the clinical symptoms of sepsis and, in models of endotoxic and septic shock, survival is enhanced by the administration of anti-TNFα antibodies or by deletion of the functional gene for TNFα [41]. Furthermore, infusion of recombinant TNFα or IL-1 into human volunteers induces systemic inflammation [42]. Observations such as these paved the way for the initiation of anti-TNFα clinical trials in patients with severe sepsis. An additional incentive for this approach was that anti-TNFα therapy improved the management of patients with rheumatoid arthritis (RA) [43]; and later of patients with Crohn's disease [44]. However, the clinical trials in severe sepsis were disappointing and in the following section we will consider the most likely reasons to explain why encouraging laboratory findings were not successfully translated into the ICU.

3. Why did antagonising TNFα or IL-1 fail to improve the survival of patients with sepsis?

Table 2 shows that during the last twenty years 19 clinical trials investigated whether i/v infusions of antagonists of TNFα and IL-1 improved the survival of patients with sepsis or septic shock [45–63]. Sixteen of the trials targeted TNFα [45–60]: 8 used neutralizing monoclonal antibodies [45–48,50,52–54]; 3 applied soluble receptor fusion proteins [49,51,56] and; 5 used either Fab dimer or monomer fragments directed against TNFα, so as to achieve a high level of neutralization and to enhance tissue entry [55,57–60]. A significant improvement was seen in only one of the anti-TNF trials [63], with outcome worse in patients administered the Fc fusion protein [49,51]. Anti-TNFα antibodies produced a fall in blood TNFα concentrations in six of the 12 studies in which they were measured although a significant reduction occasionally occurred following treatment with placebo. A meta-analysis of all the anti-TNFα studies revealed an overall 5% reduction in mortality though this report inadvertently included a trial of recombinant tissue factor [64]. Three studies administered the recombinant form of IL-1RA [61–63]. The initial observation that recombinant IL-1RA improved patient survival [61] was not supported by two larger investigations [62, 63].

Reasons for the failure of these trials include insufficient patient enrolment, inadequate potencies of the therapies, variations in patients' immunological responsiveness to infections, and whether patients were in the early or CARS phase of sepsis [65,66]. There is the consideration that sepsis is not a single clinical entity but a set of heterogeneous conditions [67]. Several of the patients entered into the clinical trials were designated as having sepsis on the basis of a strong clinical suspicion without microbiological confirmation. Blood concentrations of TNFα are greater in sepsis patients with confirmed microbiological evidence of infections than in patients with just a strong clinical suspicion

Table 1
Cytokines that are elevated in the circulation of patients with sepsis.

Pro-inflammatory cytokines	Reference		Anti-inflammatory cytokines	Reference	
IL-1	Lewis et al. (2007)	[17]	IL-1RA	Samson et al. (1997)	[28]
IL-8	Harbeth et al. (2001)	[18]	IL-4	Dipora et al. (1995)	[29]
IL-12	Hazelzet et al. (1997)	[19]	IL-10	Monneret et al. (2004)	[30]
IL-17/23	Bosman& Ward (2012)	[20]	IL-13	Collighan et al. (2004)	[31]
IL-18	Tschoeke et al. (2006)	[21]	TGF-β	Marie et al. (1996)	[32]
IL-22	Bingold et al (2010)	[22]			
TNFα	Damas et al. (1989)	[23]	Both pro-and anti-inflammatory		
HMGB-1	Karlsson et al. (2008)	[24]			
MIF	Chuang et al. (2007)	[25]	IL-6	Petilla et al. (2002)	[33]
IFN-γ	Matera et al. (2013)	[26]			
MIP 3α	Tsai et al. (2013)	[27]			