Perspective

Why a second look might be worth it: immuno-modulatory therapies in the critically ill patient

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Abstract: Sepsis and septic shock are associated with high mortality rates and remain a serious menace for the critically ill patient. Concurrent activation of pro- and anti-inflammatory pathways and an excessive cytokine release represent initial key features in the deregulation of the humoral and cellular antimicrobial defense. Research of the last decades addressed both the ebullient inflammation as well as the resulting long-term failure of the host immunity. While the reestablishment of an adequate immune-competence is still under investigation, many promising experimental trials to limit the inflammatory response during sepsis were challenged by missing beneficial effects in clinical studies. Nevertheless, due to advanced knowledge about the complex regulation of inflammatory mediators and their overlapping involvement in other potentially life-threatening diseases, further evaluation of these approaches in relevant subgroups could help to identify critically ill patients with potential benefit from anti-inflammatory therapies.

Keywords: Sepsis; recombinant human interleukin-1 receptor antagonist; inflammation; macrophage activation syndrome

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Introduction

According to the recently published *Third International Consensus Definitions for Sepsis and Septic Shock*, sepsis takes place when a dysregulated host response to infection results in a life-threatening organ dysfunction (1). Unfortunately, despite many advances in modern intensive care medicine, sepsis still belongs to the most frequent causes of death in the critically ill (2-4), occurs in 30% of the patients in European intensive care units (ICU) (2) and remains a major challenge in treatment. The pathology standing behind sepsis remains a complex continuum characterized by an initial release of numerous mediators and cytokines affecting a large number of cells and organ systems. Older concepts of the pathophysiology were based on the paradigm of an initial hyper-inflammatory "cytokine storm", that is at some point no longer advantageous for the host and finally contributes to multi-organ dysfunctions and death (5). Consequently, many trials aimed to modulate the pro-inflammatory response. The more recent view of sepsis however assumes a concurrent activation of both pro- and anti-inflammatory pathways (6). While the pro-inflammatory response is characterized by a release of cytokines such as interleukine-1ß (IL-1β), IL-6 and tumor-necrosis factor α (TNF- α) as well as the activation of endothelial cells and components of the coagulation system, compensatory anti-inflammatory mechanisms are associated with an increased expression of anti-inflammatory mediators, i.e., IL-1 receptor antagonist (IL-1RA), IL-4 and IL-10 (7). The failure of the cellular immune response i.e., due to an increased apoptosis of lymphocytes (8) or the dysfunction of antigen-presenting cells like monocytes (9) indicates the resulting net sepsis-induced immune suppression (7).

Immunologic dysfunctions contribute to the high mortality

An infectious focus leads to a systemic cytokine induced inflammatory response dominating the initial phase of sepsis. Interestingly, post-mortem findings in surgical ICU patients who died from sepsis or septic shock revealed that in the majority of cases, a septic focus was still detectable even after treatment duration of 7 days (10). Histological analyses further confirmed a high rate of undetected or non-adequately addressed pulmonary or abdominal foci (10,11). Thus, the continuing presence of a pathologic trigger might contribute to the dramatic disease progress, leading to organ failure and death in these critically ill patients (12). Consequently, there is no denying that strategies to improve early and adequate source control are of striking importance (13). However, the findings of Torgersen *et al.* also underscore the warranty of complementary research approaches to modulate the dysregulation of pro- and anti-inflammatory mediators caused by an infectious focus.

Of note, it is not the initial host reaction to pathogenic stimuli, which merely contributes to the high mortality of septic patients. More than 70% of septic patients die within the later course of disease (11,14,15). This late phase is associated with an increased risk of opportunistic infections due to a paralysis of the immune system (16). Survivors of the acute septic event are confronted with chronic organ dysfunctions [concept of *persistent critical illness* (17)] and reduced long-term survival rates (18). Thus, beside the initial hyper-inflammation, persisting infectious stimuli and secondary inflammatory processes due to opportunistic infections can be assumed as key components in the overall mortality of sepsis.

Immuno-stimulatory strategies

Since epidemiologic studies highlight the dramatic impact of the failing immune system on patients' survival in the late phase of sepsis, research focusing on the "reestablishment of the antimicrobial defense" is of particular interest. Therefore, important questions are how to measure an "adequate" function of the immune system and how to detect the switch from a "more pro-inflammatory" to a "more immunosuppressive" state.

It is well known, that a dysfunction and an increased apoptosis of lymphatic and myeloid cells are common features in the later course of sepsis and significantly contribute to the sepsis-induced immunosuppression (19). Over the last decades, several biomarkers like the soluble form of the tumor necrosis factor related apoptosis inducing ligand (TRAIL) or the major histocompatibility complex (MHC) class II cell surface receptor human leukocyte antigen-DR (mHLA-DR) have been investigated to monitor the immune function. So far, mHLA-DR represents the only valid biomarker for monocyte function. While inflammatory stimuli result in an initial upregulation of the mHLA-DR expression (20), low mHLA-DR levels indicate a disability of the monocytes to adequately interact with T cells in terms of antigen presentation (21,22). Low mHLA-DR levels of septic patients in the late phase of sepsis are further accompanied with a decline of tumor necrosis factor α (TNF-α) production after LPS challenge *in vitro* (23). Vice versa, mHLA-DR expression has been used to guide a therapeutic reconstitution of the monocyte immunocompetence. Nearly twenty years ago, Döcke *et al.* tested whether interferon-γ (IFN-γ) could counteract monocyte deactivation in experimental models and critically ill patients. In septic patients with low mHLA-DR levels, IFN-γ treatment reconstituted the expression of the receptor, increased monocyte function and had beneficial effects concerning disease severity in eight of nine septic patients (23). In a prospective, randomized and placebo controlled trial including 38 patients with severe sepsis or septic shock and less than 8,000 mHLA-DR molecules/monocyte, stimulation with granulocyte-macrophage colony-stimulating factor (GM-CSF) resulted in an increased release of TNF-α triggered by LPS (24). Regeneration of the monocyte function reduced in-hospital and ICU stay (24,25). In addition, several trials showed a lower susceptibility for nosocomial infections under GM-CSF therapy in paediatric patients (24,26). Beside IFN-γ and GM-CSF, IL-7 seems to be of potential value in (re)activation of the immune system. IL-7 endorses the differentiation of pluripotent stem cells into lymphocytes, the proliferation of lymphoid cell lineages and plays a role in T-cell activation. The interleukin promotes the expression of cellular adhesion molecules and other T-cell receptors and seems to improve the defence capacity against pathogens (11,27-29). Overall, although some promising results have been achieved, the literature regarding immune-stimulatory therapies in sepsis remains limited.

Early modulation of pro-inflammatory mediators: history of recombinant human IL-1 receptor antagonist

The identification of numerous host-derived mediators

of inflammation expanded our knowledge about the pathophysiology of sepsis. Although these molecules are integral part of the antimicrobial defense, they also promote an ebullient inflammatory state. As a result, several trials targeted pro-inflammatory pathways to counteract this potentially harmful response, like the manipulation of IL-1 signaling. IL-1 has been discovered by Dinarello *et al.* in 1977 (30) and plays an important role in the acute-phase response and the pathogenesis of septic shock (31). Endotoxins and other Toll-like receptor (TLR) agonists induce synthesis and secretion of IL-1, which then triggers the release of IL-6 in the liver, the liberation of neutrophils from the bone marrow and the endothelial production of prostaglandin E (32). Whereas high levels of circulating cytokines belonging to the IL-1 superfamily are associated with increased mortality in patients with septic shock (33), the IL-1 receptor antagonist (IL-1RA) inhibits IL-1 signal transduction (34). By functional receptor blockade, the recombinant form of the human protein [rhIL-1RA (35)] exerted beneficial effects in a broad range of experimental trials of systemic inflammation and sepsis (36-39). Subsequently, a number of clinical studies investigated the value of rhIL-1RA as therapeutic option in patients with sepsis, severe sepsis or septic shock (40-44). A phase I trial including 25 healthy male volunteers ascertained safety of IL-1 receptor blockade after continuous intravenous infusions for three hours with rhIL-1RA doses ranging between 1 and 10 mg/kg (40). In another study by Granowitz *et al.*, an increase of blood neutrophils induced by low-dose endotoxemia could be reduced by 3-hour continuous intravenous co-infusion with rhIL1-RA, although this treatment did not alter clinical symptoms like febrile temperature or tachycardia induced by Escherichia coli endotoxin (41). A prospective open-label placebo-controlled and multicenter phase II trial approved safety of additional rhIL-1RA treatment in 99 patients with sepsis or septic shock (42). However, two phase III trials failed to show survival benefits after rhIL1-RA treatment (43,44) with one study being discontinued after an interim analysis (44).

Anti-inflammatory therapies in sepsis: a hopeless case?

The findings of these rhIL-1RA studies are in line with the results of numerous other trials, which revealed only moderate impact of anti-inflammatory agents on the outcome of septic patients and thus challenged the idea to rescue septic patients solely by limiting the inflammatory response (45). A potential association between the individual risk of death and the effectiveness of anti-inflammatory therapies in sepsis has been discussed as a possible explanation for the inconsistent findings of preclinical approaches and clinical sepsis studies (46). In a retrospective metaregression analysis, Eichacker *et al.* found significant differences between human trials and preclinical studies concerning the control mortality and suggested that disease severity is a key determinant of anti-inflammatory drug efficacy and safety (47). This hypothesis was disputed by a systematic review showing a wide range of disease severity in randomized, placebo-controlled phase III trials with significant reduction of 28-day mortality including patients with sepsis, severe sepsis, or septic shock (48). Interestingly, concerning rhIL1-RA, the first phase III trial detected beneficial effects in the treatment arm of the subgroup of patients with an at least predicted risk of death of 24%, while mortality was higher in rhIL-1RA treated patients with lower risk (43). In contrast, the latter study by Opal *et al.* showed lower mortality in patients with a predicted risk of death beneath 24% treated with rhIL-1RA (44). Nevertheless, the heterogeneous and dynamic nature of sepsis requires an adequate risk stratification in terms of not only research, but also therapeutic strategies (49). For example, a phase II trial by Reinhart *et al.* found beneficial effects of treatment with the anti-TNF antibody fragment MAK 195F only in septic patients with IL-6 blood levels above 1,000 pg/mL (50).

Although rhIL-1RA as well as many other agents used to modulate the inflammatory host response did not show outstanding effects on patients' survival yet, a meta-analysis merging these clinical trials could reveal a small and statistically significant overall survival benefit in sepsis syndrome (47). Taken together, further evaluation of these approaches in clinically relevant and risk-stratified subgroups based on larger sample sizes could help to identify populations of critically ill patients, who could benefit from anti-inflammatory therapies.

New perspectives: IL-1 receptor blockade in septic patients with clinical signs of macrophage activation syndrome

A recently published reanalysis of a former phase III rhIL-1RA trial (51) illustrates, why a second evaluation of specific subgroups can be reasonable although the original study was stopped due to futility in patients with severe sepsis (44). The reanalysis aimed to determine putative advantages of rhIL-1RA treatment in septic patients presenting clinical

characteristics of a macrophage activation syndrome (MAS) (51). IL-1 receptor blockade has proved beneficial in MAS, which is characterized by a devastating release of various pro-inflammatory cytokines by activated T lymphocytes and macrophages (52). Beside fever and excessive cytokine production, hepatobiliary dysfunction (HBD) and hemorrhagic complications (disseminated intravascular coagulation, DIC) are common clinical signs of MAS. This fulminant inflammatory response primarily occurs as complication in systemic rheumatologic diseases and promotes the development of multi-organ failure, fatal disease progresses and death (53).

Due to numerous similarities of severe sepsis and MAS concerning symptoms and biochemical profile, Shakoory and coworkers assumed that rhIL-1RA treatment could improve survival of patients with severe sepsis in combination with DIC and HBD as clinical signs of MAS. Their reanalysis is based on a prospective, randomized, double-blind, placebo-controlled, multi-center phase III rhIL-1RA trial with a designed study population of 1,300 patients presenting severe sepsis or septic shock. Twenty-eight-day mortality was set as the primary end-point. Sepsis and sepsis-related organ dysfunction met the consensus definitions existent at the time of study enrollment (54). Classification of HBD included the presence of at least two criteria (prolonged prothrombin time, elevated blood levels of aspartate or alanine aminotransferase and/or serum bilirubin levels above 2.5 mg/dL). DIC was defined as abnormal platelet counts accompanied by prolonged prothrombin or partial thromboplastin time in participants without anticoagulation or elevated fibrin split products or D-dimer in anticoagulated patients, respectively. Treatment consisted of an initial IV bolus of 100 mg rhIL-1RA, followed by continuous intravenous infusion (2.0 mg/kg/hr) for 3 days and patients assigned to the placebo group received equivalent doses of placebo (44).

Data sets of 763 patients of the original study were included in the recent post hoc investigation. Fourty-three subjects presented both DIC and HBD and were treated with rhIL-1RA in 26 cases, while 484 of the 720 patients solely offering clinical signs of DIC, HBD or neither were assigned to the treatment arm. Overall, combination of DIC/HBD was associated with decreased 28-day survival probability (53.5% *vs.* 70.0%). In these patients, rhIL-1RA treatment lead to a significant 47% reduction of 28-day mortality compared to the placebo group (34.6% *vs.* 64.7%), an effect that could not be seen in the non-DIC/HBD group.

Although the comparison of 26 rhIL-1RA treated patients with 17 placebo participants may be underpowered to draw conclusions, the findings of Shakoory *et al.* underscore the need for further investigation of IL-1 receptor blockade in patients with combined features of MAS and sepsis.

Conclusions

Concurring pro- and anti-inflammatory mechanisms contribute to the pathophysiologic complexity of sepsis. The ebullient and life-threatening host response not only affects short-term survival, but also generates "immunologic scars", which may account for the high mortality in the post-acute phase. Subsequently, development and (pre-) clinical testing of mediator specific therapies may offer new opportunities to improve survival in these critically ill patients. There are many lessons we learned from cancer research, such as the need for individualized and stratified therapies, since no drug can fit all. Sepsis is a rapid and dynamic syndrome demanding for fast diagnostic tools and an adequate clinical management. Many hopeful results were achieved during the last decades, and some promising strategies might have been dropped due to faulty study design or heterogeneous patient populations. The findings of beneficial rhIL-1RA effects in subjects with sepsis and features of MAS by Shakoory *et al.* illustrate the impact of the individual disease profile on the success of immune-modulatory therapies. Ongoing investigations of auspicious sepsis-associated biomarkers can help to link the evaluation of the inflammatory state to an individual therapeutic regime. A better understanding of how inflammatory pathways are dynamically regulated may represent another important step to identify patients at risk, who potentially benefit from immune-modulatory approaches. In addition, recent studies could demonstrate that genetic variances of intra- and extracellular signaling molecules influence the individual inflammatory response and mortality in critical illness. For instance, in case of endogenous IL-1RA, a current trial discovered the preferentially transcription of a synonymous coding variant in the IL-1RA gene in European ancestry patients associated with elevated IL-1RA blood concentrations and higher survival rates in septic shock (55). Since sepsis and septic shock remain a serious threat associated with high mortality (1), future research may provide further insights into the (epi-) genetic heterogeneity and thus support individual treatment approaches as well as the avoidance of potentially harmful

therapies in patients with sepsis and/or immunologic disorders.

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Footnote

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