

COMMENTARY

# Immunostimulation using granulocyte- and granulocyte-macrophage colony stimulating factor in patients with severe sepsis and septic shock

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## Abstract

Sepsis is associated with failure of multiple organs, including failure of the immune system. The resulting 'sepsis-associated immunosuppression' resembles a state of immunological anergy that is characterized by repeated 'infectious hits', prolonged multiple-organ failure, and death. As a consequence, adjunctive treatment approaches using measures of immunostimulation with colony-stimulating factors (CSFs) were tested in animal experiments and clinical trials. Herein, data from randomized clinical trials will be discussed in the context of a recently published meta-analysis investigating the effects of granulocyte- and granulocyte-macrophage colony-stimulating factor therapy in patients with severe sepsis and septic shock.

Sepsis is a serious medical problem and constitutes an enormous burden for health care systems. A recent meta-analysis published in *Critical Care* [1] evaluated clinical effects of colony-stimulating factors in patients with severe sepsis/septic shock. Here, the results will be discussed in the context of the available data.

A large body of evidence indicates that the early 'hyper-inflammatory' phase in sepsis is often followed by a persistent 'hypo-inflammation' with severe alterations in both innate and cellular immunity [2-5]. Findings during this state of 'sepsis-associated immunosuppression' include diminished phagocytotic activity, cytokine expression profile changes towards an anti-inflammatory phenotype, increased expression of negative (co-)stimulatory molecules, reduced monocyte antigen presentation via

the major histocompatibility (MHC) class II complex (mHLA-DR), dysfunction and apoptosis of lymphocytes, and upregulation of regulatory T cells [2-7]. Mounting data show that patients with persistent 'sepsis-associated immunosuppression' are at increased risk for nosocomial infections [8], prolonged ICU stay, and death [4,9]. Typically, these patients will be resuscitated successfully in the early shock phase, will then develop an 'anergic' immunological state, and will finally succumb to repeated infections from rather avirulent secondary pathogens.

Keeping this in mind, immunostimulation in sepsis seems tempting but only few trials have investigated the immunological and clinical effects of immune reconstructive therapies [4-6,10]. Such approaches include immunostimulation with interferon- $\gamma$  [11], selective extracorporeal reduction of immunodepressants [12], and medication with granulocyte-colony stimulating factor (G-CSF)/granulocyte-macrophage colony stimulating factor (GM-CSF) (summarized in [1]). However, when analysing the available data on CSF therapy in sepsis, it seems important that G-CSF and GM-CSF have distinct properties. Both are potent immunostimulators, induce leukocytosis, augment the activity of granulocytes and have anti-infectious (mostly anti-bacterial) capabilities. GM-CSF additionally stimulates monocytes/macrophages, induces monocytic cytokine expression (for example, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ ) and induces antigen presentation (mHLA-DR) [13].

As demonstrated in the recent meta-analysis [1], a total of 12 placebo-controlled randomized controlled trials (RCTs;  $n = 2,380$  patients) investigated the clinical effects of G-CSF ( $n = 8$  RCTs) and GM-CSF ( $n = 4$  RCTs) in patients with severe sepsis/septic shock. The main outcome measure of this systematic review was all-cause short-term (14-day; data from  $n = 138$  patients available) and 28-day mortality. No significant difference in 28-day mortality (relative risk (RR) 0.93, 95% confidence interval (CI) 0.79 to 1.11,  $P = 0.44$ ) and in-hospital mortality (RR 0.97, 95% CI 0.69 to 1.36,  $P = 0.86$ ) was observed when patients receiving G-CSF or GM-CSF were

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compared to placebo-treated controls. Analysis of G-CSF (n = 2,044, 6 RCTs) or GM-CSF (n = 89, 3 RCTs) treatment subgroups revealed no 28-day mortality benefit. In line with previous findings from non-randomized trials, CSF therapy appeared safe. Nevertheless, although an effect on mortality was not observed, the meta-analysis identified that patients receiving G-CSF or GM-CSF therapy have a significantly increased rate of reversal from infection (RR 1.34, 95% CI 1.11 to 1.62,  $P = 0.002$ ). Although this finding is mainly based on available G-CSF data, it supports earlier findings from animal models that CSF therapy may indeed induce a faster reversal from infection. This seems especially the case in pneumogenic sepsis [14]. In line with data from animal models and G-CSF trials, we recently demonstrated in the first biomarker-guided immunostimulatory placebo-controlled RCT in sepsis that GM-CSF therapy significantly shortens the time of mechanical ventilation [15].

However, a number of limitations of the meta-analysis need to be discussed. First, a combined G-CSF/GM-CSF analysis might be challenged due to the distinct biology and underlying treatment concepts of each. Whereas G-CSF is typically given to increase antimicrobial defense via numerical induction of granulocytes, GM-CSF therapy aims to re-stimulate antigen-presenting cell function/adaptive immunity. Moreover, as G-CSF is often applied in induction-chemotherapy-induced neutropenia, the role of neutropenia-related sepsis in the included trials remains unclear. Second, the heterogeneity of the trials under investigation is noteworthy as the trials differed greatly in regard to applied CSF doses, routes of administration, pharmacological CSF subtypes and patient characteristics (for example, disease severity). This certainly constrains data comparability. Third, most trials did not stratify study patients according to their immunological state and the efficacy of the immunological intervention was not tested or reported. We believe that this remains a prerequisite for future immunomodulatory trials in sepsis. Although assessment of the underlying complex immunological condition using a single biomarker may be regarded as challenging, standardized quantitative tests (for example, flow-cytometric mHLA-DR assessment) were recently developed that may both serve as global biomarkers for cellular immunity and help to guide future immunotherapies [7,10,16].

Future trials on CSF therapy should be performed in immunologically stratified patients and concomitant immune monitoring seems mandatory. As CSF therapy seems to contribute to a faster reversal of infection and may shorten the time of mechanical ventilation, there is an urgent need for larger RCTs adequately powered for 28-day mortality, respective surrogates, or reduction of nosocomial infection rates. Currently, on the basis of the

limited heterogenous data available, a mortality benefit for CSF therapy cannot be demonstrated. At this point in time, CSF therapy should thus be applied in the context of clinical trials only, with the exception being individual off-label rescue approaches.

#### Abbreviations

CI, confidence interval; CSF, colony-stimulating factor; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; mHLA-DR, monocytic human leukocyte antigen-DR; RCT, randomized controlled trial; RR, relative risk.

#### Competing interests

The author declares that he has no competing interests.

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