Cell Reports Medicine

CellPress
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Preview

Identifying inflammatory phenotypes to target mechanism-specific treatments in sepsis

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https://doi.org/10.1016/j.xcrm.2022.100823

A clinical trial by Leventogiannis et al.[1] suggests that ferritin and HLA-DR monocyte receptor expression can identify septic patients with macrophage-activation-like syndrome (MALS), or immunoparalysis, and that targeting IL-1ra treatment with this strategy may improve outcomes.

Conceptually, the biologic heterogeneity of sepsis is an accepted notion in clinical practice. The classic example, all too familiar to many clinicians, is that of two patients who, despite presenting with a similar infection and comparable clinical characteristics, diverge completely in their trajectory and outcome. However, answering "why" this divergence occurs is challenging for several reasons. First, multiple mechanisms often interact synergistically to drive organ injury during sepsis. Second, the disconnect between driving mechanisms and the clinical expression of the septic syndrome[2] makes it improbable to identify mechanistic drivers based on clinical observation. Challenges like these have delayed the permeation of the conceptual framework of heterogeneity into the design of large randomized clinical trials (RCT) and account, at least in part, for the failure in identifying effective therapies for sepsis.

Despite its unreserved complexity, embracing this concept of heterogeneity is necessary to identify therapies that will improve outcome in sepsis. From a pragmatic clinical standpoint, the focus should be on reliably identifying patient subgroups with common, proven mechanistic drivers of organ injury—or *endotypes*—and/or subgroups with common clinical traits, trajectories, outcomes, and responsiveness to a specific therapy—or *treatment-responsive phenotypes*.

One approach to achieving this goal centers on applying clustering techniques to large datasets of patients with sepsis while remaining agnostic to the characteristics and number of resulting subgroups. This strategy has proven effective in identifying phenotypes with higher adjusted risk for poor outcomes, as highlighted by a recent scoping review summarizing the results of 17 studies.[3] For instance, by clustering septic patients based on clinical and laboratory, genome-wide expression, or leukocyte gene expression datasets, several independent groups have identified multiple phenotypes with distinct disease trajectories, immune states, outcomes, and responses to "routine" treatments,[2,4] suggesting that this may serve as an effective trial enrichment strategy.

An alternative approach centers on the premise that there are known phenotypes and/or endotypes. This applies to macrophage-activation syndrome (MAS), a hyperinflammatory condition found in patients with rheumatologic autoimmune disorders or malignancy but that can be triggered in ~6% of septic patients.[5,6] Mechanistically, evidence suggests that activation of a positive feedback loop involving interleukin-1 (IL-1), IL-18, and ferritin is a central driver of the development of MAS in sepsis. Supporting this notion is the finding that combined IL-1/IL-18 blockade effectively turned off hyperinflammation and improved outcomes in patients with rheumatologic conditions complicated by MAS.[7] When applied to all patients with sepsis in a large phase III RCT, though, treatment with IL-1 receptor antagonists (IL-1ra) appeared futile.[8] However, in a post-hoc analysis of the same trial, Shakoory et al. demonstrated that, in patients with features of MAS characterized by hepatobiliary dysfunction and disseminated intravascular coagulation, treatment with IL-1ra was associated with a 30% absolute risk reduction in mortality.[5]

In this issue of *Cell Reports Medicine*, Leventogiannis et al.[1] take an important step toward targeting therapies to specific phenotypes in a two-stage prospective clinical study. The first stage assessed the reliability of plasma ferritin >4,420 ng/mL or <30% expression of HLA-DR receptors in CD14/CD45 monocytes in identifying two sepsis phenotypes: macrophage-activation-like syndrome (MALS),[9] or immunoparalysis. The second stage consisted of a double-blind, double-dummy, phase II RCT investigating the effect of treatment with IL-1ra or interferon γ (IFN-γ) on 28-day mortality, in patients with sepsis complicated with MALS or immunoparalysis compared with placebo.

The authors enrolled 240 patients with sepsis. During the first stage, 48/240 (20%) patients were found to have a plasma ferritin >4,420 ng/mL, 44/177 (23%) with septic shock, and 4/63 (6%) without septic shock. Despite using the same ferritin threshold, the occurrence of MALS in this study was higher than in their original series (3.7%–4.3%),[9] suggesting that ferritin as the sole criterion may identify patients with other hyperinflammatory conditions that may not be responsive to treatments tailored for MALS.

Similarly, there is no universal definition for sepsis-induced immunoparalysis. In this study, <30% expression of HLA-DR in CD14/CD45 monocytes only identified two patients, failing as an enrichment strategy. The authors retrospectively derived an alternative criterion based on the expression of <5,000 HLA-DR

receptors/monocyte, which was present in 103 of the 240 patients. Although in need of further validation, the authors provide proof of plausibility as patients reaching this criterion had biologic evidence of immunoparalysis based on decreased tumor necrosis factor alpha (TNF-α) production in stimulated peripheral blood mononuclear cells.

Like other groups using unsupervised clustering approaches,[2,4,10] Leventogiannis et al. identified subgroups of patients with increased risk of mortality. Patients with high ferritin or low HLA-DR receptor expression had a mortality of 79.1% and 66.9%. However, analysis of the 36 patients randomized to receive IL-1ra or placebo before the study was prematurely stopped showed no differences in 28-day mortality. Despite this, we urge the reader to resist the temptation to conceive this study as a negative trial. While the authors adopted a valid strategy to select potential therapy-responding phenotypes, the execution failed in part due to lack of proven definitions for these specific disease mechanisms. Furthermore, the authors report that survival at day 7 with decreased Sequential Organ Failure Assessment (SOFA) score was higher in patients treated with IL-1ra compared with placebo. They hypothesize that this exploratory outcome did not translate to 28-day survival due to the short duration of treatment with IL-1ra, and they have now launched a subsequent study to extend the therapeutic window (NCT04990232). While the expectations for the results of this new trial are high, a critical lesson from Leventogiannis et al. work remains. Deriving, unifying, and validating criteria to define sepsis endotypes or treatment-responsive phenotypes that facilitates trial enrichment, epidemiologic tracking, and matching to specific therapeutics must be a research priority for the immediate future.

Overall, Leventogiannis et al. are to be commended for taking a bold step toward the next generation of clinical trials in sepsis. They have provided invaluable insight into the challenges that investigators will face in identifying endotypes and treatment-responsive phenotypes in a manner that is pragmatic and applicable to daily clinical practice. For now, however, the answer as to whether anti-IL-1ra or IFN-γ will be effective in treating specific subgroups of patients with sepsis will have to await the successful implementation of a future trial.

DECLARATION OF INTERESTS

H.G. discloses consulting agreements with Novartis and Trilinear Bioventures.

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