IL-1 receptor antagonist in sepsis: new findings with old data?

David Grimaldi, Eduardo Wilfrido Goicoechea Turcott, Fabio Silvio Taccone

Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Bruxelles, Belgium
Correspondence to: Prof. Fabio Silvio Taccone. Department of Intensive Care Unit, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808, 1070 Brussels, Belgium. Email: ftaccone@ulb.ac.be.

In a recent issue of Critical Care Medicine, Shakoory *et al.* reported the potential benefits of IL-1 receptor antagonist (IL-1 RA, anakinra) administration in the treatment of severe sepsis and septic shock when associated with hepatic dysfunction and coagulopathy (1). This study is an ancillary sub-analysis of a negative randomized clinical trial (RCT), which evaluated the effect of IL-1 RA in the larger population and published almost two decades ago (2). In this post-hoc analysis, the authors observed that treatment with IL-1 RA improved the 28-day survival in the subgroup of patients with hepato-biliary dysfunction or disseminated intravascular coagulopathy (HBD/DIC) occurring either on admission or during the ICU stay; 26/35 (65%) patients with HBD/DIC and treated with IL-1 RA survived at one month after randomization when compared to 6/17 (35%) HBD/DIC patients treated with placebo [hazard ratio for death 0.28 (0.11–0.71); P=0.007 using a Cox regression analysis]. This study presented several methodological weaknesses, which were also recognized by the authors: a retrospective design with post-hoc analysis, an inclusion period during which sepsis management was far different that nowadays, a limited cohort of patients who showed the particular phenotype of interest (n=43 with HBD/DIC), the use of old and inaccurate definition for coagulation disorders based only on platelets count, prothrombin time (PT) or partial thromboplastin time as well as a disequilibrium in treatment allocation (2:1 instead of the 1:1 ratio for the original study protocol). However, the magnitude of the effect was so relevant that a more accurate discussion on the rationale of this therapy as well as its applicability in septic patients is warranted.

The use of IL-1 RA therapy in sepsis began with the idea that counteracting the cytokine storm induced by overwhelming infections would decrease the occurrence of organ failure and/or reduce its severity in critically septic patients, with a potential improvement also in overall outcome. In particular, IL-1 RA binds to IL-1 receptor and prevents IL-1 (e.g., one of the major pro-inflammatory cytokines) signal transduction. Promising results in a phase II trial (3) prompted the conduction of a first phase III trial (n=893), in which IL-1 RA failed to demonstrate a benefit in 28-day survival but showed some positive effects on outcome among the most severe patients (e.g., those with multiple organ dysfunction and/or predicted mortality >24% based on APACHE II score; n=580) (4). On the basis of these findings, a confirmatory phase III trial was initiated but then prematurely halted after the first interim analysis because of no statistically significant reduction in mortality observed between the IL-1 RA (n=350; mortality 33%) and placebo (n=346; mortality 36%) group (2). Although abandoned for the therapy of sepsis, IL-1 RA administration demonstrated a significant efficacy in the treatment of rheumatoid polyarthritis and cryopyrin-associated periodic syndromes (e.g., a rare neonatal-onset multisystem inflammatory diseases) and was eventually approved in Europe as one of the "effective" therapies for such conditions. IL-1 RA was also reported to provide some benefits in other inflammatory diseases (5), probably because of the broaden implication of IL-1 in the pathogenesis of these disorders.

Among them, clinical responses to IL-1 RA therapy has been described for the macrophage activation syndromes [also called hemophagocytic lymphohistiocytosis (HLH)] or reactive hemophagocytic syndromes (6). HLH is a rare life-threatening condition resulting from natural killer and cytotoxic T-cell dysregulation, leading to cytokine overproduction and hemophagocytosis. It may be inherited due to mutations in the granule machinery of cytotoxic

T-cells and NK lymphocytes, or acquired (e.g., the so-called "reactive" HLH) due to multiple etiologies and triggers, mostly viral infections, lymphoproliferative disorders and/or systemic autoimmune diseases (7). The diagnosis of HLH relies on the combination of clinical, laboratory and histological findings and may be difficult at bedside. Typical laboratory abnormalities include central cytopenia, a major elevation in ferritin and triglycerides levels as well as low fibrinogen concentrations (7). Hepatic involvement is frequent but is not required for the diagnosis, while DIC is rare, because thrombocytopenia and hypofibrinogenemia are in general related to others mechanisms than intravascular activation and consumption. The main histological finding in HLH is the presence of macrophages engulfing blood cells or precursors but, although hallmark of the disease, hemophagocytosis may be hardly demonstrated in HLH while sporadic hemophagocytosis may be observed in other inflammatory conditions, including severe sepsis (8). Therefore, hemophagocytosis does not indicate a diagnosis of HLH unless other clinical and laboratory features of the syndrome are concomitantly present. Diagnostic guidelines in children have been proposed and the diagnosis can be established upon the fulfilment of five out of eight criteria, which include fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent NK-cell-activity, high ferritin and and high-soluble interleukin-2-receptor levels (9). More recently a score dedicated to adults' reactive hemophagocytic syndromes have been developed and validated, including nine variables (known underlying immunosuppression, high temperature, organomegaly, triglyceride, ferritin, serum glutamic oxaloacetic transaminase and fibrinogen levels, cytopenia and hemophagocytosis features on bone marrow aspirate) (10). Importantly, HLH first-line treatment relies on the cytotoxic drug etoposide in association with steroids, as well as the control of the underlying pathologic trigger, other potential choices being cyclosporine and intravenous immunoglobulin (11).

When the pathophysiology of HLH is translated to sepsis-associated liver and coagulation dysfunction, it had been shown that innate cells (rather than CD8 cells as in HLH) are the primary source of pro-inflammatory cytokines while an intense anti-inflammatory response occurs simultaneously in this setting (12). This is undoubtedly one of the reason why all attempts to counteract the pro-inflammatory response in sepsis have failed to improve outcome in the clinical setting. Moreover, although the existence of sepsis-induced HLH has been

suggested (13), the absence of common HLH biological features, such as high triglycerides and ferritin levels, in septic patients is in favour for different mechanisms underlying the hemophagocytosis process observed in some cases and, then, for different therapeutic strategies than in primary HLH. In the study from Shakoory et al. (1), biological and clinical criteria of HLH were not recorded and one may argue that the assumption made by the authors that coagulopathy and hepato-biliary dysfunction in this cohort of patients were potential features of HLH could be largely criticized. Thus, if any benefit could be expected by IL-1 RA on the liver and coagulation disorders associated with sepsis, this may be independent from the effects of this treatment on the development of hemophagocytosis.

Besides the controversial rationale of this study, a second point deserves to be mentioned. Indeed, this study evaluated a subgroup of septic patients with a specific phenotype that may respond to a particular immunomodulatory therapy, whereas the whole cohort of patients did not. In the last decades, numerous RCTs aiming to improve the prognosis of sepsis have failed and one of the causes advanced was the large heterogeneity of the patients included in those studies (14). Indeed, sepsis is a syndrome caused by a wide range of different pathogens, driven by the interplay of a diverse pathological processes and it corresponds to the specific response of the host to a given infectious challenge. Genetic variability exists both in host and pathogen, while comorbidities and the time frame of the infection (e.g., community- vs. hospital-acquired) may also largely influence patients' outcome. These multiple factors and even some stochastic effects, explain the diversity of phenotype in term of the development of organ failure and the immune response status. Due to this heterogeneity, the finding of a single treatment that could improve all septic patients is highly unlikely if not impossible and there is an urgent need for a better understanding on how to target specific interventions to phenotypic characteristics of such patients. In the present study (1), coagulopathy and hepato-biliary dysfunction were observed only in 5% (43/763) of the enrolled patients. Moreover, the original flow-chart of the study did not provide the number of eligible patients; however, we could hypothesize that for a ratio of 1:10 between screened and eligible patients, only one out of 200 septic patients could be included in a RCT evaluating the impact of IL-1 RA on overall mortality, which would significantly limit the feasibility of such trial and the generalizability of this therapy in common practice. Finally, a better description of the liver and coagulation disorders

should be used, with the inclusion of other available tests for liver (e.g., PT, ammonium accumulation) and coagulation (e.g., platelets activity, thromboelastography) function as well as the report of clinical and biological features of HLH.

A last issue concerns the use of anakinra, which was administered in the present study (1), as the optimal IL-1 blocking agent in this setting. Indeed, three IL-1 blockers have been approved for clinical use; together with anakinra, which blocks the IL-1 receptor and therefore reduces the activity of IL-1α and IL-1β, a soluble decoy receptor, rilonacept, and a neutralizing monoclonal anti-interleukin-1β antibody, canakinumab, are also available (5). Moreover, a monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1α are under evaluation in clinical studies. Thus, if a better description of liver and/or coagulation dysfunction during sepsis could be obtained, different IL-1 RA therapies should be further evaluated to better assess the impact of such therapeutic strategy on the outcome of septic patients.

In conclusion, sepsis is a complex disorder that can be associated with different degree of organ dysfunction. This complexity called for the development and assessment of personalized medicine, which should separate patients into different groups having tailored diagnostic and therapeutic interventions based on their predicted response or risk of disease (15). As septic non-survivors may have biochemical, cellular and/or immune-histochemical findings consistent with a significantly different immune response than survivors, the understanding on how these abnormalities influence the occurrence of sepsis-related organ dysfunction and how targeted immune-enhancing therapy may be a valid approach in selected patients needs to be further clarified.

Acknowledgements

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Footnote

Comment on: Shakoory B, Carcillo JA, Chatham WW, *et al.* Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Crit Care Med 2016;44:275-81.

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