Management of Sepsis-Induced Immunosuppression

Fabienne Venet, PharmD, PhD[a,b], Thomas Rimmelé, MD, PhD[b,c], Guillaume Monneret, PharmD, PhD[a,b,d,*]

KEYWORDS

• Sepsis • Septic shock • Immunosuppression • HLA-DR • Immunostimulation • IL-7 • GM-CSF • Lymphopenia

KEY POINTS

- Profound acquired immunosuppression develops within a few days after septic shock in patients.
- Magnitude and/or persistence of sepsis-induced immunosuppression are associated with increased occurrence of nosocomial infections and mortality.
- In animal models, immunostimulation is associated with clinical improvement.
- Results from clinical trials based on interleukin 7 and granulocyte macrophage colony-stimulating factor immunoadjuvant therapies in septic shock patients are expected for 2018.

INTRODUCTION: THE PROCESS OF SEPSIS-INDUCED IMMUNOSUPPRESSION

Although sepsis has been frequently described as solely inducing a tremendous systemic inflammation, current data indicate that it leads to a more complex immune response that evolves over time, with the simultaneous implication of both proinflammatory and anti-inflammatory mechanisms.[1] As a result, after a short unbridled proinflammatory phase, an important subgroup of septic patients presents with profound

Disclosure Statement: The authors declare they do not have any conflicts of interest regarding this article.

[a] Laboratoire d'Immunologie, Cellular Immunology Laboratory, Hospices Civils de Lyon, Hôpital Edouard Herriot, Pavillon E - 5 place d'Arsonval, Lyon Cedex 03 69437, France; [b] EA 7426 PI3 "Pathophysiology of Injury-induced Immunosuppression", Université Claude Bernard Lyon I, Hospices Civils de Lyon, bioMérieux, Hôpital Edouard Herriot, Place d'Arsonval, Lyon Cedex 03 69437, France; [c] Departement of Anesthesiology, Hospices Civils de Lyon, Hôpital Edouard Herriot, Pavillon E - 5 place d'Arsonval, Lyon Cedex 03 69437, France; [d] TRIGGERSEP (TRIal Group for Global Evaluation and Research in SEPsis), F-CRIN Network, France
* Corresponding author. Cellular Immunology Laboratory, Hôpital Edouard Herriot, Hospices Civils de Lyon, Pavillon E - 5 place d'Arsonval, Lyon Cedex 03 69437, France.
E-mail address: guillaume.monneret@chu-lyon.fr

Crit Care Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.ccc.2017.08.007 criticalcare.theclinics.com

acquired immunosuppression, which could be associated with difficulties to efficiently eradicate the primary infection despite adequate antibiotic treatment.[1–3] Such immune deficiency is also proposed to predispose patients to reactivation of latent viruses (cytomegalovirus or herpes simplex virus) or nosocomial infections due to pathogens, including fungi usually held in abeyance by a functional immune system.[4–7] In addition, it likely contributes to delayed excess mortality (over weeks and years) for which infectious etiologies are frequently involved.[8] Collectively, these immune alterations are believed responsible for worsening outcome in septic patients who survived initial resuscitation.[9]

Consequently, new therapeutic options based on adjunctive immunostimulation (interferon gamma [IFN]-γ, granulocyte macrophage colony-stimulating factor [GM-CSF], interleukin [IL-7], anti–programmed cell death 1 protein [PD1]/anti–PD1–ligand [L]1 antibodies) are emerging.[9,10] Recent data have shown that most aspects of immune responses are modulated in septic patients. Neutrophils lose their anti-infectious properties and shift toward an immature profile and cells with immunosuppressive functions. Monocytes and dendritic cells lose their capacity to produce inflammatory cytokines and to appropriately present antigens to lymphocytes (due to the loss of major histocompatibility complex class II expression [eg, HLA-DR]). The few effector lymphocytes surviving intense apoptotic process occurring after sepsis present with an exhausted phenotype (loss of major effector functions: proliferation, cytokine production, and increased coinhibitory receptor expression) whereas regulatory T- cell and B-cell subpopulations are expanding.[1] Consequently, treatments able to rejuvenate immune functions represent interesting therapeutic candidates in sepsis.[1,8,10] Nevertheless, because there is no clinical sign of immune dysfunctions, such therapeutic intervention must rely on biomarkers[11] for identifying the patients who could benefit from immunostimulation (ie, those presenting with profound and/or long-lasting immune dysfunctions).

MANAGEMENT GOALS AND STRATEGIES

Is There Still Room for Anti-inflammatory Strategies in Sepsis?

Although the main focus of this review is on immunostimulatory therapies in sepsis, there is likely still room for anti-inflammatory treatments in the very first hours of the syndrome. As discussed previously for immunostimulation, however, a major challenge is to identify patients who could benefit from such treatments (ie, in this case, patients who are still on ascending curve of the proinflammatory response). To date, despite a few promising reports,[12] data are still missing regarding this approach.

Extracorporeal Therapies

Several extracorporeal blood purification therapies can potentially positively interfere with the host immune response by removing both inflammatory and anti-inflammatory mediators and consequently preventing forthcoming immunosuppression. In a porcine model, high-volume hemofiltration could prevent endotoxin hyporesponsiveness. CD14 expression on monocytes, oxidative burst, and phagocytosis capacity of granulocytes were also improved by the technique.[13] The IVOIRE multicenter randomized controlled trial (RCT), however, comparing ultrafiltration flow rates of 35 mL/kg/h versus 70 mL/kg/h in patients with septic shock and acute kidney injury, did not show any survival benefit.[14] Hemoperfusion is based on the interaction between a sorbent and molecules targeted for removal via adsorption. In a recent meta-analysis, the beneficial effect of blood purification on mortality was mainly driven by the results of studies assessing hemoperfusion with polymyxin B.[15] Because it targets the endotoxin, polymyxin B hemoperfusion is proposed for the treatment of