Immunotherapy – a potential new way forward in the treatment of sepsis

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The article from Wu and colleagues investigates the question of using immunostimulation as a new approach in treating sepsis [1]. The incidence of sepsis, and particularly severe sepsis, is expected to markedly increase in the next decade due to the aging population and more widespread use of therapies that compromise host immunity in cancer and autoimmune diseases. A better strategy to reduce mortality in severe sepsis thus remains an absolute necessity.

Advances in sepsis therapy have occurred and the Surviving Sepsis Campaign recommendations have led to a reduction in sepsis mortality from roughly 50% to ~30 to 35% [2]. The remaining high rate of death and the failure of the most recent high-profile clinical trials in sepsis still argue for an innovative adjuvant approach to this highly lethal disease [3]. Beyond the design of these trials, incertitude on some key pathophysiologic mechanisms should be clarified to allow change in the paradigms of sepsis syndrome and patient care. Among the newly accepted concepts, the occurrence of immunodepression soon after the initial phase of sepsis has gained credibility. To be clinically relevant, such a concept has: to be confirmed in a large-size population; to be diagnosed and quantified by standardized methods; to be observed not only on circulating immune cells, but also within organs that fail in sepsis; to be based on molecular mechanisms; and to be reversible, even partially, by clinical-based therapy able to improve outcome. Almost all of these criteria have been validated in clinical conditions, except the proven benefit for outcome. The article from Wu and colleagues addressed this question using thymosin alpha-1 (Tα1) [1], a molecule with known immunostimulating properties [4].

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The concept of sepsis-induced immunodepression has been extensively described ex vivo, especially in septic monocytes, with impaired responses to additional immune challenges compared with healthy cells. Importantly [5], such immunodepression was recently demonstrated to occur in immune cells infiltrating into organs in patients dying from severe sepsis [6]. Remarkable to note is that most immune effector cells are involved, resulting in defects in both innate and adaptive immunity [7]. Moreover, the magnitude and duration of immunosuppression are now well documented to be associated with worse outcome and increased risk for nosocomial infections [8]. The underlying mechanisms are complex:
the predominance of anti-inflammatory cytokines [9]; the alteration of T-lymphocyte populations in number and function [6]; the fractional increase in T-regulatory inhibitory lymphocytes [10]; metabolic failure of immune cells [11]; and epigenetic modifications induced by the cell microenvironment [12].

Interestingly, this immunodepression has been shown to be reversible using different immunostimulatory therapies including IFNγ [13], granulocyte–macrophage colony-stimulating factor [14], and, recently, IL-7 [15]. Such treatments may boost host immunity, thereby leading to more effective eradication of the primary infection, prevention of secondary infection, decreasing latent virus reactivation and, hopefully, improving outcome.

The present randomized control trial of Ta1 is in line with this new direction. Despite a lack of understanding of some of its mechanism(s) of action, immunomodulatory activity of Ta1 on effector cells of the innate immunity has been well described [4]. Ta1 can induce T-cell and dendritic cell maturation as well as increasing IL-12 expression.

This randomized controlled trial tested the early administration of Ta1 on day–7 and day–28 mortality and on severity of organ failure and mHLA-DR expression. The main result was a reduction in 28-day mortality in the Ta1 group (26%) versus the control group (36%) (P < 0.06) with an associated increase in mHLA-DR and no change in severity of organ failure.

The moderate outcome benefit may result from several limitations well mentioned by the authors. Perhaps more importantly, two issues may limit the observed benefit. First, the trial is designed to reduce crude mortality, which includes both sepsis-attributable mortality and mortality related to underlying disease. An adjunctive immune therapy would only impact septic-induced organ failure and death and would require a larger study population. Second, the drug or the placebo was given to all patients having the entry criteria that were not based on immune competence. The results might have been different if enrollment of the patients had been based on immune monitoring and restricted to those patients with documented immunosuppression.

Despite its significant limitations and undefined mechanism of action, this randomized control trial is one of the first such trials using a known immunostimulating agent to reduce 28-day mortality. Despite the largely unknown mechanism of action of the drug and nonselction based on assessed immunodepression, the observed marginal positive P value in favor of Ta1 confirms the interest to perform other carefully conducted immunotherapeutic trials based upon markers of immune suppression.

Competing interests
DP has received grant support from Meditor. RH has received grant support from Bristol Meyers Squibb and Medimmune. GM has no competing interests.

Abbreviations
IFN, interferon; IL, interleukin; Ta1, thymosin alpha-1.

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