

## COMMENTARY

# Treatment with recombinant human activated protein C: one size does not fit all

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See related research by Shorr *et al.*, <http://ccforum.com/content/14/6/R229>

### Abstract

Protein C plays an important role in the coagulopathy associated with sepsis and probably also in the pathogenesis of sepsis-induced organ dysfunction. Plasma levels of protein C strongly correlate with clinical outcome in patients with severe sepsis. The RESPOND (Research Evaluating Serial Protein C Levels in Severe Sepsis Patients on Drotrecogin Alfa [Activated]) study shows that administration of recombinant human activated protein C in patients with severe sepsis with alternative dose regimens adjusted to plasma levels of protein C results in higher plasma levels of protein C. This may potentially translate to a better clinical outcome in patients with severe sepsis, although that was not directly shown in this trial.

Protein C is a physiological anticoagulant factor and has been implicated in the pathogenesis of sepsis for many years. In the previous issue of *Critical Care*, Shorr and colleagues [1] add to our knowledge of the role of protein C in sepsis by presenting data from the RESPOND (Research Evaluating Serial Protein C Levels in Severe Sepsis Patients on Drotrecogin Alfa [Activated]) study, which demonstrates that administration of recombinant human activated protein C may modulate protein C levels and thereby potentially affect outcome in patients with severe sepsis. In 40% to 60% of patients with severe sepsis, plasma levels of protein C are low or very low because of impaired synthesis, consumption, and degradation by proteolytic enzymes, such as neutrophil elastase [2,3]. Several studies point to the fact that the plasma level of protein C may be regarded as a strong

predictor for the outcome in sepsis, and early improvement in protein C levels strongly correlates with survival [4-6]. Apart from being a relevant biomarker, protein C is likely to be involved in the pathogenesis of sepsis. The most typical example is meningococcal septicemia, in which very low plasma levels of protein C play a pivotal role in the occurrence of purpura fulminans [7]. In addition, transgenic mice show that deficiency of protein C in sepsis is associated with enhanced inflammatory activity [8]. Also, restoration of low protein C levels in septic baboons resulted in an amelioration of coagulopathy and reduced mortality [9]. Hence, there is ample evidence that increasing protein C levels in patients with sepsis could significantly improve clinical outcome.

Shorr and colleagues show that the effect of variable dose regimens of recombinant human activated protein C can achieve this therapeutic goal. Patients who were randomly assigned to a strategy in which administration of recombinant human activated protein C was adjusted to their endogenous protein C levels – and who thereby sometimes received higher doses of recombinant human activated protein C (that is, 30 or 36  $\mu\text{g}/\text{kg}$  per hour compared with the usual dose of 24  $\mu\text{g}/\text{kg}$  per hour) and for a longer duration – achieved 7% higher levels of protein C as compared with conventional treatment. Remarkably, the authors' results confirmed the finding that normalization of protein C levels within 7 days had a major impact on mortality (10.3% in patients with normalized protein C levels compared with 32.0% in patients who did not normalize).

One of the strengths of the study by Shorr and colleagues is that it is the first major clinical study investigating differential doses of recombinant human activated protein C. It is fair to say that dose-finding studies with recombinant human activated protein C are quite limited and that the currently used dose of 24  $\mu\text{g}/\text{kg}$  per hour has been based on a plateau effect on D-dimer levels in a single phase II clinical trial [10]. It may well be that some patients with severe sepsis may need higher doses of activated protein C concentrate and for a duration longer than the standard 4-day schedule. The study by Shorr and colleagues demonstrates that this is

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not associated with an increase in major bleeding complications during the infusion period. As major bleeding is a concern in patients with severe sepsis and as recombinant human activated protein C has been shown to significantly (albeit, in absolute terms, very modestly) increase this risk [11], it is reassuring that the studied dose regimens in the RESPOND study did not clearly increase the bleeding rate.

Rather than intensifying or prolonging the treatment with activated protein C, many clinicians have adopted the practice of terminating the administration of recombinant human activated protein C in patients who are admitted with severe sepsis but who demonstrate a rapid and significant improvement in their clinical condition. Although this seems to be a logical and cost-conscious measure, we need to realize that this practice is not supported by sound clinical trial data.

A limitation of the study by Shorr and colleagues is that focusing on zymogen protein C levels may ignore the fact that, in patients with severe sepsis, protein C activation may be markedly impaired. Indeed, a significant down-regulation of thrombomodulin, caused by proinflammatory cytokines such as tumor necrosis factor- $\alpha$  and interleukin-1, may occur in patients with severe sepsis, resulting in diminished protein C activation [2,12]. It may well be that directly administering activated protein C will overcome this impaired activation and that plasma protein C levels will act as merely an easy-to-measure biomarker to guide this treatment. To further explore this issue, it would be interesting to perform a head-to-head comparison between administration of recombinant human activated protein C and zymogen protein C concentrate in patients with severe sepsis, looking at restoration of plasma levels of protein C but also at clinically relevant outcomes, such as organ dysfunction and mortality.

In conclusion, the RESPOND study shows that a differential approach to the administration of recombinant human activated protein C may result in a more effective normalization of protein C levels. It is tempting to speculate on the translation of these findings to better treatment outcome in patients with severe sepsis, but we need additional clinical studies that would demonstrate such an effect. In the meantime, it is clear that, in regard to activated protein C treatment in patients with sepsis, one size apparently does not fit all.

#### Abbreviation

RESPOND, Research Evaluating Serial Protein C Levels in Severe Sepsis Patients on Drotrecogin Alfa (Activated).

#### Competing interests

The author declares that he has no competing interests.

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