Commentary

Recombinant activated protein C: the key is clinical assessment of risk of death, not subset analysis

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Abstract

The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial demonstrated a 6.1% absolute decrease in mortality with a *p* value of 0.005. Despite the impressive results of this trial, criticism of the study has targeted various aspects of design, analysis and interpretation. Additional studies of recombinant activated protein C (rhAPC) have added to our understanding about this drug and to controversy as well. So how do we deal with rhAPC use in our clinical practice?

The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial demonstrated a 6.1% absolute decrease in mortality with a *p* value of 0.005 [1]. Recombinant activated protein C (rhAPC) was approved by the FDA for use in patients with 'sepsis induced organ dysfunction associated with a high risk of death, such as an APACHE [Acute Physiology and Chronic Health Evaluation] II of ≥25'. APACHE II ≥25 was used as one marker of high risk of death because a subset data analysis demonstrated that the treatment benefit in the PROWESS trial was predominantly in this group of patients. The European regulatory body approved rhAPC for multiple organ failure (again based on subset data analysis from the PROWESS trial demonstrating increased treatment effect as the number of organ failures increased). The Surviving Sepsis Campaign (SSC) Guidelines for the Management of Severe Sepsis and Septic Shock recommend the use of rhAPC in patients with high risk of death due to sepsis-induced organ dysfunction [2]. Since the publication of the SSC guidelines additional large clinical trials of rhAPC have concluded: the ENHANCE (Extended Evaluation of Recombinant Human Activated Protein C), ADDRESS (Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis) and pediatric trials [3-5]. The ENHANCE trial provided supportive evidence for the favorable benefit/risk ratio observed in the PROWESS trial and suggested that earlier therapy was more effective [3]. The ENHANCE trial also revealed a somewhat greater incidence of serious hemorrhage with rhAPC than was evident in the PROWESS trial. The results of the ADDRESS trial, designed with the purpose of prospectively studying the effect of rhAPC in patients with severe sepsis at low risk of death, supported the FDA labeling that rhAPC was not of utility in such patients [4]. However, a post hoc subset analysis of patients who were admitted to a trial designed to target a low risk of death but who also had an APACHE II ≥25 failed to show benefit in this group. The pediatric trial failed to show efficacy [5].

The FDA labeling recommends use in patients with sepsis-induced organ dysfunction and at high risk of death but only goes as far as identifying patients with APACHE II ≥25 as an example of such a group. Patients at high risk of death from severe sepsis would indeed seem the appropriate target group for rhAPC. But how are these patients identified? The SSC recommendation lists four groups of patients that satisfy high risk of death: acute respiratory distress syndrome, septic shock, multiple organ failure and APACHE II ≥25.

So which adult patients should be targeted for rhAPC therapy? The key seems to be in the clinical assessment of risk of death. PROWESS enrolled patients with single and multiple organ failure, APACHE II ≥25 and APACHE II <25, and enrolled patients who could have been classified a priori as having either high or low clinical assessment of risk of death. Unfortunately we do not know what the assessments of risk of death were because clinicians treating the patient were not required to make that assessment and it was not part of the data collection. The FDA then recommended the

ADDRESS = Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ENHANCE = Extended Evaluation of Recombinant Human Activated Protein C; PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis; rhAPC = recombinant activated protein C; SSC = Surviving Sepsis Campaign.

use of rhAPC in patients at high risk of death and required a repeat trial in patients at low risk of death. The specified intent of the ADDRESS trial was to enroll patients at low risk of death, which would typically be those with single organ failure and lower APACHE II, whereas the PROWESS study had patients that clinicians could have clinically assessed as being at high risk of death and others at low risk of death. Perhaps if there had been an a priori assignment of clinical assessment of risk of death in the PROWESS trial, the effect of rhAPC in these patients would have been enhanced. So the key to patient selection for administration of rhAPC might be a priori assessment of risk of death. Septic shock, acute respiratory distress syndrome (ARDS) and multiple organ failure are typically those states that would make a clinician clinically assess a patient as high risk of death. Or should we garner direction by looking at subgroup analyses of the PROWESS trial as to which patient groups appeared to benefit (septic shock, APACHE II ≥ 25, multiple organ failure and thrombocytopenia). How does one balance or blend clinical assessment of high risk of death (PROWESS minus ADDRESS patient populations) against subset analyses from PROWESS. Not an easy answer here.

Is APACHE II ≥ 25 alone, regardless of risk of death assessment, a valid criterion for patient selection? This issue has been raised by the ADDRESS trial results; however, it must be remembered that this analysis in the ADDRESS trial was a post hoc subset analysis. This type of analysis is problematic. If the ADDRESS trial was the only randomized prospective trial so far performed and the only group that showed benefit in that trial was the APACHE II ≥ 25 subgroup (as a post hoc subset analysis), no one would be arguing that it should be used in that group. It is even more interesting when we recognize that the advocates of this line of thinking are now using a post hoc subset analysis from one trial to refute a post hoc subset analysis from another trial! So perhaps the APACHE II was never appropriate for patient identification from the start.

Which is more important in identifying risk of death prospectively: a clinical assessment of risk of death or APACHE II scoring? The PROWESS trial had no inclusion criteria related to clinical assessment of risk of death. In that trial there was a 44% mortality rate in placebo patients with APACHE II ≥ 25 whereas in the ADDRESS trial, which targeted the enrollment of patients with a clinical assessment of a low risk of death, the mortality was 25% in the APACHE II ≥ 25 group [4,6]. This suggests that the key is clinical assessment of death and not APACHE II score.

Finally, one additional subset analysis deserves mentioning. In the ADDRESS trial, patients with recent surgery and single organ dysfunction who received rhAPC had significantly higher 28-day mortality rates (20.7% versus 14.1%, $p = 0.03$, $n = 635$) [4]. Should this ADDRESS post hoc subset analysis also influence our prescribing of rhAPC as being different in surgery patients? If this had been the only subgroup that was different in the ADDRESS trial but the post-hoc subset analysis had shown benefit instead of harm, would we be recommending that it be used in this group? If we let this influence our practice, should it be only for post-operative patients with clinical assessment of low risk of death and single organ failure?

In my opinion the decision on administration of rhAPC should be based on a seasoned clinician's clinical assessment of high risk of death from sepsis-induced organ failure and acceptable risk of bleeding complications. Typically high risk of death will be associated with septic shock, ARDS or multiple organ failure.

Competing interests

RPD serves as a non-reimbursed member of the steering committee of the Surviving Sepsis Campaign, whose activities are partly funded by unrestricted educational grants from industry, including Eli Lilly, makers of rhAPC. In addition, he has received one honorarium from Eli Lilly over the past two years for a non-product-oriented lecture at the invitation of a regional medical society.

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