Holder and Huang *Critical Care* 2013, **17**:309
http://ccforum.com/content/17/2/309

CRITICAL CARE

JOURNAL CLUB CRITIQUE

A dream deferred: the rise and fall of recombinant activated protein C

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Expanded abstract

Citation

Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD: **Drotrecogin alfa (activated) in adult patients with septic shock.** *N Engl J Med* 2012, **366:**2055-2064.

Background

There have been conflicting reports on the efficacy of recombinant human activated protein C, or drotrecogin alfa (activated) (DrotAA), for the treatment of patients with septic shock.

Methods

Objective: To test the hypothesis that DrotAA, as compared with placebo, would reduce mortality in patients with septic shock.

Design: A randomized, double-blind, placebo-controlled, multicenter trial, conducted from March 2008 through August 2011. Patients were followed until either 90 days or death.

Setting: Patients were enrolled from 208 sights in Europe, North and South America, Australia, New Zealand, and India.

Subjects: Subjects included 1,697 patients with infection, systemic inflammation, and shock who were receiving fluids and vasopressors above a threshold dose for 4 hours.

Intervention: DrotAA (at a dose of 24 μg per kilogram of body weight per hour) or placebo for 96 hours.

Outcomes: Death from any cause 28 days after randomization.

Results

At 28 days, 223 of 846 patients (26.4%) in the DrotAA group and 202 of 834 (24.2%) in the placebo group had died (relative risk in the DrotAA group, 1.09; 95% confidence interval (CI), 0.92 to 1.28; P = 0.31). At 90 days, 287 of 842 patients (34.1%) in the DrotAA group and 269 of 822 (32.7%) in the placebo group had died (relative risk, 1.04; 95% CI, 0.90 to 1.19; P = 0.56). Among patients with severe protein C deficiency at baseline, 98 of 342 (28.7%) in the DrotAA group had died at 28 days, as compared with 102 of 331 (30.8%) in the placebo group (risk ratio, 0.93; 95% CI, 0.74 to 1.17; P = 0.54). Similarly, rates of death at 28 and 90 days were not significantly different in other predefined subgroups, including patients at increased risk for death. Serious bleeding during the treatment period occurred in 10 patients in the DrotAA group and 8 in the placebo group (P = 0.81).

Conclusions

DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock.

Commentary

Sepsis has been described as a multisystem process involving a dysregulated host response that can lead to organ dysfunction, cardiovascular collapse and death [1]. Endogenous activated protein C is believed to play a role in many of the pathways thought to be integral to the septic response, including proinflammatory, procoagulant, and apoptotic signals [2]. When the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study showed a 28-day mortality decrease of 6.1% with drotrecogin alpha activated (DrotAA) administration in patients with severe sepsis [2], the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) approved the drug for treatment of high-risk septic patients. Approval criteria were based on *post hoc* reanalysis of PROWESS by the FDA; DrotAA was efficacious only in the sickest patients with severe sepsis - those with multiorgan failure

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and Acute Physiologic and Chronic Health Evaluation (APACHE) score ≥25 [3].

PROWESS-SHOCK was a randomized, double-blind, placebo-controlled trial designed to show whether DrotAA administration improves 28-day mortality in patients with septic shock. Using an intention-to-treat analysis, they reported no decrease in 28-day or 90-day mortality in patients with septic shock who received DrotAA compared to those who received placebo. There was also no difference in 28-day mortality in subgroups based on baseline organ dysfunction, protein C deficiency severity, and time from vasopressor-to-infusion onset. There was a 2.8% increase in at least one serious event by day 28 in the DrotAA group compared to placebo, with a trend toward statistical significance (P = 0.11). All of these events were intraluminal or compartmental hemorrhage in at least one organ (Table S6 in the supplemental appendix of the study by Ranieri and colleagues).

There are many strengths built into the design of this trial. In keeping with *a priori* objectives, the PROWESS-SHOCK investigators were successful in recruiting very sick patients. End-organ hypoperfusion or dysfunction was required according to the inclusion criteria, and subjects needed to be on vasopressors that could not be weaned. The mean lactate level was 3.3 mmol/L in both placebo and treatment groups. Eighty-four percent of the patients in PROWESS-SHOCK had dysfunction of at least 2 organs, compared to 45% in the PROWESS trial [2]. The investigators were also very thorough and transparent in their study design and analysis. The overall mortality in the trial was 27%, lower than the anticipated mortality of 35% based on septic shock patients from PROWESS [4]. They were able to retain statistical power by recruiting 196 additional patients using an *a priori* mechanism to increase enrollment if overall mortality was less than 30%. The PROWESS-SHOCK investigators were very conservative with any decision to stop the study for efficacy. The decision to stop PROWESS for efficacy became controversial because it may have overestimated the treatment effect [5]. The PROWESS-SHOCK investigators required what they called 'overwhelming efficacy' - $P < 0.001$ and at least 250 deaths - for early trial termination [4].

This study has few recognizable flaws, but one could question whether study design choices or findings had an impact on the outcome of PROWESS-SHOCK. Some have argued that the study may have been underpowered to detect its primary outcome [6]. However, there was never a detectable difference in mortality during any data safety monitoring checks. In fact, the study concluded with a 2.2% higher mortality in the treatment group, though statistically insignificant. It is difficult to believe that the study would show a mortality benefit with DrotAA if more patients were enrolled. Some have suggested that the PROWESS-SHOCK investigators should have administered DrotAA earlier for better efficacy [7]. They argue that by waiting for the development of refractory shock, the investigators may have missed the ideal window for DrotAA administration. However, the development of septic shock and organ dysfunction takes time, and to date the one study of DrotAA administration to septic patients with less severe disease showed no benefit [8]. The sickest patients with refractory septic shock were the last group of septic patients, for which little data existed about potential efficacy. Given the division in the critical care community, the investigators needed to select this group for study [4].

Do we believe PROWESS or PROWESS-SHOCK? They both may have been correct. Sepsis management has improved between the times these studies were published. The implementation of sepsis bundles in many hospital settings has been associated with decreased mortality [9]. The attributable benefit DrotAA may have once had on mortality could have been lost because of improved overall sepsis care. The heterogeneous nature of the sepsis population could also be a reason for the inconsistencies between PROWESS and PROWESS-SHOCK [10]. Sepsis is not a single disease entity but a clinical syndrome that is a common endpoint among many causes of infection. There were about 10% more patients with abdominal causes of sepsis in PROWESS-SHOCK compared to PROWESS, and proportionately less with pneumonia as a cause (Table S3 in the supplementary appendix of the study) [2]. Perhaps a difference in the case mix between the two trials contributed to the difference in study results. While one meta-analysis has since evaluated DrotAA efficacy and safety and shown possible benefit, less than 10% of the patients represented were from randomized controlled trials [6].

Recommendation

This study showed a higher risk of bleeding and no mortality benefit from DrotAA in septic shock. DrotAA should no longer be recommended in sepsis guidelines as a standard of care.

Abbreviations

DrotAA, drotrecogin alpha activated; FDA, Food and Drug Administration; PROWESS, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.

Competing interests

The authors declare that they have no competing interests.

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Published: 12 March 2013

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doi:10.1186/cc12533
Cite this article as: Holder AL, Huang DT: **A dream deferred: the rise and fall of recombinant activated protein C.** *Critical Care* 2013, **17:**309.