



Evidence-Based Medicine Journal Club

EBM Journal Club Section Editor: Eric B. Milbrandt, MD, MPH

Journal club critique

Drotrecogin alfa (activated) should not be used in patients with severe sepsis and low risk for death

Sanjay Gupta,¹ Eric B. Milbrandt,² and Lakshmipathi Chelluri³

¹ Clinical Fellow, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

² Assistant Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

³ Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Published online: 3 November

This article is online at <http://ccforum.com/content/10/6/316>

© 2006 BioMed Central Ltd

Critical Care 2006, 10: 316 (DOI 10.1186/cc5071)

Expanded Abstract

Citation

Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005, 353:1332-1341 [1].

Background

In November 2001, the Food and Drug Administration (FDA) approved drotrecogin alfa (activated) (DrotAA) for adults who had severe sepsis and a high risk of death. The FDA required a study to evaluate the efficacy of DrotAA for adults who had severe sepsis and a low risk of death.

Methods

Design and setting: Double-blind, randomized, placebo-controlled trial conducted in 516 centers in 34 countries.

Subjects: Adult patients with severe sepsis and a low risk of death (defined by an Acute Physiology and Chronic Health Evaluation [APACHE II] score <25 or single-organ failure).

Intervention: Subjects were randomized to receive an intravenous infusion of placebo or DrotAA (24 µg per kilogram of body weight per hour) for 96 hours.

Measurements: The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of the infusion. In-hospital mortality within 90 days after the start of the infusion was measured, and safety information was collected.

Results: Enrollment in the trial was terminated early because of a low likelihood of meeting the prospectively

defined objective of demonstrating a significant reduction in the 28-day mortality rate with the use of DrotAA. The study enrolled 2640 patients and collected data on 2613 (1297 in the placebo group and 1316 in the DrotAA group) at the 28-day follow-up. There were no statistically significant differences between the placebo group and the DrotAA group in 28-day mortality (17.0 percent in the placebo group vs. 18.5 percent in the DrotAA group; $P=0.34$; relative risk, 1.08; 95 percent confidence interval, 0.92 to 1.28) or in in-hospital mortality (20.5 percent vs. 20.6 percent; $P=0.98$; relative risk, 1.00; 95 percent confidence interval, 0.86 to 1.16). The rate of serious bleeding was greater in the DrotAA group than in the placebo group during both the infusion (2.4 percent vs. 1.2 percent, $P=0.02$) and the 28-day study period (3.9 percent vs. 2.2 percent, $P=0.01$).

Conclusion

The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25.

Commentary

Severe sepsis is a syndrome defined as acute organ dysfunction secondary to infection and characterized by dysregulation of inflammation, coagulation, and other acute phase responses. Hospital mortality for patients with severe sepsis is approximately 30%, rising to as high as 50% in the presence of septic shock. Activated protein C, or drotrecogin alfa (activated) (DrotAA), inhibits coagulation factors Va and VIIIa, reducing coagulopathy in patients with severe sepsis [2]. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, DrotAA resulted in a 6.1% absolute

reduction in 28-day mortality in adults with severe sepsis as compared to placebo. The greatest benefit was seen in patients at high risk of death. Based on these results, in 2001 the United States and European drug regulatory agencies approved DrotAA for use in adult patients with severe sepsis and high risk of death, as defined by an Acute Physiology and Chronic Health Evaluation (APACHE II) score ≥ 25 or multiorgan failure. As a condition for approval, the manufacturer, Eli Lilly and Company, agreed to complete a number of phase IV studies evaluating the use of DrotAA in lower-risk patients with severe sepsis, in children with severe sepsis, and in patients receiving low-dose heparin [3].

In the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) study [1], Abraham and colleagues assessed the role of DrotAA in patients with severe sepsis and low risk of death. Subjects had a known or suspected infection and an APACHE II score of less than 25 or single organ system failure. The protocol also permitted the enrollment of patients who were thought by the investigator to have a low risk of death despite a higher APACHE II score or multiorgan failure. Initially designed to include 11,444 patients, the trial was stopped early because of futility after 2,640 subjects were enrolled.

Data from 2,613 patients were available for analysis. Control and experimental groups were evenly matched in terms of their baseline characteristics, disease severity, type of organ dysfunction, and source of infection. There were no statistically significant differences in 28-day or hospital mortality between groups, but rates of serious bleeding were greater in the DrotAA group both during the infusion (2.4% vs. 1.2%, $P=0.02$) and in the 28-day study period (3.9% vs. 2.2%, $P=0.01$) and were similar to rates seen in the PROWESS trial.

There has been considerable discussion in the literature about the subgroup of subjects at high-risk of death, who were included in ADDRESS at the discretion of the investigators [4-6]. Among the 324 (12.3%) subjects with APACHE II scores of 25 or more, there was no observed benefit for DrotAA use. In fact, 28-day mortality was higher in DrotAA-treated subjects (29.5% vs. 24.7%), although this difference was not statistically significant. While this finding would seem to contradict the results of PROWESS, there were important imbalances in baseline characteristics between the DrotAA and control groups in the high-risk subset of ADDRESS subjects. Specifically, DrotAA treated subjects were older and more likely to have multiorgan dysfunction and respiratory failure, making any conclusions about DrotAA's effectiveness in high-risk patients limited at best.

In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock, under the auspices of the Surviving Sepsis Campaign [7]. Though DrotAA is an important drug with well-documented

beneficial effects in patients with severe sepsis and high risk of death, it is just one of the recommended components for the management of septic patients (**table**). As with many disease states, time is of the essence in severe sepsis. Early goal-directed therapy has been shown to improve outcome in severe sepsis [8]. Furthermore, two studies have shown that time to treatment with DrotAA has an influence on mortality [9,10], with the maximum beneficial effect being observed if treatment is started within 24 hours of the onset of sepsis-induced organ dysfunction. Recognizing this, some hospitals are establishing teams of emergency department and intensive care unit specialists to facilitate rapid sepsis identification, assessment, and treatment.

Table: Select components of the Surviving Sepsis Campaign [7]

- Early goal-directed resuscitation
- Appropriate diagnostic studies prior to antibiotics
- Early broad-spectrum antibiotics
- Narrowing antibiotic therapy based on microbiology and clinical data
- Source control
- Stress-dose steroids for septic shock
- DrotAA for patients with severe sepsis and high risk for death
- Target hemoglobin values of 7–9 g/dL in absence of coronary artery disease or acute hemorrhage
- Lung protective ventilation for ALI/ARDS
- Semirecumbent bed position
- Protocols for weaning and sedation/analgesia
- Avoidance of neuromuscular blockers
- Maintenance of blood glucose <150 mg/dL
- Deep vein thrombosis/stress ulcer prophylaxis

ALI/ARDS = Acute lung injury/acute respiratory distress syndrome

Recommendation

We concur with the ADDRESS authors. DrotAA should not be used in patients with severe sepsis and low risk for death.

Competing interests

The authors declare no competing interests.

References

1. Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL: **Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death.** *N Engl J Med* 2005, **353**:1332-1341.
2. Dhainaut JF, Yan SB, Margolis BD, Lorente JA, Russell JA, Freebairn RC, Spapen HD, Riess H, Basson B, Johnson G, III, Kinasevitz GT: **Drotrecogin alfa (activated) (recombinant human activated protein C)**

- reduces host coagulopathy response in patients with severe sepsis.** *Thromb Haemost* 2003, **90**:642-653.
3. Siegel JP: **Assessing the use of activated protein C in the treatment of severe sepsis.** *N Engl J Med* 2002, **347**:1030-1034.
 4. Baillie JK, Murray G: **Drotrecogin alfa (activated) in severe sepsis.** *N Engl J Med* 2006, **354**:94-96.
 5. Friedrich JO: **Drotrecogin alfa (activated) in severe sepsis.** *N Engl J Med* 2006, **354**:94-96.
 6. LaRosa SP: **Drotrecogin alfa (activated) in severe sepsis.** *N Engl J Med* 2006, **354**:94-96.
 7. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Intensive Care Med* 2004, **30**:536-555.
 8. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**:1368-1377.
 9. Vincent JL, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J: **Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment.** *Crit Care Med* 2005, **33**:2266-2277.
 10. Wheeler A, Steinbrug J, Linde-Zwirble W, Shwed J, Zeckel M: **Results of MER CURY, a retrospective multicenter observational study [abstract]. Presented at 33rd Critical Care Congress, Orlando, 2004.** *Crit Care Med* 2003, **31**:A120.