Drotrecogin-α (activated) did not reduce death and increased bleeding in patients with severe sepsis and low risk for death

Abraham E, Laterre PF, Garg R, et al. **Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death.** N Engl J Med. 2005;353:1332-41.

Clinical impact ratings: Hospitalists ★★★★★★☆ Infectious Disease ★★★★★★☆ Critical Care ★★★★★★☆

QUESTION

Is drotrecogin-α (activated) (DrotAA) effective and safe in patients with severe sepsis and low risk for death?

METHODS

Design: Randomized placebo-controlled trial (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis [ADDRESS]).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (investigators and patients).*

Follow-up period: Hospital discharge or 90 days.

Setting: 516 centers in 34 countries.

Patients: 2640 patients (mean age 59 y, 57% men) with severe sepsis (presence of a suspected or known infection and sepsis-induced dysfunction of ≥ 1 organ) and low risk for death (defined in some centers as Acute Physiology and Chronic Health Evaluation [APACHE] II score < 25, in others as lack of multiorgan failure, or by the physician judging the patient to be at low risk regardless of APACHE score or number of organ failures). Exclusion criteria were indications or contraindications to DrotAA (slightly different in different countries, usually either multiorgan dysfunction or APACHE score ≥ 25), increased risk for bleeding, moribund state or expected survival < 28 days, or no commitment to aggressive management.

Intervention: 96-hour intravenous infusion of DrotAA, 24 μg/kg of body weight per hour (n = 1333), or placebo (n = 1307). Patients had to begin treatment within 48 hours of documentation of the first organ dysfunction.

Outcomes: All-cause mortality at 28 days. Secondary outcomes were in-hospital mortality within 90 days and adverse events, including bleeding.

Patient follow-up: 2613 patients (99%) (intention-to-treat analysis). The study was terminated early for futility after an unplanned interim analysis was done at the request of the external data-monitoring committee.

MAIN RESULTS

DrotAA and placebo groups did not differ for mortality at 28 days or for in-hospital mortality within 90 days (Table). Mortality rates between groups were not affected by prespecified subgroup analyses (according to APACHE II score < 20, 20 to 24, or > 24; single or multiple organ dysfunction; recent surgery; first patient enrolled; and use of heparin at baseline). More patients had serious bleeding events in the DrotAA group than in the placebo group (Table).

CONCLUSION

In patients with severe sepsis and a low risk for death, drotrecogin-α (activated) did not reduce mortality and increased serious bleeding.

Source of funding: Eli Lilly.

For correspondence: Dr. E. Abraham, University of Colorado Health Sciences Center, Denver, CO, USA. E-mail edward.abraham@UCHSC.edu.

*See Glossary.

Drotrecogin-α (activated) (DrotAA) vs placebo for severe sepsis with low risk for death†

Outcomes	Follow-up	DrotAA	Placebo	RRI (95% CI)	NNH (CI)
All-cause mortality	28 d	18.5%	17%	8% (–8 to 28)	Not significant
In-hospital mortality	≤ 90 d	20.6%	20.5%	0% (–16 to 14)	Not significant
Serious bleeding events	During infusion (≤ 6 d)	2.4%	1.2%	103% (11 to 271)	84 (44 to 521)
	28 d	3.9%	2.2%	79% (14 to 181)	59 (33 to 249)

†Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

Approval of DrotAA by the U.S. Food and Drug Administration required a randomized trial to establish the safety and effectiveness of the drug in patients with severe sepsis and low risk for death. This was considered important because the drug was approved only in patients at high risk for death. The sample size calculation for the ADDRESS study indicated the need to enroll 11 444 patients to show a difference of 4% in mortality between groups (16% in DrotAA and 20% in placebo). The study was stopped because of futility after 2640 patients were randomized.

4 salient findings of this study are noteworthy: First, the drug does not reduce 28-day mortality or hospital mortality in patients at low risk for death. Second, because of the design of the study and because indications for the drug differ (unfortunately) between Europe and the United States, some patients who could be considered high risk were also treated in this study (321 patients [12.3% of all included] with an APACHE II score > 24, and 862 [33%] with ≥ 2 organ dysfunctions). DrotAA and placebo group patients did not differ for 28-day mortality in those subgroups (high APACHE II score 29.5% vs 24.7%, respectively, and ≥ 2 organ failures 20.7% vs 21.9%, respectively). Until a confirmatory study of the PROWESS results (1) is available, it is difficult to interpret these findings. Third, there was no excess mortality at hospital discharge in 997 patients with recent surgery. Fourth, serious bleeding events were more frequent in patients in the DrotAA group than in the placebo group, but this difference was not caused by bleeding involving the central nervous system. Bleeding requiring transfusion was more common in patients in the DrotAA group (6.8% vs 3.4%, P = 0.001).

The ADDRESS study confirmed that DrotAA should not be used in patients with severe sepsis and low risk for death. Mortality is not increased in this group of patients, but risk for bleeding is increased. Furthermore, although the power of this study to detect a beneficial effect in subgroups was limited, it is interesting that there was no noticeable mortality decrease in actively treated, higher-risk patients, corresponding to the North American and European indications for the compound.

Jean Carlet, MD
Fondation Hôpital St Joseph
Paris, France

Reference

1. **Bernard GR, Vincent JL, Laterre PF, et al.** Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699-709.