THERAPEUTICS

Recombinant human activated protein C reduced all-cause mortality in patients with severe sepsis

Bernard GR, Vincent J-L, Laterre P-F, et al., for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. **Efficacy and safety of recombinant human activated protein C for severe sepsis.** N Engl J Med. 2001 Mar 8;344:699-709.

QUESTION

In patients with severe sepsis (known or suspected infection) plus ≥ 3 signs of systemic inflammation and sepsis-induced dysfunction of ≥ 1 organ or system for < 24 hours within 24 hours, does drotrecogin alfa (recombinant human activated protein C [APC]) reduce all-cause mortality?

DESIGN

Randomized (allocation concealed*), blinded (patients, clinicians, outcome assessors, and sponsors),* placebo-controlled trial with 28-day follow-up and planned interim analyses.

SETTING

164 centers in 11 countries.

PATIENTS

1728 patients with severe sepsis were allocated, and 1690 (mean age 61 y, 57% men, 82% white) received study drugs and were analyzed. Exclusion criteria were pregnancy, breast-feeding, platelet count < 30 000/mm^3, age < 18 years, weight > 135 kg, increased risk for bleeding, hypercoagulability, short-term expected survival, end-stage HIV infection (CD4+ cell count ≤ 50), history of transplantation, chronic renal failure, liver conditions, pancreatitis, or need for many medications. Follow-up was 98%.

INTERVENTION

850 patients received APC, 24 µg/kg of body weight per hour intravenously for 96 hours, and 840 received placebo. The infusion was stopped 1 hour before any percutaneous procedure or major surgery and started 1 or 12 hours later, respectively. Cointerventions were at the discretion of intensive care unit (ICU) staff.

MAIN OUTCOME MEASURE

All-cause mortality at 28 days.

MAIN RESULTS

The study was stopped early after the second interim analysis because of differences in mortality. Patients in the APC group had lower mortality than did patients in the placebo group (P = 0.005) (Table). The groups did not differ for proportion of patients who had ≥ 1 serious adverse event, new infections, or thrombotic events. Patients in the APC group showed a trend toward a higher rate of serious bleeding during drug infusion (3.5% vs 1.0%, P = 0.06).

CONCLUSION

Drotrecogin alfa (recombinant human activated protein C) reduced all-cause mortality in patients with severe sepsis without increasing the rate of adverse effects.

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*See Glossary.

Drotrecogin alfa (activated protein C [APC]) vs placebo for severe sepsis†

Outcome at 28 d	APC	Placebo	RRR (95% CI)	NNT (CI)
All-cause mortality	25%	31%	19% (7 to 31)	16 (10 to 54)

†Abbreviations defined in Glossary; NNT and its CI calculated from data in article.

COMMENTARY

The international multicenter randomized controlled trial of APC by Bernard and colleagues unequivocally showed a favorable mortality benefit among patients with severe sepsis. Its methods are strong, and the number needed to treat of 16 to save 1 additional life at 28 days is impressive.

The results are generalizable to patients with low or normal protein C levels, patients with gram-positive and gram-negative infection, and patients with or without bacteremia. Given the evolving definitions of sepsis, sepsis syndrome, and septic shock over the past decade, clinicians should familiarize themselves with the inclusion criteria used in this trial to encourage the timely administration of this drug to appropriate patients.

Trends toward increased bleeding in the APC group should not deter use of this effective agent in most patients. Notably, subcutaneous heparin for venous thromboembolism prevention was admissible. However, the known anticoagulant properties of APC mandate individualized treatment decisions that weigh the risks and benefits in some patient subgroups. Of potential concern are patients concomitantly requiring several potent, synergistically effective, antithrombotic drugs for acute coronary events (e.g., thrombolytics, aspirin, clopidogrel, and low-molecular-weight heparin). Further analyses from this trial and additional studies are needed to improve our understanding of these potential interactions.

A cost-effectiveness analysis of APC is anxiously awaited. Diversion of wasteful expenditures away from unnecessary, unwanted, or ineffective ICU interventions will help to ensure that the most seriously ill hospitalized patients with severe sepsis will receive this exciting, but expensive, new therapy.

Meanwhile, sepsis remains one of the commonest problems in the ICU. This report is the first pivotal, high-quality randomized trial of treatment for the sepsis syndrome with such a clear and compelling survival benefit.

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