Neuroanesthesia and Intensive Care

Best evidence in anesthetic practice

Prevention: recombinant human activated protein C reduces mortality in severe sepsis

Article appraised

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; 344: 699–709.

Structured abstract

Question: Does recombinant human activated protein C (drotrecogin alfa activated, DAA) reduce the 28-day all-cause mortality rate in patients with severe sepsis?

Design: Multicenter, randomized, blinded (patients, investigators, sponsor), placebo-controlled trial.

Setting: One hundred sixty-four hospitals in 11 countries.

Patients: One thousand seven hundred twenty-eight adult patients with known or suspected infection with three or more signs of systemic inflammation within 24 hr and sepsis-induced organ or system dysfunction of 24 hr. Exclusion criteria were pregnancy, breastfeeding, age <18 yr, weight >135 kg, platelet count <30000 mm³, medications or conditions that increase the risk of bleeding, hypercoagulable conditions, transplantation (bone marrow, lung, liver, pancreas, or small bowel), chronic renal failure requiring dialysis, chronic liver disease, acute pancreatitis without infection, moribund state with imminent death, survival expected to be <28 days, refusal of aggressive treatment or advanced directives to withhold life-sustaining treatment, or participation in another study within 30 days.

Intervention: Eight hundred seventy-one patients were allocated to DAA 24 µg·kg⁻¹·hr⁻¹ infusion for 96 hr; 857 patients were allocated to 0.9% saline ± 0.1% albumin placebo infusion for 96 hr. Thirty-eight patients (21 in DAA group; 17 in placebo group) did not receive the intervention. Infusions were stopped one

hour before invasive procedures or major surgery and were resumed one hour and 12 hr later respectively.

Main outcomes: Twenty-eight-day mortality from any cause was the primary outcome. Plasma D-dimer and serum interleukin-6 (IL-6) levels and frequency of serious adverse events were secondary outcomes.

Main results: Analysis was intention-to-treat. Clinical characteristics, surgical history, and indicators of disease severity were similar. Enrollment was terminated after the second interim data analysis because differences in mortality rates exceeded *a priori* levels. The 28-day all-cause mortality rate was lower in the DAA group (216 of 871) than in the placebo group (268 of 857; *P*=0.003) with a relative risk of 0.79 (95% CI 0.68–0.92), an absolute risk reduction of 6.5% (95% CI 2.2–10.7%), and a number-needed-to-treat of 16. Plasma D-dimer levels were lower in the DAA group on the first seven days after start of infusion; serum IL-6 levels were higher in the DAA group on days one, four, five, six, and seven after start of infusion. The difference in rate of serious adverse events was not statistically significant between the two groups.

Conclusion: Recombinant human activated protein C decreases 28-day all-cause mortality in patients with severe sepsis.

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Correspondence: Dr. Gordon R. Bernard, Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, T-1208 Medical Center North, Vanderbilt University School of Medicine, Nashville, TN 37233. Email: gordon.bernard@mcmail.vanderbilt.edu

Commentary by R. Butler

Sepsis, particularly sepsis with organ dysfunction or severe sepsis, remains a significant critical care problem. Despite advances in critical care, the mortality rate from this syndrome remains high (30 to 50%).¹

The inflammatory cascade initiated as a host response to infection can lead to organ damage and death. Earlier investigations of therapies directed at inflammatory mediators have had disappointing results. More recently, investigations have focused on the pro-coagulant cascade, which is closely related to the inflammatory cascade. Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation associated with severe sepsis.

In a large, well-designed, randomized placebo-controlled clinical trial Bernard *et al.* tested the efficacy of activated protein C (drotrecogin alfa activated, DAA) infusion in severe sepsis.² Eligible patients required evidence of sepsis (using four, rather than two, of five criteria proposed by Bone *et al.*),³ evidence of organ dysfunction, and enrollment within 24 hr of meeting the criteria. Exclusion criteria included age less than 18 yr and criteria related to anticoagulant use or increased bleeding risk. Randomization was stratified by centre, well concealed, and conducted at a central location. Patients, study personnel, and sponsors were blinded to treatment assignment. Co-interventions, including antibiotic use and mechanical ventilation strategies, were not standardized.

Patients were stratified by age, severity of illness, and protein C levels for the planned primary analysis. The primary outcome was survival at 28 days; the primary analysis was all patients who were randomized and received any of the study infusion. Thirty-eight patients (17, placebo; 21, DAA) were randomized but never received the study infusion. These patients' outcomes were all documented. Inclusion of these patients in a secondary analysis did not change the study result.

Randomization produced good baseline balance between the two groups. The enrolled patients were severely ill with sepsis as over 70% of patients had dysfunction of two or more organs and a similar percentage were ventilated mechanically. The results from both the stratified and unstratified analyses showed an absolute reduction in mortality of 6.5%. There was a higher rate of bleeding complications in the DAA group (3.5% *vs* 2%; $P=0.06$). Although not statistically significant, the study was not large enough to rule out an increased risk of bleeding of this magnitude. Nevertheless the increase in risk was small and transfusion requirements were similar in both groups.

The results of this trial demonstrate a significant survival benefit with DAA in severe sepsis with a small risk of increased bleeding. That the study protocol did not standardize the management of critical care further strengthens the generalizability of the results;

however, enrolled patients were carefully selected using strict criteria for the definition of sepsis with evidence of organ dysfunction. The study deliberately excluded those patients who might be at higher risk for bleeding. The risk-benefit ratio may not be as favourable if DAA is applied to patients who are less sick or at higher risk for bleeding. Furthermore, children were not included in this study and caution should be exercised when extrapolating these results to children with sepsis. There is need for further study of this drug in these population groups.

Ron Butler MD MSC FRCPC

London, Ontario

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Commentary by B. Laufer

Over two decades ago, membrane oxygenation was achieved in animals without anticoagulants, suggesting that endogenous anticoagulants could be generated in response to foreign substances. Subsequent experiments showed that these animals fared well when exposed to endotoxin.¹ There is now strong evidence that activation of endogenous protein C is impaired in sepsis. Faust *et al.*² recently demonstrated a marked reduction in the expression of thrombomodulin, an endothelial protein involved in the activation of protein C, and endothelial protein C receptor on the endothelium of both thrombosed and non-thrombosed dermal vessels in children with early meningococcal disease. Bacterial endotoxins and other inflammatory mediators released into the bloodstream set off a cascade of events that result in inflammation, endothelial damage, coagulation, and thrombosis. Activated protein C (APC) also seems to have a role in cell signalling, modulating gene expression from a key cytokine-induced inflammatory pathway as well as apoptosis pathways. These results define new mecha-

nisms for APC and link coagulation to inflammation and cell death.³

The high mortality rate (20% to 60%) accompanying severe sepsis and septic shock has led to multiple attempts to manipulate the link between clinical manifestations of sepsis and the host inflammatory response. Over 60 trials of various therapies have been performed with generally disappointing results. The accumulation of data indicating that APC could anticoagulate as well as enhance fibrinolysis and counter inflammation has eventually led to the trial reported by Bernard *et al.* The study was stopped when a second interim analysis showed a relative risk reduction in 28-day mortality of 19.4% in favour of APC after 1,728 patients were randomized to either APC or placebo.

This large randomized double-blind international study was well conducted overall, although questions have arisen concerning baseline characteristics, timing of antibiotic therapy, the lack of standardized care and the lack of other outcome measures [such as intensive care unit (ICU) and hospital length of stays and quality of life issues]. Concerning specific issues of therapy, one wonders how many patients in each group received other anticoagulants or corticosteroids which, at moderate doses, seem to hold promise in septic shock. There was also evidence of increased risk of serious bleeding in the treatment group, although the absolute difference was small (1.5%). The number-needed-to-treat to prevent one death by 28 days was 16, an impressive result.

The potential impact of this study, in view of our past disappointments, is important, but only a fraction of patients admitted to the ICU will meet all inclusion and exclusion criteria used by Bernard *et al.* The overall impact of APC will likely be limited. The substantial cost of this new treatment will warrant strict adherence to this study's criteria before initiating therapy. The systemic response to infection may be variable as suggested by Munford and Pugin⁴ and future investigations should include a look at which subgroups, if any, will gain more benefit from APC. The role of APC may have to be reconsidered should steroids or other future therapies prove to be beneficial. Hopefully, a current worldwide open-label study will yield more information on financial implications and safety of this new agent.

Brian Laufer MD FRCPC
Montréal, Québec

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