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Recombinant human activated protein C for treatment of severe sepsis: Therapeutic and economic considerations

BY ROBERT FOWLER, MD, MS(EP1)

Sepsis is characterized by a systemic inflammatory and procoagulant response to infection.^{1,2} When sepsis is accompanied by dysfunction of one or more vital organs, the condition is called *severe sepsis*.² Sepsis afflicts up to 25% of all intensive care unit (ICU) patients and accounts for approximately 750,000 cases each year in the United States alone.^{3,4} The crude mortality rate of sepsis is estimated to be between 30% and 50% and corresponds to at least 225,000 deaths in North America each year.³⁻⁷

The standard treatment for sepsis consists of broad-spectrum antimicrobial therapy and aggressive supportive care. This care is expensive as it often occurs in an ICU and frequently involves organ supportive measures such as mechanical ventilation, invasive cardiovascular support, or hemodialysis. Notwithstanding the effectiveness of antibiotics in killing bacteria, the inflammatory process and endovascular injury that frequently accompanies sepsis can result in significant multi-organ dysfunction, prolonged morbidity, and substantial mortality. Recombinant human activated protein C (rhAPC, drotrecogin alfa) is a new addition to the armamentarium of medications for the treatment of severe sepsis. This issue of *Critical Care Rounds* focuses on both the therapeutic and economic aspects of the introduction of rhAPC into Canadian critical care practice.

Background

Protein C is an endogenous protein that inhibits vascular thrombosis and inflammation, which complicates severe sepsis.^{1,8} A recent, randomized, controlled clinical trial demonstrated that rhAPC was associated with an absolute risk reduction in death of 6.1% in patients with severe sepsis.¹ Thus, 16 patients with severe sepsis would need to be treated with rhAPC in order to prevent one death. A number of concerns have arisen, however, about rhAPC as treatment for sepsis. These include its cost, an increased risk of serious bleeding events, and the observation that only patients with very severe sepsis – as determined by an acute physiology and chronic health evaluation II (APACHE II) score ≥ 25 – seem to benefit.^{1,9,10}

The US Food and Drug Administration (FDA) approved rhAPC for use in November 2001, and the Canadian Therapeutics Product Directorate granted its approval on January 31, 2003. The manufacturer's retail price is approximately \$67/mg (\$41 US/mg) and the cost of a typical 96-hour course of therapy is \$10,700 (\$6,500 US).⁹ The expense of this new therapy and its real, but limited effectiveness, have led to an examination of its cost-effectiveness by numerous authors in multiple care settings.¹¹⁻¹⁴



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Table 1: PROWESS mortality according to APACHE II score quartile

APACHE II Score (Range)	rhAPC mortality (%)	Placebo mortality (%)	RR of death (95% C.I.)
1 st (3-19)	33/218 (15)	26/215 (12)	1.25 (0.78-2.02)
2 nd (20-24)	49/218 (22)	57/222 (26)	0.88 (0.63-1.22)
3 rd (25-29)	48/204 (24)	58/162 (36)	0.66 (0.48-0.91)
4 th (30-53)	80/210 (38)	118/241 (49)	0.78 (0.63-0.96)

RR = relative risk
C.I. = confidence interval

Despite the apparent cost-effectiveness for specific patient populations, there is still the challenge of how to introduce and fund this therapy in our individual institutions.

Efficacy and safety of rhAPC

Patients with severe sepsis are known to have reduced levels of endogenous protein C and this deficiency is associated with an increased risk of death.^{1,15} Activated protein C is converted from its inactive precursor by a thrombomodulin-thrombin complex and this conversion may be impaired during severe sepsis.¹⁶ Preclinical and clinical trials have suggested that administration of activated protein C may improve outcomes in severe sepsis.^{17,18}

The PROWESS investigators examined the safety and efficacy of rhAPC in a large, multicentre, randomized, placebo-controlled trial.¹ They allocated 1690 patients with severe sepsis (known or suspected infection plus ≥ 3 signs of systemic inflammation and sepsis-induced dysfunction of ≥ 1 organ or system) from 164 centres to receive placebo or rhAPC 24 $\mu\text{g}/\text{kg}$ body weight for 96 hours. The exclusion criteria are important as they may affect the generalizability of the study's findings to our individual patient populations. They included: pregnancy, breast-feeding, age < 18 years, weight > 135 kg, end-stage HIV infection, organ transplantation, chronic renal failure requiring dialysis, liver failure, pancreatitis, low short-term life-expectancy, hypercoagulability, platelet count $< 30 \times 10^9/\text{L}$, or an increased risk for bleeding (including recent treatment with therapeutic doses of heparin, warfarin, high-dose acetylsalicylic acid, glycoprotein IIb/IIIa antagonists or thrombolytic agents). The mean age of patients was 61 years (nearly 80% were < 75 years) and the mean APACHE II score was 25. Most patients had either a pulmonary or abdominal source of infection, shock

Table 2: Practical definition of severe sepsis for treatment with rhAPC

- Suspected or proven infection
- Evidence of systemic inflammation by ≥ 3 SIRS criteria
 - Temperature $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$
 - Heart rate > 90 beats per minute
 - Respiratory rate > 20 or $\text{PaCO}_2 < 32$
 - WBC $> 12,000/\text{mm}^3$ or $< 4000/\text{mm}^3$ or $> 10\%$ immature neutrophils
- Sepsis-induced acute organ dysfunction or dysfunction in ≥ 2 organs
 - Cardiovascular, renal, respiratory, hematological, unexplained metabolic acidosis

SIRS = systemic inflammatory response syndrome
WBC = white blood cell count

requiring vasopressors, a need for mechanical ventilation, and no recent surgery. Treatment with rhAPC resulted in a 6.1% absolute reduction in mortality (30.8% versus 24.7%, $p = 0.005$). It was also discovered that treatment with rhAPC was associated with an increased risk of serious bleeding (3.5% versus 2.0%, $p = 0.06$). In a *post hoc* analysis performed by the US FDA, patients with a higher severity of illness as determined by APACHE II scores were shown to derive the most benefit from rhAPC, while patients with less severe forms of sepsis did not (Table 1). Stratification of patients by number of dysfunctional organs revealed a similar trend. The FDA subsequently recommended treatment with rhAPC only for those patients with severe sepsis who have a high risk of death (eg, as determined by an APACHE II score of ≥ 25). Similarly, the European Agency for the Evaluation of Medicinal Products has recommended treatment only for those with multiple organ dysfunction.¹⁹

Health Canada approved rhAPC for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (eg, as determined by APACHE II, or multiple acute organ dysfunctions), when added to current best practice. Efficacy has not been established in adult patients with severe sepsis and a lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

Published guidelines for the use of rhAPC in Canada

Preliminary Canadian guidelines for the use of rhAPC have been developed that emphasize the importance of appropriate patient selection.²⁰ Based upon the PROWESS entry criteria, patients should have:

Table 3: Suggested exclusion criteria due to possible increased risk of bleeding

- Platelet count < 30 x 10⁹/L
- Recent (≤ 7 days) administration of > 650 mg/day ASA or other platelet inhibitors
- Oral anticoagulant therapy within 7 days or INR > 3.0
- Concurrent administration of therapeutic heparin (eg, >15 units/kg/hour, or >15,000 units during dialysis for acute renal failure)
- Thrombolytic therapy within 3 days
- Active postoperative bleeding
- Planned or anticipated surgery under general or spinal anesthesia
- Recent (< 6 weeks) gastrointestinal bleeding, unless definitive intervention performed
- Intracranial surgery, severe head trauma, or stroke within 3 months
- Intracranial arteriovenous malformation, aneurysm, or mass lesion
- Known bleeding diathesis, with the potential exclusion of acute coagulopathy due to sepsis
- Other conditions in which bleeding constitutes a significant hazard or if bleeding would be difficult to manage because of location

ASA = acetylsalicylic acid

INR = international normalized ratio

- evidence of infection (elevated white blood cell count in a normally sterile body fluid, a perforated viscus, purulent sputum and radiographic evidence of pneumonia, or a syndrome associated with a high risk of infection)

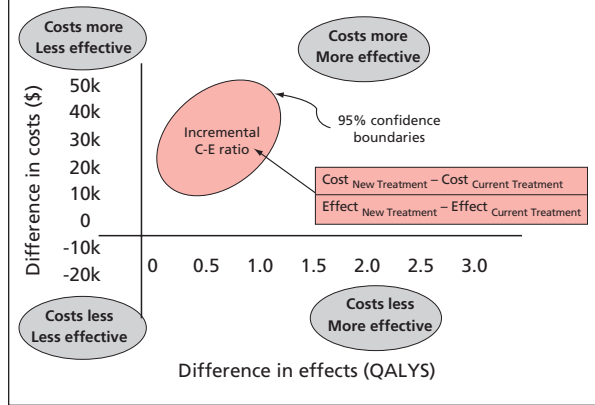
- evidence of systemic inflammatory response (≥ 3 of core temperature > 38°C or < 36°C; tachycardia > 90 beats per minute; tachypnea > 20 breaths per minute or PaCO₂ < 32 mmHg; white blood cell count > 12,000/mm³ or < 4000/mm³ or > 10% immature neutrophils);

- sepsis-induced dysfunction of ≥ 2 organs or systems (Table 2).

The authors of the guidelines recommend flexibility regarding the PROWESS treatment window of 48 hours from onset of initial organ dysfunction if clinicians feel such patients may benefit from treatment with rhAPC.

Precautions must be taken to minimize the risk of bleeding if treating with rhAPC. Patients with a significant risk of bleeding or at particular risk if bleeding occurs generally should not be treated with rhAPC (Table 3). Also, when invasive procedures are planned, rhAPC should be discontinued for an appropriate duration before and after the procedure. It is recommended that rhAPC administration should stop 1 hour before, and restart immediately following, central venous catheterization, arterial catheterization, tracheostomy,

Figure 1: Framework of a cost-effectiveness analysis



or endotracheal tube change. It is recommended that rhAPC administration should be held for 2 hours before and 1 hour after chest tube insertion, thoracentesis, lumbar puncture, tracheostomy, or sinus puncture. The infusion of rhAPC should be stopped for 2 hours prior to epidural catheter insertion or major surgery and not restarted until 12 hours after catheter removal or completion of the surgery.²⁰

Clinicians should consider treatment with rhAPC in patient groups excluded from the PROWESS trial on a case-by-case basis, weighing the potential benefits and risks associated with treatment (eg, patients with organ transplantation or chronic liver disease). Currently, there is no strong rationale for excluding patients for treatment with rhAPC based upon body weight. The study of pediatric administration of rhAPC has been completed and preliminary results indicate that there may be benefit in specific subgroups of children < 18 years of age (eg, those with sepsis due to meningococemia).²¹

Concerns and controversies: Cost-effectiveness

When determining the cost-effectiveness of a new intervention, all costs and effects associated with the new treatment must be compared to all those costs and effects associated with the current best therapy. From this, we can derive an incremental cost-effectiveness ratio (Figure 1). Cost-effectiveness results are often presented in terms of costs (\$) per quality-adjusted life year (QALY) gained, which takes into account not only the duration of survival after a treatment, but also the quality-of-life to be expected for surviving patients. If new therapies are more effective and cost less, we clearly would adopt them. However, we generally do not adopt therapies that are significantly less effective than the current standard, even if they do cost less, and clearly not if they cost more. Most new treatments

we consider incorporating into practice are both more effective and more expensive. This is the case for activated protein C.

Given the expense of this new therapy, there has been considerable concern about the cost-effectiveness of rhAPC treatment for patients with severe sepsis.¹⁰ A number of economic evaluations of rhAPC have been undertaken to determine if there are circumstances when treatment with rhAPC represents good value for the healthcare dollar.¹¹⁻¹⁴ The evaluations have all relied upon the short-term (28-day) clinical outcomes as reported in the PROWESS trial. Longer-term outcomes and costs have been extrapolated from cohorts of patients with severe sepsis in Canada^{12,14} and the United States.^{11,13} Additionally, these evaluations have incorporated sensitivity analyses to examine the differing cost-effectiveness for patients with differing severity of illness, age, and life expectancy.

Utilizing 28-day outcome data from the PROWESS study, multiple investigators have found rhAPC treatment for patients with severe sepsis to be good value for the healthcare dollar, by the usual conventions of cost-effectiveness (ie, an incremental cost-effectiveness ratio < \$50,000/QALY).¹¹⁻¹⁴ However, both the benefits and cost-effectiveness appear limited to those patients with severe sepsis and a high risk of death (eg, APACHE II score ≥ 25).¹¹⁻¹⁴ As well, very elderly patients and those with a life-expectancy < 4 years appear to derive less benefit from rhAPC. Treatment may not be cost-effective for patients within these subgroups, at a threshold of \$50,000/QALY.^{11,12}

Remaining questions

The clinical effects observed in a clinical trial (efficacy) are usually greater than that obtained in clinical practice (effectiveness).²² Deleterious side effects may also increase. This may be due to differences in patient selection, medication administration, and differences in the level of care and follow-up outside clinical trials. Cost-effectiveness in clinical practice can therefore also be less attractive than that determined in a clinical trial. Additionally, a favourable cost-effectiveness ratio from a societal perspective (perhaps a cost-effectiveness ratio < \$50,000/QALY) does not address the near-term affordability of a therapy for individual critical care units or pharmacies. It is possible that the benefits to society, over time, may offset this increased proximate expense to critical care units;

however, such benefits, if they do occur, will not likely be reallocated back to Canadian healthcare providers in a timely or complete manner. Canadians currently spend approximately 9.4% of the gross domestic product on healthcare, in comparison to approximately 14% in the United States.^{23,24} If we continue to adopt innovations that are more effective, but also more costly, we will need to continue to increase the proportion of resources devoted to healthcare, or reduce resource use that is either ineffective or associated with the lowest cost-effectiveness profiles.²⁴

Further investigation into the effects of activated protein C may provide insight into some of our remaining questions. A multicentre, randomized, placebo-controlled trial will evaluate the efficacy and safety of rhAPC specifically in the group of patients with early stage, less severe sepsis. Ongoing follow-up of patients treated with rhAPC will be helpful in determining longer-term benefits. Additional trials are planned to evaluate the risk of bleeding in patients concurrently treated with rhAPC and heparin. Further information on previously excluded subgroups of patients will arise from open-label use and clinical experience with rhAPC.

Conclusions

The economic challenge precipitated by the introduction of rhAPC – an effective yet expensive therapy for certain patients with severe sepsis – highlights the need for continual reassessment of therapies and services offered by intensive care departments and hospitals, in general. We must reassess the services we employ in light of the evolving evidence of effectiveness, ineffectiveness, and associated costs. Resources previously allocated to therapies with unproven effectiveness for specific patient populations (eg, routine pulmonary artery catheterization for high-risk surgical patients or indiscriminate use of inhaled nitric oxide for hypoxemic respiratory failure), might be reallocated towards treatments with more established benefit, particularly when associated with lower or neutral costs (eg, perioperative β -blocker administration to high-risk surgical patients, or lung-protective mechanical ventilation strategies for those with acute lung injury).²⁵⁻²⁸ We will, however, need continued caution before broadly adopting new therapies, especially costly ones, as we continue to learn of real-world effectiveness, safety, and long-term outcomes.

Robert Fowler, MD, MS(Epi), is a physician in the Department of Medicine, Division of General Internal Medicine and Critical Care Medicine, Sunnybrook and Women's College Health Sciences. Dr. Fowler has previously completed an independent economic evaluation of activated protein C for the treatment of patients with severe sepsis. He will be a site investigator for the ADDRESS trial investigating the efficacy and safety of activated protein C in adult patients with early stage severe sepsis.

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