Activated Protein C for Severe Sepsis

Summary

✓ Severe sepsis is a systemic inflammatory response to infection involving organ dysfunction. Severe sepsis is a common cause of death and is associated with a 20%¹ to 56%¹⁻⁶ mortality rate.

✓ Drotrectogin alpha (activated) is a recombinant human activated protein C (rhAPC) approved in the U.S. for the reduction of mortality in adult patients with severe sepsis who have a high risk of death.⁶

✓ Drotrectogin alpha (activated), when administered to adult patients with clinically-defined severe sepsis, demonstrated a 6.1% absolute reduction (p=0.005) in 28-day all-cause mortality in one published, randomized, double-blind study of 1,690 patients (PROWESS).⁷

✓ Drotrectogin alpha (activated) is used as an adjunct to standard therapy and is therefore and "add-on" cost.

✓ Close attention must be paid to proper patient selection for treatment with drotrectogin alpha (activated). Certain individuals, such as those at a greater risk of bleeding, could be harmed from therapy. The benefit or harm in individuals not meeting the trial selection criteria is uncertain.

The Technology

Acquired protein C deficiency is prevalent in most patients with severe sepsis. This deficiency is associated with increased morbidity and mortality.⁴

Protein C is involved in regulating inflammation and coagulation that occurs during severe sepsis. The activated protein C (APC) inhibits cofactors Va and VIIIa, integral components of the coagulation cascade and thus, inhibits clot formation. APC can also decrease inflammation by inhibiting cytokines and increase fibrinolysis by inhibiting plasminogen activator inhibitor (PAI-1), a potent inhibitor of the fibrinolysis pathway.⁹ Drotrectogin alpha (activated) is a recombinant form of human APC.

Regulatory Status

In the U.S., drotrectogin alpha (activated), brand name Xigris™, received FDA approval in November 2001, and is indicated to reduce mortality in adult patients with severe sepsis who have a high risk of death (e.g. as determined by APACHE II).⁶ Lilly has made submissions for approval of drotrectogin alpha (activated) in Canada, the European Union and Australia during the first quarter of 2001 (Patricia Mosnia, Eli Lilly Inc., Toronto (ON): personal communication, 2002 Jan).

* Acute Physiology and Chronic Health Evaluation (APACHE II) score uses a point score (0 to 71) based upon physiologic measurements, age and previous health status to provide a general measure of severity of disease, where a higher score is related to a more severe disease state.²⁹

Patient Group

The incidence of severe sepsis in the U.S. is three cases per 1,000³ and it is associated with a 20%¹ to 56%¹⁻³ mortality rate. An estimated US $17 billion is spent on treating severe sepsis annually in the U.S.³⁻⁰ There are currently no Canadian incidence or cost data available.

A systemic inflammatory response syndrome (SIRS) can occur in response to a variety of clinical insults, such as trauma, burns and pancreatitis.¹¹⁻¹² According to the American College of Chest Physicians/Society of Critical Care Medicine, SIRS is defined as two or more of the following conditions: (1) a temperature >38°C or <36°C, (2) an elevated heart rate, (3) an elevated respiratory rate and (4) an elevated white blood cell
count. When the SIRS is in response to infection, it is termed sepsis. It is classified as severe sepsis if it involves organ dysfunction, a hypoperfusion abnormality, or sepsis-induced hypotension. Septic shock occurs when sepsis-induced hypotension does not resolve despite adequate fluid resuscitation and hypoperfusion abnormalities are still present.

The coagulation and inflammation surrounding sepsis can have a profound effect on various organ systems, and may result in myocardial dysfunction, acute renal failure, or acute respiratory distress syndrome (ARDS). Death usually occurs if one or more organ systems fail.

Resistant microorganisms as well as the use of aggressive invasive procedures in patient management and diagnosis are contributing factors to the incidence of sepsis. However, the mortality associated with sepsis has remained relatively unchanged over the past three decades.

Current Practice

Antibiotic therapy is necessary in the treatment of sepsis, however, 10% of patients do not receive prompt antibiotic therapy for the causative pathogen. This results in a 10-15% increase in mortality compared to those patients who receive appropriate antibiotic therapy. A common approach is to start with broad-spectrum antibiotic therapy, then to use pathogen-specific therapy when the causative agent is identified.

The supportive treatment of septic patients largely depends on the signs and symptoms the patient is exhibiting. Sepsis places extreme demands on the lungs, and tachypnea and hypoxemia are often present. Eighty-five percent of patients require ventilatory support such as intubation and mechanical ventilation for approximately 7-14 days to lessen the demand on the lungs. Fifty percent of these patients may develop ARDS, where the air spaces fill with fluid and gas exchange is deteriorated. ARDS is associated with a 60-90% mortality rate.

Aggressive fluid resuscitation alone may be sufficient to treat hemodynamic instability in some patients. However, vasopressor support is often necessary to restore minimal tissue perfusion and enhance myocardial contractility. Other supportive therapies such as hemodialysis, nutrition and various surgical maneuvers may also be required.

Administration and Cost

In the U.S., the recommended dose of drotrecogin alpha (activated) is 24 µg/kg/hr for 96 hours via intravenous infusion. It is supplied in 5 mg and 20 mg vials. The average wholesale price in the U.S. is US $252 for the 5 mg vial and US $1,008 for the 20 mg vial. For example, treating a 70 kg adult would cost approximately US $8,000.

Rate of Technology Diffusion

The uptake of this technology may vary between individual institutions as budgetary considerations and physician preference may dictate its acceptance.

Concurrent Developments

New therapies are being directed against endotoxins (e.g. immunoglobulins), cytokines (e.g. tumor necrosis factor, interleukin-1), biological systems (e.g. coagulation), mediators (e.g. platelet activating factor) and others. Agents in phase III trials include recombinant platelet-activating factor acetylhydrolase and afelimomab. Recently, antithrombin III and tifacogin were believed to provide beneficial treatment for sepsis. However, phase III trials of both agents failed to demonstrate an impact on 28-day mortality due to all causes.

The Evidence

The phase III PROWESS study enrolled 1,690 patients in a double blind, placebo-controlled, international trial. Patients were included if they had a known or suspected infection, as well as three or more signs of systemic inflammation plus sepsis-induced dysfunction of at least one organ for less than 24 hours. Patients with an increased risk of bleeding, a hypercoagulable state and patients receiving medications that may increase the risk of bleeding were among those patients excluded from the trial. Patients were randomized to receive...
placebo or recombinant human activated protein C (rhAPC), drotrecogin alpha (activated) infusion, at a rate of 24 µg/kg/hr for 96 hours. Supportive therapies, such as antibiotics, fluids, vasopressors, or ventilatory support were used at the physician's discretion. The primary efficacy endpoint was 28-day all-cause mortality after the initiation of the infusion.

At 28 days, 30.8% of patients receiving placebo, and 24.7% of patients receiving treatment died, representing a 19.4% relative reduction and a 6.1% absolute reduction (p=0.005) in death from any cause.7 This represents a number-needed-to-treat (NNT) of 16 to prevent an additional death.

The percentage of patients experiencing at least one serious adverse event was comparable between the treatment (12.5%) and the placebo group (12.2%) (p=0.84).7 Serious bleeding (defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required administration of three units of packed red cells on two consecutive days) was higher in the treatment group when compared to placebo, 3.5% vs. 2.0% (p=0.06). This represents a number-needed-to-harm (NNH) of 66. This difference was observed during the infusion period and occurred primarily in patients with an identifiable predisposition to bleeding.

The PROWESS study demonstrated a reduction in 28-day mortality in treated patients. However, the consequences of morbidity of the survivors is unclear. Assessments measuring organ dysfunction (sepsis-related organ dysfunction (SOFA) score) and activities of daily living (ADL scores) identified comparable functional results between survivors in the placebo and treated groups at 28 days.10,24

A greater number of patients in the treatment group had discontinued the infusion due to an adverse event (6.4% vs. 3.6%, p=0.009).25 Gastrointestinal bleeds were the most common reason for discontinuation of treatment (1.3% vs. 0.6%, p=0.138). Myocardial infarction was also reported as an adverse event causing discontinuation of treatment, and was reported at a higher rate when compared to placebo (0.7% vs. 0%, p=0.015).25

An open-label, dose escalation, dose duration study was performed to investigate the safety, pharmacokinetics, and pharmacodynamics of drotrecogin alpha (activated) in pediatric patients with severe sepsis.23 The study demonstrated similarities between the pediatric and adult populations in these areas. However, direct efficacy studies have not been performed in pediatric patients. Currently, an international, open-label, phase IIIb trial (ENHANCE) is evaluating 28 day all-cause mortality among 2,300 adult and pediatric patients with severe sepsis.26

### Implementation Issues

Treatment is not proven to benefit patients who do not meet the predefined inclusion and exclusion criteria of the PROWESS study.9 In order for this therapy to be used appropriately by physicians, protocols must be developed to ensure that suitable patients receive this therapy and to exclude those who might not benefit or be harmed.27

Additional investigation is required regarding the safety of APC. Therapy should be carefully evaluated in patients who have conditions likely to increase bleeding. Since formal drug interaction studies have not been conducted, physicians must pay attention to proper patient selection and in particular pay close attention to drug interactions, especially those that may increase the risk of bleeding.

Although treatment is indicated for adult patients with severe sepsis who have a high risk of death as determined by the APACHE II, the determination of an APACHE II prior to administration of drotrecogin alpha (activated) may not be practical or not commonly used in the hospital setting.

Drotrecogin alpha (activated) is used as an adjunct to standard therapy rather than replacing a current treatment regimen and is therefore an "add on" cost. Health care expenditures will likely increase from the acquisition cost, along with an increase in individuals requiring ICU and hospital care.28 The management of cost by the health care institutions may be challenging as the cost of drotrecogin alpha (activated) could be substantial.

### References


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