Drotrecogin alfa (activated): the first FDA-approved treatment for severe sepsis

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Drotrecogin alfa (activated) (Xigris, Eli Lilly and Company, Indianapolis, Ind) is a recombinant form of human activated protein C. It was approved by the Food and Drug Administration in the last quarter of 2001 for the reduction of mortality due to severe sepsis in adult patients who are at high risk of death (1). This is a unique indication. While many investigational drugs have been proposed as treatments for sepsis in the past, and several have even made it to clinical trials (2), only drotrecogin alfa (activated) has shown a survival benefit.

The definition of sepsis given by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference has 2 parts: infection and 2 of the 4 systemic inflammatory response syndrome (SIRS) criteria (temperature ≥38°C or ≤36°C, heart rate ≥90 beats/minute, respiratory rate ≥20 breaths/minute or $PaCO_2$ ≤32 mm Hg, white blood cell count ≥12,000/μL or ≤4000/μL or >10% immature forms). The definition of severe sepsis includes the above plus organ dysfunction, hypoperfusion, or hypotension (3). This syndrome is a result of the body's systemic inflammatory and procoagulant responses to infection and is associated with significant morbidity and mortality (4, 5).

While reports of the incidence of severe sepsis have varied, a recent study of the incidence and outcomes of severe sepsis in the USA yielded an estimate of 751,000 cases of severe sepsis per year (3 cases per 1000 population) (6, 7). Another study found confirmed severe sepsis in 6.3 per 100 intensive care unit patients, with an associated mortality of 56% (8). The average cost per case of severe sepsis was estimated at $22,100, representing an annual figure of $16.7 billion in the USA (7).

During severe sepsis the proinflammatory mediators released, including tumor necrosis factor-alfa (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), not only induce the systemic inflammatory symptoms that are seen in the SIRS response but are also capable of activating the coagulation cascade and inhibiting fibrinolysis. The thrombin generated as coagulation occurs then acts to further stimulate multiple inflammatory pathways. This process leads to the sequelae of severe sepsis, including endovascular injury, multiorgan dysfunction, and death (9).

PHARMACOLOGY

Drotrecogin alfa (activated) is a recombinant human activated protein C (9). Protein C has been shown to be an important prognostic indicator in patients with sepsis. Decreased protein C levels have been linked to mortality in both sepsis and septic shock (9, 10). It is theorized that during sepsis, in addition to the absolute reductions in protein C levels, there is a reduction in the conversion of protein C to its active form due to the down-regulation of thrombomodulin by inflammatory cytokines. Thrombomodulin coupled to thrombin is necessary to activate protein C. Activated protein C is believed to have antithrombotic, profibrinolytic, and anti-inflammatory effects (9).

The antithrombotic effects of activated protein C are mediated by its ability to inhibit the formation of clotting factors Va and VIIIa. The inhibition of these factors hinders prothrombin activation, limiting thrombin formation and causing an overall decrease in the host's coagulation potential (9, 10). A decrease in inflammatory cytokines noted in in vitro studies also has antithrombotic effects due to the associated reduction in the release of tissue factor from monocytes and the endothelium (9).

The indirect profibrinolytic effects of activated protein C (based on in vitro data [1]) are mediated by the inhibition of plasminogen activator inhibitor-1, which then inhibits endogenous tissue-plasminogen activator. Activated protein C is also thought to inhibit thrombin-activatable fibrinolytic inhibitor, the suppression of which indirectly enhances fibrinolysis (9, 10).

In vitro data also indicate that drotrecogin alfa (activated) may exert anti-inflammatory effects through several mechanisms. First, activated protein C inhibits the production of the inflammatory cytokine TNF-α. Second, it binds selectins on injured endothelium, which limits the rolling of monocytes and neutrophils. Third, it limits the generation of thrombin by inhibiting clotting factors Va and VIIIa. This is significant because thrombin can stimulate multiple inflammatory pathways (9, 10).

During severe sepsis, the procoagulant, fibrinolytic, and inflammatory effects induced by the cascade of cytokines released in the presence of bacterial endotoxin lead to the clinical findings of SIRS, activation of the coagulation system, progressive endovascular injury, shock, organ dysfunction, organ failure, and death (5, 9). While the specific mechanisms by which drotrecogin alfa (activated) reduces mortality in severe sepsis are not

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completely understood, it is thought that the combined antithrombotic, profibrinolytic, and anti-inflammatory effects seen in vitro are involved (1, 5, 9).

PHARMACOKINETICS

Drotrecogin alfa (activated) is inactivated by endogenous plasma protease inhibitors. Infusions of 12 to 30 μg/kg/hr produce steady-state concentrations proportional to infusion rates, with a median steady-state concentration of 45 ng/mL being achieved within 2 hours of starting the infusion. The median clearance of drotrecogin alfa (activated) was 40 L/hr, and in most patients levels had fallen below the level of detectability (10 ng/mL) within 2 hours of stopping the infusion. The clearance of drotrecogin alfa (activated) in patients with severe sepsis is approximately 50% higher than in healthy patients (1).

ADVERSE EFFECTS AND TOXICITIES

Drotrecogin alfa (activated) has been noted to cause an increased incidence of adverse bleeding events when compared with placebo. This effect was limited primarily to the duration of the infusion. In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, the incidence of bleeding with drotrecogin alfa (activated) was 3.5% versus 2% for placebo ($P = 0.06$) despite the exclusion of patients at an increased risk of bleeding *(Table 1)* (9).

The incidence of intracranial hemorrhage during the 28-day study period in the PROWESS study was 0.2%. Intracranial hemorrhage has been reported in patients receiving drotrecogin alfa (activated) in non–placebo-controlled trials at a higher rate of approximately 1% during the infusion period. The risk for this complication may be higher in patients with risk factors for bleeding, such as severe coagulopathy and thrombocytopenia (1).

The incidence of new infections was similar between the placebo and treatment groups. Because this product is a recombinant form of a human protein, antibodies to activated protein C may develop. Two patients developed detectable antibodies to drotrecogin alfa (activated): one had no sequelae related to the antibodies, but the other developed multiple thrombi and died of multiorgan failure on day 36 posttreatment. It was unclear if the death was related to the development of antibodies (11).

Table 1. Adverse bleeding and thrombotic events of drotrecogin alfa (activated) and placebo in the PROWESS study*

Event	No. of patients (%)		*P* value
	Placebo (n = 840)	Drotrecogin alfa (activated) (n = 850)	
Gastrointestinal bleeding	9 (1.1)	9 (1.1)	
Intra-abdominal bleeding	4 (0.5)	3 (0.4)	
Intrathoracic bleeding	1 (0.1)	6 (0.7)	
Retroperitoneal bleeding	0	4 (0.5)	
Intracranial bleeding	1 (0.1)	2 (0.2)	
Skin or soft tissue bleeding	0	2 (0.2)	
Genitourinary bleeding	0	2 (0.2)	
Unidentified source bleeding	2 (0.2)	2 (0.2)	
Total serious bleeding events	17 (2.0)	30 (3.5)	0.06
Thrombotic events	25 (3.0)	17 (2.0)	0.2

*From reference 9.

PROWESS indicates the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.

CONTRAINDICATIONS AND PRECAUTIONS

Drotrecogin alfa (activated) increases the risk of bleeding and is therefore contraindicated in patients with the following clinical situations in which bleeding could lead to a high risk of morbidity and mortality (1):

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

All patients should be carefully evaluated to determine if the risks of bleeding outweigh the possible benefits of therapy. Certain conditions are likely to increase the risk of bleeding during therapy with drotrecogin alfa (activated). In patients with one or more of the following conditions, the risk of bleeding should be carefully evaluated before instituting therapy (1):

- Concurrent therapeutic heparin (≥15 U/kg/hr)
- Platelet count $<30{,}000 \times 10^6$/L, even if the platelet count is increased after transfusions
- Prothrombin time–international normalized ratio >3.0
- Recent (within 6 weeks) gastrointestinal bleeding
- Recent (within 3 days) administration of thrombolytic therapy
- Recent (within 7 days) administration of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
- Recent (within 7 days) administration of aspirin >650 mg per day or other platelet inhibitors
- Recent (within 3 months) ischemic stroke
- Intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis
- Chronic severe hepatic disease
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Should clinically important bleeding occur, the infusion of drotrecogin alfa (activated) should be immediately stopped, and the continued use of other agents that may affect the coagulation system should be assessed. Once adequate hemostasis has returned, restarting the drotrecogin alfa (activated) infusion can be considered (1).

Drotrecogin alfa (activated) should be discontinued 2 hours before an invasive surgical procedure or a procedure with an inherent risk of bleeding. Once adequate hemostasis has returned, restarting drotrecogin alfa (activated) may be considered 12 hours after a major invasive or surgical procedure or immediately after an uncomplicated or less invasive procedure (1).

DRUG INTERACTIONS

No published information is available regarding drug interactions with drotrecogin alfa (activated). Due to its association with increased bleeding events, drotrecogin alfa (activated)

Table 2. Organ system dysfunction criteria*

Organ system	Criteria
Cardiovascular	Arterial systolic blood pressure ≤90 mm Hg or mean arterial pressure ≤70 mm Hg for at least 1 hour despite adequate fluid resuscitation and adequate intravascular volume status or the use of vasopressors to maintain the above criteria
Kidney	Urine output <0.5 mL/kg/hr for 1 hour despite adequate fluid resuscitation
Respiratory	Ratio of Pao_2 to Fio_2 ≤250 in the presence of other organ system dysfunction or ≤200 if the lung was the only dysfunctional organ
Hematologic	Platelet count <80,000/μL or decreased by 50% in the 3 days preceding enrollment
Unexplained metabolic acidosis	pH ≤7.30 or base deficit ≥5.0 mmol/L in association with a plasma lactate level that was >1.5 times the upper limit of normal for the reporting laboratory

*From reference 9.

should not be administered to patients receiving other systemic anticoagulants. However, the use of low-dose heparin (≤15,000 U/day) did not appear to affect patient safety in the PROWESS trial (1).

DOSAGE

The dose of drotrecogin alfa (activated) for the reduction of mortality in adult patients with severe sepsis is a continuous infusion of 24 μg/kg/hr for 96 hours. Dose adjustments based on clinical or laboratory parameters are not recommended (1, 9). In the event of clinically important bleeding, the infusion should be stopped immediately (1).

CLINICAL EFFICACY

The clinical efficacy and safety of drotrecogin alfa for severe sepsis have been evaluated in 2 randomized, double-blind, placebo-controlled clinical trials (9, 11–15).

In a phase II trial designed to assess the safety and utility of recombinant human activated protein C, 131 patients were randomized to receive placebo (n = 41) or 1 of 4 doses of drotrecogin alfa (activated) for 48 or 96 hours (12). The doses of drotrecogin alfa (activated) were classified as low (12 or 18 μg/kg/hr) (n = 51) or high (24 or 30 μg/kg/hr) (n = 39). The outcomes assessed included D-dimer levels, platelet counts, IL-6 levels, and 28-day mortality.

D-dimer levels decreased from baseline in all groups at 24 hours, but the decrease in the high-dose group was greater than that seen with placebo at 48, 72, and 96 hours ($P < 0.01$). There was a trend towards higher platelet counts in the high-dose drotrecogin alfa (activated) group that was not significant. IL-6 levels were significantly reduced in the high-dose group ($P = 0.05$). This phase II trial was not powered to detect differences in mortality; however, the 28-day mortality rates for the placebo group (34%) and low-dose group (35%) versus the high-dose group (21%) indicated a trend towards increased survivorship with the higher doses ($P = 0.21$) (12).

Since effects were greatest with the high-dose group and continued throughout the 96-hour dosing infusion, the authors decided to use the 24 μg/kg/hr dose for 96 hours in the phase III trials. They also concluded that recombinant human activated protein C produced a dose-dependent improvement in markers of inflammation and coagulation commonly associated with severe sepsis and produced a trend towards decreased mortality (12).

The PROWESS study was a phase III multicenter trial with the primary endpoint of death at 28 days from any cause among patients with severe sepsis (9, 11, 13, 14). The study enrolled 1690 patients who had a known or suspected infection at the time of screening and within 24 hours met 3 of the 4 modified SIRS criteria and had sepsis-induced dysfunction of at least one organ or system *(Table 2)* that had been present for no longer than 24 hours. Exclusion criteria included conditions that would lead to an increased risk of bleeding. Enrollment was halted after a planned interim analysis of the first 1520 patients, which indicated a difference in mortality that exceeded the a priori guideline set for stopping the trial (9).

A total of 840 patients were randomized to receive placebo, and 850 patients were randomized to receive drotrecogin alfa (activated) 24 μg/kg/hr; both were delivered as a continuous infusion for 96 hours. Patients were required to begin treatment within 24 hours of meeting the inclusion criteria. Baseline characteristics were similar between groups, including D-dimer levels, IL-6 levels, and percentage of patients with protein C deficiency at baseline (9, 13). The infusion was paused 1 hour before and restarted 1 hour after any percutaneous procedure and paused 1 hour before and restarted 12 hours after any major surgery. No other care was dictated by the study protocol (9).

The primary endpoint assessed was 28-day all-cause mortality (9, 14). At 28 days, there were 259 deaths in the placebo group (30.8%) and 210 deaths in the drotrecogin alfa (activated) group (24.7%), which correlates to an absolute risk reduction of 6.1% ($P = 0.005$) as analyzed in an intent-to-treat fashion. This represents a relative risk reduction of 19.4% (95% confidence interval, 6.6% to 30.5%) for treatment with drotrecogin alfa (activated). In a prospectively defined stratified analysis based on Acute Physiology and Chronic Health Evaluation II score, age, and baseline protein C activity, similar results were obtained (absolute risk reduction, 6.2%; $P = 0.005$). These reductions in mortality were detected very early in treatment and were consistent throughout the 28-day period. The calculated number needed to treat in order to save 1 life was 16. The subgroup of patients with protein C deficiency at baseline was also similar (absolute risk reduction, 6.4%; $P = 0.009$); however, in patients without a baseline protein C deficiency, a significant difference was not detected (9).

The secondary endpoints of D-dimer levels and IL-6 levels also indicated a difference in favor of treatment with drotrecogin alfa (activated). D-dimer levels were significantly lower in the drotrecogin alfa (activated) group on days 1 to 7 ($P \leq 0.014$), while IL-6 levels were significantly lower in the treatment group on days 1 and 4 to 7 ($P \leq 0.025$) (9, 15).

ECONOMIC ISSUES

The acquisition cost of drotrecogin alfa (activated) is $210 for a 5-mg vial and $840 for a 20-mg vial. This translates to a

total cost of $6720 for the indicated 96-hour infusion for a 70-kg patient. For each 10 kg of body weight above 70 kg, the added cost is approximately $1050.

Another economic consideration is whether a therapy that increases survivorship increases morbidity and cost of hospitalization. Current data indicate that increased survivorship with drotrecogin alfa (activated) did not cause an increase in either time requiring mechanical ventilation or organ dysfunction (11).

SUMMARY

Drotrecogin alfa (activated) is a new therapeutic agent approved for reduction of mortality in adult patients with severe sepsis. Currently no other treatments are available or pending approval for severe sepsis. Drotrecogin alfa (activated) is a recombinant form of human activated protein C. It has anti-inflammatory, antithrombotic, and profibrinolytic effects. In the PROWESS study, it demonstrated a significant 28-day mortality benefit. The only adverse effect noted to date is an increase in adverse bleeding events. This effect was noted despite the exclusion from the trial of patients at an increased risk of bleeding. While the difference in the rates of significant bleeding events in the trial was not statistically significant, it was clinically significant. Since the trial was stopped early at a planned interim analysis, it is possible that the difference would have been statistically significant had the trial gone to its planned completion. It is also important to note that adverse effects are often found to be more prevalent once a drug is used outside the strict guidelines of a trial setting, as has already been seen with the increased incidence of intracranial hemorrhage in drotrecogin alfa (activated) patients in non–placebo-controlled trials.

The real-world utility of this new drug remains to be seen. Due to the seriousness of the possible adverse effects of this treatment and the high cost associated with it, guidelines for appropriate patient selection and a protocol that ensures appropriate administration and monitoring have been put in place at Baylor University Medical Center. Until further data have been published, decisions about using this agent should be made cautiously.

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