

by Lorna Goshman, RPh

Column Editor: Lee Vermeulen, MS, RPh,

Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

## Drotrecogin Alfa, Activated

(Xigris<sup>®</sup>, Eli Lilly and Co)

### Summary

**Indication:** Severe sepsis associated with acute organ dysfunction. Treatment with drotrecogin resulted in a 20% reduction in 28-day all cause mortality compared to placebo in the PROW-ESS trial (25% vs 31%, respectively;  $p < 0.005$ ).

**Monitoring Parameters:** The most frequent adverse reaction associated with drotrecogin use in clinical trials was bleeding, particularly procedure-related. Treated patients should be closely monitored for bleeding. If bleeding is severe, drotrecogin should be discontinued and only resumed if the bleeding can be brought under control. Platelets and INR should be obtained at baseline and daily during therapy. Drotrecogin alfa may prolong PTT, so that aPTT cannot be reliably used to monitor therapy.

**Contraindications:** Serious bleeding risks, including internal bleeding, recent hemorrhagic stroke (within 3 months), recent intracranial or intraspinal surgery or severe head trauma (within 2 months), trauma with an increased risk of life-threatening bleeding, presence of an epidural catheter, intracranial neoplasm or evidence of cerebral herniation. Patients should be carefully monitored for other conditions that could lead to an increased risk of bleeding, such as recent G-I bleeding.

**Dose:** Continuous intravenous infusion at a rate of 24 mcg per kilogram per hour for 96 hours. If a patient is receiving drotrecogin and needs surgery or an invasive procedure, the infusion should be stopped for at least 2 hours before the procedure. The infusion may be resumed immediately after hemostasis has been achieved

for minor procedures, but not for 12 hours after major invasive procedures or surgery.

**Pediatrics:** Evaluation not completed in pediatric patients. Pharmacokinetic and safety trials were conducted in children ranging in age from newborn to 18 years of age. No differences in the rates of bleeding and mortality were seen in the 58 pediatric patients compared to the adult study population.

**Geriatrics:** The mean age of the patients in clinical trials was 60 years.

**Pregnancy Category:** C

**Stability and Storage:** The lyophilized powder should be stored at 2-8°C and protected from light. It should be reconstituted with sterile water and further diluted for use in 0.9% saline. Intravenous administration should be completed by 12 hours after solution preparation. In solution, the drug may be mixed only with 0.9% saline, lactated Ringer's, dextrose or dextrose with saline.

**Cost:** The drug is supplied as a lyophilized powder for reconstitution in 5-mg and 20-mg vials. The average wholesale price is \$252 for 5 mg and is \$1,008 for 20 mg vials. The dose for a 70-kg patient is 161.3 mg at a cost of \$8,064.

**P&T Action:** Drotrecogin (along with guidelines for its use) was added to the UWHC medication formulary at the December 20, 2001 P&T committee meeting.

### Introduction

Severe sepsis annually claims the lives of one-third or more of the 750,000 patients it affects in the United States. In spite of the increasing sophistication and improved technology applied in critical care units, mortality remains as high as 50%.<sup>1</sup> In the past, treatments for severe sepsis have proved largely ineffective because, by the time therapy was begun, severe and often irreversible organ damage was already present and eventually led to death in the septic patient.<sup>2</sup> Recently, the importance of the coagulation cascade in the development of sepsis has been recognized. Bacterial endotoxins and inflammatory responses favor coagulation. Patients who die of sepsis are more likely to have coagulation defects, including lower levels of circulating anticoagulants such as antithrombin III and protein C.<sup>3</sup>

### Pharmacology

The protein C coagulation pathway has emerged as the major regulatory mechanism that can cause excess thrombin production and inappropriate thrombosis that leads to strokes and heart attacks.<sup>4</sup> Activated protein C interacts with protein S to inactivate both coagulation factors Va and VIIIa and subsequently decrease thrombin production. In addition, protein C has antiinflammatory properties, and has been shown to decrease both the inflammatory and coagulant effects of gram-negative sepsis in the baboon.<sup>5</sup> By limiting leukocyte activation, cytokine production, and microvascular coagulation, activated protein C has been

*Lorna Goshman is the Senior Clinical Pharmacist, Center for Drug Policy, University of Wisconsin Hospital and Clinics*

*The information given and views expressed herein do not necessarily reflect the opinions of PSW, its Board or members.*

shown to prevent organ damage in experimental models of sepsis.<sup>6</sup> In sepsis, protein C deficiency appears before the onset of detectable indicators of severe sepsis or septic shock and may function as a prognostic indicator.<sup>7</sup> Replacement of protein C has the potential to prevent vascular injury, organ damage and death.

Human protein C is a plasma serine proteinase that controls the conversion of prothrombin to thrombin by feedback inhibition.<sup>7</sup> Drotrecogin alfa (activated) is a recombinant human activated protein C produced by inserting the complementary DNA for human protein C into an established mammalian cell line.<sup>7,8</sup> Activated protein C has a plasma half-life of about 15 minutes.<sup>6</sup> Maximum plasma concentrations of drotrecogin alfa are attained within two hours of infusion administration, and decline below assay limits within two hours of discontinuation.<sup>8</sup>

## Clinical trials

### *The PROWESS Trial*

One large multicenter, randomized, double blind, placebo-controlled clinical trial of drotrecogin alfa in 1690 patients with severe sepsis has been published.<sup>1</sup> Patients with a known or suspected infection had to meet study criteria for systemic inflammation and sepsis-induced organ dysfunction present for less than 24 hours. The criteria included three or more of 1) a core temperature of  $\geq 38^{\circ}\text{C}$  or  $\leq 36^{\circ}\text{C}$ , 2) a heart rate  $\geq 90$  beats/minute, 3) a respiratory rate of  $\geq 20$  breaths per minute, a  $\text{PaCO}_2$  of  $\leq 32$  mm Hg, or mechanical ventilation, and 4) a white cell count  $\geq 12,000/\text{mm}^3$  or  $\leq 4000/\text{mm}^3$  or a differential count showing more than 10% immature neutrophils. Indicators of sepsis-induced organ function included at least one of the following: 1) arterial systolic pressure  $\leq 90$  mm Hg or mean arterial pressure  $\leq 70$  mm Hg, 2) urine output  $< 0.5$  ml/kg for at least one hour, 3) a  $\text{PaO}_2$  to  $\text{FiO}_2$  ratio of  $\leq 250$  (or  $\leq 200$  if the only dysfunction was pulmonary), 4) platelets  $\leq 80,000/\text{mm}^3$  (or a decrease of 50% in the preceding three days), and 5) when unexplained metabolic acidosis developed, a  $\text{pH} \leq 7.30$  or a base deficit  $\geq 5$  mmol/L with a plasma lactate level  $> 1.5$  times normal.

The patients were randomized to receive placebo (normal saline with or without 0.1% albumin) or drotrecogin alfa, activated, 24 mcg/kg/hour, by intravenous infusion over 96 hours. The primary end point of the trial was death from any cause by 28 days after the study drug was started. A total of 840 patients received placebo, while 850 received drotrecogin. Less than 25% of the patients were older than 75 years of age. At 28 days, 30.8% of patients in the placebo group, but only 24.7% of those in the drotrecogin arm had died. This result represents an absolute reduction in death of 6.1% ( $p=0.005$ ), or a relative reduction of 19.5% (95% confidence interval 6.6 to 30.5). Enrollment of patients was stopped after an interim analysis of over 1500 patients showed that drotrecogin was significantly more effective than placebo.

When patients were stratified into subgroups according to age, APACHE score, type of infection, number of system dysfunctions or detectable protein C deficiency, the treatment effect was consistent. Accordingly, the authors suggest that measurement of protein C would not be necessary to screen for patients who might have a therapeutic response.

Product prescribing information provides further information on efficacy stratified by the baseline APACHE II scores of the patients.<sup>8</sup> For less seriously ill patients with APACHE scores in the first and second quartiles, no difference in mortality between drotrecogin alfa and placebo was observed. For more seriously ill patients in the third and fourth quartiles having APACHE scores  $> 25$ , the absolute mortality difference was –13% for the drotrecogin patients. The relative risk reduction of death was 29%. The package insert explicitly states that the efficacy of drotrecogin alfa has not been established for patients with baseline APACHE II scores of  $< 25$ .

## Adverse effects

Serious bleeding, observed mainly during the course of the infusion, occurred at a rate of 3.5% in patients treated with drotrecogin alfa, compared to 2% of the placebo patients.<sup>1</sup> This difference was not statistically significant ( $p=0.06$ ). Patients with bleeding episodes did have predisposing factors including platelet deficiencies, gastrointestinal ulcers, aPTT greater than 120 seconds, INR in excess of 3.0 or a traumatic injury to a blood vessel. The serious bleeding events included two cases of fatal intracranial hemorrhage. At least one bleeding event occurred in 25% of drotrecogin-treated patients compared to 18% of placebo patients during the 28-day duration of the study.<sup>8</sup> The additional administration of heparin increased the incidence of bleeding only to 3.7% in drotrecogin-treated patients. More thrombotic events occurred in the placebo patients.

No neutralizing antibodies to protein C were detected.<sup>1</sup>

## Cost, dose and how supplied

Drotrecogin alfa activated is administered as a continuous intravenous infusion at a constant rate of 24 mcg/kg/hour for 96 hours. Therapy must be initiated within 24 hours of the time that patients meet the guideline treatment criteria. Patients weighing in excess of 135 kg were excluded from the study so the impact of obesity on the dose-response or adverse effect profile is unknown.

The drug is supplied as a lyophilized powder for reconstitution in 5-mg and 20-mg vials. It should be reconstituted with sterile water for injection and further diluted to a concentration of 100–200 mcg/ml in 0.9% sodium chloride. The diluted solution is infused at a constant rate of 24 mcg/kg/hr for 96 hours. In accordance with Hospital Administrative Policy 8.31, Guidelines For Hospital-Location Specific Administration Of IV Medications, drotrecogin is a level 4 medication. As a level 4 medication, drotrecogin may only be administered on Intensive

Care Units, the Emergency Department, Operating Room and Recovery Room at UW Hospital and Clinics.

The average wholesale price is \$252 for 5 mg and is \$1,008 for 20 mg vials. The dose for a 70-kg patient is 161.3 mg at a cost of \$8,064. The total cost impact of drotrecogin will have on a pharmacy budget will depend on how closely the PROWESS eligibility criteria are followed.

### Conclusion

One of the keys to the success of the PROWESS trial was that therapy was begun within 24 hours of the time that patients met the inclusion criteria for severe sepsis. In clinical practice, it is likely that, in spite of institutional guidelines, drotrecogin therapy will be recommended prospectively for less seriously ill patients who do not meet use criteria, but who appear to be at risk for septic complications.

Drotrecogin alfa (activated) was added to the UWHC formulary with use restricted to approved guidelines. Any use outside of the guidelines requires the approval of the director of Critical Care, the chief of Infectious Diseases, or their designee. These cases will be reviewed by both the P&T committee and the appropriate QI committee. ■

### References

1. Bernard GR, Vincent J-L, Laterre P-F et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
2. Matthay MA. Severe sepsis – a new treatment with both anticoagulant and antiinflammatory properties. *N Engl J Med* 2001;344:759-762.
3. Lorente JA, Garcia-Frade LJ, Landin L et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. *Chest* 1993;103:1536-1542.
4. Esmon CT. Regulation of blood coagulation. *Biochim Biophys Acta* 2000;1477:349-360.
5. Taylor FB, Chang A, Esmon CT et al. Protein C prevents the coagulation and lethal effects of *Escherichia coli* infusion in the baboon. *J Clin Invest* 187;79:918-925.
6. Esmon CT. Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. *Critical Care Med* 2001;29(7suppl):S48-S51.
7. Grinnell BW and Joyce D. Recombinant human activated protein C: a system modulator of vascular function for treatment of severe sepsis. *Critical Care Med* 2001;29(7suppl):S53-S60.
8. Drotrecogin alfa (activated) (Xigris®) Prescribing Information, Eli Lilly and Co, Indianapolis IN, November 2001.

RPh on the Go

# UWHC Guidelines for the Use of Drotrecogin Alfa, Activated (Activated Protein C, Xigris®)

**Guidelines developed by:** UWHC Center for Drug Policy and Clinical Economics (CDPCE)

**Author:** Deborah Dunham, MA, RPh

**Coordination:** Lee Vermeulen, MS, Director, CDPCE

**Reviewed by:** Timothy Corden, MD; Jeff Fish, PharmD; Cindy Gaston, PharmD; Greg Hollman, MD; Susan Johnston, PharmD; Brian LaRowe, MS, RPh; Dennis Maki, MD; Kenneth Wood, DO

**Approved by P&T:** December 2001

**Scheduled Review Date:** December 2002

## A. Background

Each year in the US there are nearly 750,000 patients with severe sepsis. Despite advances in medicine, the mortality rate remains in the range of 40%. In the septic patient, homeostasis is lost due to an uncontrolled cascade of inflammation and disseminated intravascular coagulation. Drotrecogin alfa, a recombinant form of the naturally occurring protein C, is the first agent approved for the treatment of sepsis. Treatment with drotrecogin resulted in a 20% reduction in 28 day all cause mortality compared to placebo in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial (25% vs 31%, respectively;  $p < 0.005$ ). While drotrecogin is the first drug shown to reduce death from sepsis, it has only been studied in a tightly circumscribed patient population. Patients who were dialysis-dependent for chronic renal failure or had a history of transplantation were excluded from the study, and the effect of drotrecogin in these patients is unknown.

## B. Requirements for Initiation of Drotrecogin Therapy

- 1.0 Drotrecogin should only be used in potentially salvageable, critically ill patients who are receiving all necessary standard treatment to support life and treat infection. Drotrecogin should not be used in patients not expected to survive because of uncorrectable medical conditions such as widespread cancer or other end-stage disease.
- 2.0 Generally, use of drotrecogin is limited to the intensive care setting because of the critically ill nature of the patients treated with the drug. Indications for use as outlined in this document should be followed. Exceptions must be reviewed by the director of Critical Care, the chief of Infectious Diseases, or their designee.
- 3.0 Drotrecogin is a potent anticoagulant (a "virtual heparin"). Prior to the initiation of therapy a careful assessment of the patient's bleeding risk should be conducted. Drotrecogin should only be used if the potential benefit outweighs the risk of bleeding.

## C. Allowed Indications

- 1.0 To be eligible to receive drotrecogin patients must meet ALL of the following criteria:
  - 1.1 Has a reasonable expectation of survival exclusive of sepsis
  - 1.2 Has 3 or more systemic inflammatory response criteria (see Table 1)
  - 1.3 Has evidence of sepsis-induced end organ dysfunction in two or more systems (see Table 2) within 24 hours
  - 1.4 Has evidence of infection such as
    - 1.4.1 Positive culture(s)
    - 1.4.2 White blood cells in normally sterile body fluid
    - 1.4.3 Perforated viscus
    - 1.4.4 Radiographic evidence of pneumonia with production of purulent sputum
    - 1.4.5 Syndrome/diagnosis associated with high risk of infection
    - 1.4.6 Other
- 2.0 Investigational Review Board-approved protocols
- 3.0 Prescribing drotrecogin for all other indications requires the approval of by the director of Critical Care, the chief of Infectious Diseases, or their designee and review of the case by the appropriate QI committee. A copy of these reports will be forwarded to the Pharmacy and Therapeutics committee for review.

## D. Situations Where Drotrecogin Alfa Is Not Indicated

- 1.0 Mild-to-moderate sepsis without evidence of end-organ dysfunction

- 2.0 Moribund patients in whom death is imminent
- 3.0 Patients whose families or physician are not committed to the aggressive management of their underlying medical condition, i.e., DNR status
- 4.0 Patients with uncorrectable coagulation disorders
- 5.0 Because drotrecogin has not been studied in bone marrow, small bowel, liver, lung, or pancreas transplantation, use in these patients requires case review by the appropriate QI committee and a follow-up report to the Pharmacy and Therapeutics committee.

**E. Precautions/Contraindications**

- 1.0 Drotrecogin is contraindicated in patients with
  - 1.1 Active internal bleeding
  - 1.2 Recent (within 3 months) hemorrhagic stroke
  - 1.3 Recent (within 2 months) intracranial or spinal surgery, or severe head trauma
  - 1.4 Trauma with an increased risk of life-threatening bleeding
  - 1.5 Recent or planned epidural catheter
  - 1.6 Intracranial neoplasm or mass lesion or evidence of cerebral herniation
- 2.0 Drotrecogin should be used with caution in the following situations:
  - 2.1 Thrombocytopenia (platelets < 30,000)
  - 2.2 Elevated INR (>3)
  - 2.3 Recent (within 6 weeks) gastrointestinal bleed
  - 2.4 Recent use of anticoagulants

**TABLE 1. Systemic Inflammatory Response Syndrome (SIRS) Criteria**

Temperature	≥ 38 C or ≤ 36 C
Heart Rate	≥ 90 beats/min (or 90 <sup>th</sup> percentile for age)
Respiratory Rate	≥ 20 breaths/min (or >90 <sup>th</sup> percentile for age) or PaCO <sub>2</sub> ≤ 32mm Hg
White Blood Cell Count	< 4000 or > 12,000/mm <sup>3</sup> , or > 10% immature (band) forms

**TABLE 2. Sepsis-Induced Organ Dysfunction**

Organ System	Criteria for Dysfunction
Cardiovascular	<ul style="list-style-type: none"> <li>• Systolic blood pressure (SBP) of ≤ 90 mm Hg (&lt; 10<sup>th</sup> percentile for age for pediatric patients) <b>or</b></li> <li>• Mean arterial pressure (MAP) ≤ 70 mm Hg (&lt; 10<sup>th</sup> percentile for age for pediatric patients) for at least one hour despite adequate fluid resuscitation or adequate intravascular volume status <b>or</b></li> <li>• Vasopressor dependent SBP or MAP</li> </ul>
Renal	<ul style="list-style-type: none"> <li>• Urine output &lt;0.5 mL/kg/hr for 1 hour, despite adequate fluid resuscitation</li> </ul>
Respiratory	<ul style="list-style-type: none"> <li>• Ratio of PaO<sub>2</sub> to FiO<sub>2</sub> ≤250 in the presence of multiple dysfunctional organs <b>or</b></li> <li>• Ratio of PaO<sub>2</sub> to FiO<sub>2</sub> ≤ 200 if the lung was the sole dysfunctional organ</li> </ul>
Hematological	<ul style="list-style-type: none"> <li>• Platelet count of &lt; 80,000/mm<sup>3</sup> (drotrecogin not recommended in patients with platelets &lt; 30,000/mm<sup>3</sup>) <b>or</b></li> <li>• &gt;50% decrease in the platelet count from the highest value recorded over the previous 3 days</li> </ul>
Unexplained Metabolic Acidosis	<ul style="list-style-type: none"> <li>• pH ≤ 7.30 <b>or</b></li> <li>• Base deficit &gt; 5.0 mmol/L <b>with</b> plasma lactate level &gt; 1.5 times the upper limit of normal (&gt;3.0 mmol/L)</li> </ul>

- 2.4.1 Concurrent therapeutic heparin ( $\geq 15$  units/kg/hour)
- 2.4.2 Thrombolytics (e.g., alteplase  $>2$  mg, tenecteplase) within the last 3 days
- 2.4.3 Glycoprotein IIb/IIIa inhibitors (e.g., abciximab, tirofiban, eptifibatide) within the past 7 days
- 2.4.4 Oral anticoagulants (e.g., warfarin) within the past 7 days
- 2.4.5 Platelet inhibitors (e.g., aspirin  $\geq 650$  mg per day) within the last 7 days
- 2.5 Recent (within 3 months) ischemic stroke
- 2.6 Intracranial arteriovenous malformation or aneurysm
- 2.7 Known bleeding diathesis
- 2.8 Chronic severe hepatic disease

## F. Adverse Effects

- 1.0 The most frequent adverse reaction associated with drotrecogin use in clinical trials was bleeding, particularly procedure-related. Treated patients should be closely monitored for bleeding. If bleeding is severe, drotrecogin should be discontinued and only resumed if the bleeding can be brought under control.
- 2.0 If a patient is receiving drotrecogin and needs surgery or an invasive procedure, the infusion should be stopped for at least 2 hours before the procedure and not resumed until at least 12 hours after major invasive procedures. Drotrecogin may be restarted immediately after less invasive procedures.

## G. Monitoring Parameters

- 1.0 Platelets and INR should be obtained at baseline and daily during therapy.
- 2.0 Drotrecogin may variably prolong activated partial thromboplastin time (aPTT). Therefore, aPTT should not be used to monitor coagulopathy during drotrecogin infusion.

## H. Dosing

- 1.0 The usual dose is 24 mcg/kg/hour for 96 hours. Infusions greater than 96 hours in duration have not been studied.
- 2.0 No dose adjustment is recommended for renal or hepatic impairment.
- 3.0 The effect of obesity on drotrecogin kinetics is unknown; clinical trials excluded patients weighing more than 135 kg. Until further information is available, it is recommended that the upper weight limit for dosing of drotrecogin be set at 135 kg (3.24 mg/hour).
- 4.0 The total infusion period for drotrecogin should be limited to 96 hours, exclusive of any times when the infusion was interrupted to accommodate the need for surgery or an invasive procedure (see F.1.0 above). Infusions longer than this should be reviewed by the director of Critical Care, the chief of Infectious Diseases, or their designee.
- 5.0 Start and stop times of drotrecogin infusions must be recorded by the nursing staff on the tracking form attached to the bag. This allows tracking of the total infusion time and reduces under- or over-dosing.
- 6.0 Drotrecogin should be administered via a dedicated line or a dedicated lumen of a multilumen central venous catheter. No other drugs should be mixed with or administered in the same line as drotrecogin.

## I. Preparation and Administration

- 1.0 Drotrecogin is available as a powder for injection in 5 mg (5.3 mg with overfill) and 20 mg (20.6 with overfill) vials.
- 2.0 Drotrecogin is prepared as a standard 100 mcg/mL concentration solution in 10 mg/100 mL and 25 mg/250 mL bags of normal saline. To prepare the infusion withdraw a small volume of normal saline from the bag and slowly add it to the vial. Avoid shaking or inverting the vial. Withdraw the entire contents of the vial (each vial contains overfill) and add it to the bag of normal saline. When adding the drotrecogin to the infusion, the stream should be directed to the side of the bag to minimize agitation. **Gently** invert the bag to mix.
- 3.0 Intravenous solutions are good for up to 14 hours at room temperature or 24 hours under refrigeration. Once it is brought to room temperature the solution must be completed within 14 hours or by the time on the label, whichever is shorter.
- 4.0 Drotrecogin **cannot** be tubed. The bag must be hand delivered to the unit.
- 5.0 To reduce waste, the Sterile Products Area (SPA) must be called by the unit pharmacist/PHA prior to the preparation of each dose to determine if therapy is to be continued. If the infusion is discontinued for any reason, the decentral pharmacist/PHA will contact the SPA immediately. The SPA will track all wasted bags of drotrecogin, determine the cause of the waste, and report their findings to the DUE committee quarterly.