IX. Guidelines for Use of Activated Protein C

UCSF Guidelines for Usage of drotrecogin alfa (Xigris™)
Division of Critical Care Medicine
Division of Infectious Diseases
Departments of Clinical Pharmacy and Pharmaceutical Services
Approved by the Pharmacy & Therapeutics Committee, Feb 5, 2002; revised Oct 24, 2005, revised April 2009

This document describes the process for identification of appropriate patients with severe sepsis who may benefit from treatment with drotrecogin alfa. The Divisions of Critical Care Medicine, Infectious Diseases, and Clinical Pharmacy and the Department of Pharmaceutical Services have developed these guidelines based on clinical trial data and the FDA labeling. Because the drug is effective only in a subset of patients with severe sepsis (those with a high risk of death), may cause potentially fatal bleeding complications, and carries a high acquisition cost, consultation between Critical Care and Infectious Diseases is required before the drug will be released for clinical use.

QUESTIONS 1-6 REQUIRE AN AFFIRMATIVE RESPONSE (To be completed by Critical Care Attending or Fellow)

1) Does the patient have known or suspected infection defined as:
   a. Culture or gram stain of normally sterile body fluid
   b. CXR consistent with diagnosis of pneumonia
   c. Clearly identifiable focus of infection, e.g. perforated viscus, or WBC's in normally sterile fluid.

2) Is the patient in an ICU, and committed to full life support measures?

3) Exclusive of severe sepsis, is this patient expected to survive hospitalization?

4) Is the suspected infection causing the sepsis syndrome being appropriately treated?
   a. All patients receiving drotrecogin alfa must be formally evaluated by the Infectious Diseases consult service within 24 hours.
   b. Appropriate blood and infectious source cultures must be obtained.

5) Are at least three of the following SIRS criteria present?
   a. Core Temperature < 36°C or > 38°C
   b. Heart Rate > 90
   c. Respiratory Rate > 20 or PaCO₂ < 32 mmHg or need for mechanical ventilation
   d. WBC < 4000 or > 12,000 or > 10% immature forms

6) HAVE more than one sepsis-induced organ failures occurred within 48 hours? (Patients with a single organ failure may be at a low risk of death and are unlikely to benefit from drotrecogin alfa). Examples of organ failure criteria include:
   a) Shock with MAP < 70 mmHg or SBP < 90 mmHg or need for the following vasopressors, after fluid resuscitation with at least 1 L crystalloid, or evidence of adequate fluid resuscitation with CVP > 8 cmH₂O:
      i) Dopamine > 5 mcg/kg/min
      ii) Epinephrine, Norepinephrine at any dose
      iii) Phenylephrine > 20 mcg/min
   b) Urine output < 0.5 ml/kg/hr after fluid resuscitation
   c) PaO₂/FiO₂ < 250, or < 200 if lung the only organ dysfunction
   d) Platelets < 80,000, or 50% decrease over 3 days
   e) Unexplained metabolic acidosis with pH < 7.3 or BE > -5

http://clinicalpharmacy.ucsf.edu/idmp/ucsf_specific/apcguide.htm
CONTRAINDICATIONS

1) Bleeding is a major complication of drotrecogin alfa and careful consideration should be given to whether the benefits outweigh the risk of bleeding in patients receiving drotrecogin alfa. Any of the following are **ABSOLUTE CONTRAINDICATIONS** to drotrecogin alfa:
   a) Active bleeding from any site
   b) Surgery within 12 hours or with uncertain hemostasis
   c) Gastrointestinal hemorrhage within 6 weeks
   d) Closed head injury, intracranial or spinal surgery within 2 months
   e) CVA within 3 months
   f) Any history of intracranial mass lesion, AVM or aneurysm
   g) Epidural catheter or spinal puncture within 12 hours
   h) Thrombocytopenia (< 30K)
   i) Age less than 60 days

2) The following may lead to excessive risk of bleeding, and should be considered **relative contraindications** to drotrecogin alfa:
   a) Age <18 years (trial in pediatric patients failed to show benefit)
   b) INR>3.0
   c) Use of oral IIb/IIIa antagonists or oral anticoagulants within 7 days
   d) Recent administration (within 3 days) of thrombolytics therapy
   e) Recent administration (within 7 days) of ASA> 650 mg/day or platelet inhibitors
   f) Functional platelet disorder (e.g. uremia, VWF deficiency)
   g) Cirrhosis with portal hypertension
   h) Known bleeding disorder (e.g. hemophilia)
   i) Low molecular weight heparin at greater than prophylactic doses

UNKNOWN INDICATIONS

The following patient populations have not been studied, and the efficacy of drotrecogin alfa is **unknown**:
   a) Pregnancy
   b) Weight > 135 kg
   c) Chronic hemodialysis
   d) Bone marrow transplantation
   e) Solid organ transplantation (with the exception of kidney transplants)
   f) HIV with CD4<50
   g) Known hypercoagulable state

**Administration and Monitoring:**

- Drotrecogin alfa must be administered centrally, through a dedicated port. The dose is 24 mcg/kg/hr (based on actual body weight) for 96 hours.
- Drotrecogin alfa has potent anticoagulant properties, and the main complications associated with its use are bleeding complications, including intracranial and retroperitoneal hemorrhage.

Administration of drotrecogin alfa should be held during invasive procedures. In clinical trials, the following criteria were used:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Stop Infusion</th>
<th>Restart Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheter insertion</td>
<td>1 hour prior to procedure</td>
<td>Immediately after procedure</td>
</tr>
<tr>
<td>Chest tube insertion</td>
<td>1 hour prior to procedure</td>
<td>1 hour after procedure</td>
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<tr>
<td>Lumbar puncture</td>
<td>1 hour prior to procedure</td>
<td>1 hour after procedure</td>
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<tr>
<td>Re-intubation (tube change)</td>
<td>1 hour prior to procedure</td>
<td>Immediately after procedure</td>
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<tr>
<td>Sinus puncture</td>
<td>1 hour prior to procedure</td>
<td>Immediately after procedure</td>
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<tr>
<td>Thoracic drainage</td>
<td>1 hour prior to procedure</td>
<td>1 hour after procedure</td>
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<tr>
<td>Tracheostomy</td>
<td>1 hour prior to procedure</td>
<td>1 hour after procedure</td>
</tr>
<tr>
<td>Major surgery</td>
<td>1 hour prior to procedure</td>
<td>12 hours after procedure</td>
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</tbody>
</table>

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Monitoring of laboratory markers of hemostasis is recommended. Drotrecogin alfa may prolong the PTT interval. If the PTT exceeds 100 seconds, the infusion should be held and restarted when <100 seconds. Although drotrecogin alfa has minimal effect on PT or platelets, it is recommended to hold the infusion if the INR rises to >3.0 or the platelet count drops <15,000, because of an increased risk for bleeding.

If all the above criteria have been met and reviewed by the critical care attending physician, the attending physician will contact Infectious Diseases Pharmacy at 443-9421 and Infectious Diseases at 443-8628. If concurrence exists that the patient qualifies for drotrecogin alfa, the infectious diseases pharmacist will contact the IV Additive Service (IVAS) and notify that rhAPC has been approved. Upon receipt of the order from the critical care attending physician, IVAS will send drug to the critical care unit. In addition to the initial review, Infectious Diseases Consult Service will formally assess all patients started on rhAPC within 24 hours of the start of therapy.

In a recently published retrospective study, (Gentry et al.; Crit Care Med 2009) 73 adult patients received drotrecogin alfa for the reduction of mortality with severe sepsis. The study reported an increased risk of serious bleeding events and of death in patients with sepsis and baseline bleeding risk factors who received this product. Serious bleeding events occurred in 7 of 20 patients (35%) who had a bleeding risk factor vs. only 2 of 53 (3.8%) patients without any bleeding risk factors. The finding by Gentry et al. of an increased risk of death and serious bleeding events in patients treated with Xigris who also have baseline bleeding risk factors is consistent with the information in the current product label. Prescribers should carefully weigh the increased risk of bleeding against the benefits of Xigris.

FDA is working with the manufacturer to further evaluate the incidence of serious bleeding events and mortality in patients who received Xigris. FDA will communicate its conclusions and any resulting recommendations to the public when the review is completed, which may take several months. The FDA urges both healthcare professionals and patients to report side effects from the use of Xigris to the FDA's MedWatch Adverse Event Reporting program.

References: See Sepsis section, ID Reference Library