Review

# Clinical review: Drotrecogin alfa (activated) as adjunctive therapy for severe sepsis – practical aspects at the bedside and patient identification

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## Abstract

Administration of drotrecogin alfa (activated) has been demonstrated to reduce mortality in patients with severe sepsis who are at high risk for death or who have multiple organ dysfunction. This benefit was associated with an increased incidence of bleeding events, but the latter were mainly procedure related. Drug infusion interruptions should be instituted, in accordance with recent recommendations. Monitoring coagulation parameters may help in identifying patients at higher risk for bleeding but it is not indicated to adjust drug dosage. Acute renal failure and hemodialysis are not contraindications to this therapy, and no drug dosage adjustment is indicated. Finally, the type and source of infection, and its anticipated natural history, may determine whether drotrecogin alfa (activated) is indicated as well as the timing of its administration.

**Keywords** drotrecogin alfa (activated), hemorrhage, indication, management, severe sepsis

## Introduction

In the Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study [1], recombinant human activated protein C (rhAPC; drotrecogin alfa [activated]) was shown to reduce 28-day all-cause mortality in patients with severe sepsis. The observed reduction in the relative risk for death was 19.4% (an absolute risk reduction of 6.1%), but this was associated with an increased risk for bleeding events. The US Food and Drug Administration has approved drotrecogin alfa (activated) for the treatment of patients with severe sepsis but, following a *post hoc* analysis of data from the PROWESS study, it has restricted the treatment to patients at a high risk for death (e.g. as determined by Acute Physiology and Chronic Health Evaluation II score) [2–4]. The European Agency for the Evaluation of Medicinal Products also approved the drug for the treatment of adult patients with severe sepsis with multiple organ failure, when added to best standard care [5]. This decision was motivated by the fact that, in the PROWESS study, those patients with two or more organ dysfunctions who were treated with drotrecogin alfa (activated) had a 22% reduction in the relative risk for death (an absolute risk reduction of 7.4%), with a similar risk for bleeding as compared with the overall study population [6]. On the other hand, in patients with a single organ failure, treatment with drotrecogin alfa (activated) was associated with a 1.7% absolute risk reduction in 28-day all-cause mortality, which did not achieve statistical significance [7]. This may partly be explained by the limited size of the subgroup, which did not provide sufficient power to demonstrate a benefit in 28-day survival. A new randomized, double-blind, placebo-controlled, multicenter study [ADDRESS; Administration of Drotrecogin alfa (activated) in Early stage Severe Sepsis], which is expected to include more than 11,000 patients, is ongoing and should resolve the issue regarding the potential benefit of drotrecogin alfa (activated) in severe sepsis with lower risk for death.

The main purpose of the present article is to review, based on data from the PROWESS study and open label studies, the bleeding risks associated with the use of drotrecogin alfa

APTT = activated partial thromboplastin time; DIC = disseminated intravascular hemorrhage; ICH = intracerebral hemorrhage; PT = prothrombin time; rhAPC = recombinant human activated protein C.

(activated), together with a discussion of practical management and suggested recommendations for procedures during the infusion period. Finally, we discuss the potential indications for the drug.

## Bleeding events associated with drotrecogin alfa (activated)

rhAPC is the first in a new class of antithrombotic coagulation inhibitors for the treatment of severe sepsis. APC has anticoagulant activity by limiting thrombin formation and by inhibition of factors VIIIa and Va, and it promotes fibrinolysis by inhibiting plasminogen activator inhibitor 1 and thrombin-activatable fibrinolysis inhibitor [1,8]. APC has also been demonstrated to modulate the host response to severe infection [9]. Finally, based on *in vitro* data, APC is able to inhibit the induction of apoptosis proteins and may reduce cell death in sepsis [10].

Because of the anticoagulant properties of APC, patients at major risk for bleeding were not included in the PROWESS study, and the excluded population consisted mainly of patients with a recent history (<3 months) of stroke, neurosurgery, mass lesion of the central nervous system, and head trauma [1]. Also, patients with severe hepatic disease, gastrointestinal bleeding (<6 weeks) unless corrected by surgery, and major trauma in which clinicians were not confident in using heparin therapy were excluded from the study.

As was anticipated, administration of drotrecogin alfa (activated) was associated with an increased incidence of serious bleeding events as compared with placebo (3.5% versus 2.0%; $P=0.06$). These events occurred primarily during the infusion period (2.4% versus 1.0%; $P=0.02$). More importantly, when analyzing the conditions and circumstances associated with bleeding events, the major difference appeared to be related to procedures [11,12]. The incidence of natural bleeding events that occurred in critically ill patients (e.g. gastrointestinal bleeding) did not differ between patients treated with drotrecogin alfa (activated) and the placebo group. Procedure-related bleeding complications consisted mainly of intra-abdominal, retroperitoneal, and intrathoracic bleeds secondary to femoral catheter insertion, suprapubic bladder catheter placement, nephrostomy tube, thoracocentesis, lung biopsy, and decortication [2,11,12]. Thus, particular attention is warranted when performing procedures during the infusion period of drotrecogin alfa (activated).

Finally, concomitant prophylactic heparin use was not associated with an increased risk for bleeding [1]. However, this observation needs further confirmation because this therapy was not randomized, and patients at higher risk for bleeding or with a lower platelet count are less likely to receive heparin prophylaxis.

## Intracranial hemorrhage

Intracranial hemorrhage (ICH) is a feared complication of any drug that has anticoagulant properties. There are few published data on the natural incidence of ICH in severe sepsis. Oppenheim-Eden and coworkers [13] reported an incidence of 0.4% of new episodes of ICH in a general intensive care unit population. The study was retrospective and did not include trauma and neurosurgical patients. The main factors associated with ICH were a platelet count below 100,000/mm$^3$, renal and hepatic impairment, and sepsis.

The Kybersept study [14] evaluated the efficacy of antithrombin III in severe sepsis. The exclusion criteria were similar to those employed in the PROWESS trial, except for criteria regarding risk for ICH, because in the Kybersept study patients with a past history of stroke, or cranial or spinal trauma were excluded if the event had occurred within the past year. In that study the incidence of ICH in the placebo group was 0.4%. In the PROWESS study, three patients had an ICH (one patient receiving the placebo and two receiving drotrecogin alfa [activated]) [1]. For these latter patients, clinically evident disseminated intravascular coagulation (DIC) was present and platelet counts decreased to below 30,000/mm$^3$ [11]. The incidence of ICH was recently reported for a total of 2786 patients treated with drotrecogin alfa (activated) included in controlled trials, open-label trials, and compassionate use studies [12]. ICH occurred in 13 out of 2786 patients (0.5%) during the infusion period and in 32 out of 2786 (1.1%) during the 28-day study period. It is important to note that meningitis or platelet counts below 30,000/mm$^3$ were present in 9 out of 13 patients. At the present time the reported incidence of ICH with commercial use of drotrecogin alfa (activated) is 0.2% (8/3991) [12].

In order to minimize the incidence of ICH during the infusion period of drotrecogin alfa (activated), the clinician should adhere to the exclusion criteria given in Table 1.

Finally, even though not listed in the exclusion criteria, particular attention should paid to infective endocarditis. Infective endocarditis is associated with neurologic complications in up to 25% of the patients, with an embolic event being the most frequent manifestation [15,16]. Mycotic aneurysms may develop with secondary ICH or subarachnoid hemorrhage. In this type of infection, brain imaging should be performed in patients with neurologic impairment before starting drotrecogin alfa (activated) in order to rule out the presence of cerebral lesions.

## Disseminated intravascular coagulation and thrombocytopenia

Thrombocytopenia (<30,000/mm$^3$) present at baseline was an exclusion criterion in the PROWESS trial, but if platelet count dropped below this threshold during the administration of drotrecogin alfa (activated) then the decision to stop the drug infusion was left to clinical judgment. Patients with a platelet count below 50,000/mm$^3$, either at entry or during the first 5 days of study, exhibited an increased incidence of

**Table 1**

**Contraindications and warnings for the use of drotrecogin alfa (activated)**

| Contraindications | Warnings |
|---|---|
| Active internal bleeding | Heparin >15 U/kg per hour |
| Recent (within 3 months) hemorrhagic stroke | International Normalized Ratio >3 |
| Recent (within 2 months) intracranial or intraspinal surgery or severe head trauma requiring hospitalization | Platelet count < 30,000/mm$^3$, even if platelet count is increased after transfusions (USA) (European Agency for the Evaluation of Medicinal Products: contraindication) |
| Trauma with increased risk for life-threatening bleeding (e.g. liver, spleen or complicated pelvic fractures) | Recent gastrointestinal bleeding (within 6 weeks) |
| Patients with epidural catheters | Recent administration of thrombolytic therapy (within 3 days) |
| Patients with intracranial neoplasm or mass lesion, or evidence of cerebral herniation | Recent administration (<7 days) of oral anticoagulant or glycoprotein IIb/IIIa inhibitors |
| | Recent administration (<7 days) of aspirin >650 mg/day or other platelet inhibitors |
| | Recent ischemic stroke (<3 months) |
| | Intracranial arteriovenous malformation |
| | Known bleeding diathesis |
| | Chronic severe hepatic disease (e.g. Child–Pugh C) |
| | Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location |

Adapted from US Food and Drug Administration [2,3].

serious bleeding events as compared with the rest of the population, and this was observed in both placebo and drotrecogin alfa (activated) treated patients [11]. Interestingly, there was a suggestion of a reduction in mortality for those patients with a platelet count below 50,000/mm$^3$ when treated with drotrecogin alfa (activated; 53% in the placebo group versus 32% in the treated group). These data must be interpreted with caution because of the small sample size (47 for placebo versus 46 for study drug) and the potential imbalance in risks for mortality. In the PROWESS study, DIC and overt DIC were not prospectively defined. In a second analysis, patients were diagnosed with overt DIC at entry if they met three of the following criteria [15]: presence of petechiae or purpura fulminans; platelet count below 80,000/mm$^3$ or 50% decrease from highest value recorded over the preceding 3 days; prothrombin time (PT) more than 21 seconds; D-dimer level greater than 8 μg/ml; and protein C activity below 40%. According to these criteria 221 patients had overt DIC. Among these 221 patients, the 28-day mortality rate was 52.4% in the placebo arm versus 30.5% in the treated arm, with an incidence of serious bleeding events of 3.9% and 3.4%, respectively.

This apparent important benefit in survival rate among patients with thrombocytopenia or overt DIC and treated with drotrecogin alfa (activated) must be weighed against an increased incidence of natural bleeding events. Because most treatment associated bleeding deaths occurred in this group of patients, clinicians should maintain platelet counts above 30,000/mm$^3$ during the drotrecogin alfa (activated) infusion period [12].

## Surgery and procedures

In the PROWESS study, 455 patients were classified as surgical because they underwent surgery within the preceding 30 days before enrollment or emergency surgery to control the source of infection [1]. Placebo bleeding rates were lower in the surgical group, but treatment emergent bleeding events rates were similar among surgical and nonoperative groups (19% versus 18%, respectively) [11]. Drotrecogin alfa (activated) has a short half-life. Following the completion of an infusion, the decline in plasma concentration is biphasic and the $t_{½}\alpha$ is 13 min with a $t_{½}\beta$ of 1.6 hours [17]. In practice, 90% of the drug is eliminated from serum after 1.8 hours. The short half-life of the drug allows rapid control of bleeding events, if they occur, by stopping the infusion. When surgery or procedures must be performed during infusion of drotrecogin alfa (activated), recommendations for infusion interruptions should be followed in order to minimize the risk for bleeding (Table 2).

Finally, drotrecogin alfa (activated) may influence naturally occurring coagulation abnormalities observed in severe sepsis [18]. Activated partial thromboplastin time (APTT) and PT are further prolonged by a few seconds by the drug, but the clinician will not be able to differentiate the influence of

**Table 2**

**Drotrecogin alfa (activated) infusion interruptions during procedures: recommended actions**

| Procedure | Action |
|---|---|
| **Minor procedures** | |
| Arterial line insertion (radial or femoral) | Hold infusion for 2 hours before procedure and restart immediately after, in the absence of bleeding |
| Venous femoral line insertion | |
| Intubation or tracheostomy change (unless urgent) | |
| **More invasive procedures** | |
| Central line or Swan-Ganz insertion (subclavian or jugular) | Hold infusion for 2 hours before and restart 2 hours after, in the absence of bleeding |
| Lumbar puncture | |
| Chest tube insertion or thoracocentesis | |
| Paracentesis | |
| Percutaneous drainage | |
| Nephrostomy | |
| Gastroscopy (possible biopsy) | |
| Wound debridment (decubitus ulcer, infected wound, packing changes in open abdomen, etc.) | |
| **Major procedures** | |
| Surgery (laparotomy, thoracotomy, major debridment, etc.) | Hold infusion for 2 hours and wait for 12 hours before restarting infusion |
| Epidural catheter | For epidural catheter, do not use drotrecogin or wait for 12 hours after removal before starting drug infusion |

Adapted from Taylor and coworkers [19].

drotrecogin alfa (activated) from that of sepsis-induced coagulopathy. For this reason, monitoring these coagulation parameters is not indicated and would not allow dose adjustment of the drug.

## Hemofiltration and dialysis

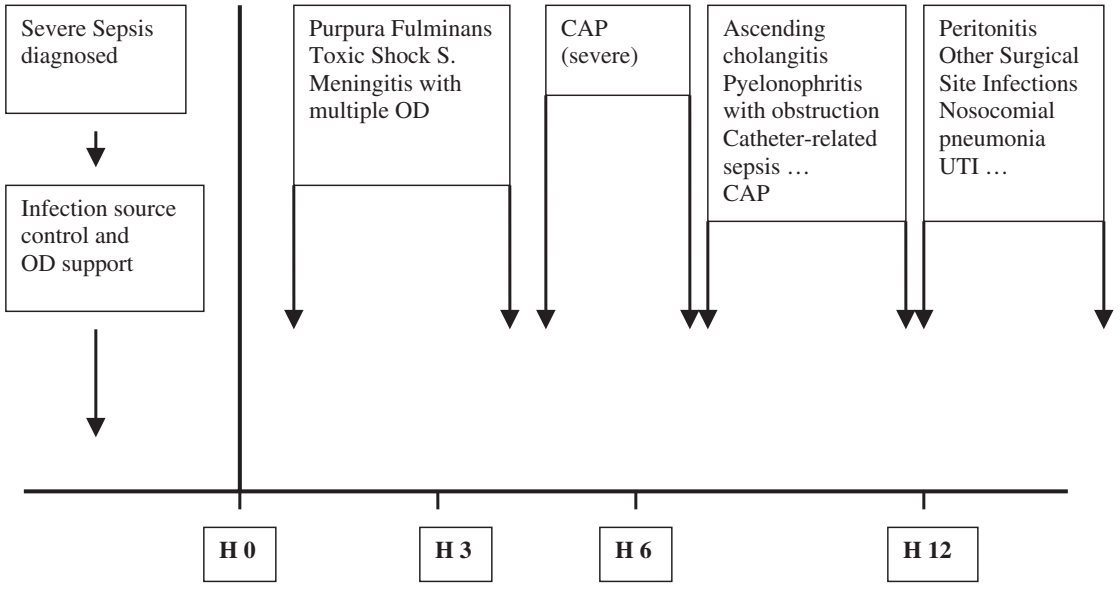
Patients with end-stage renal failure who required chronic dialysis were excluded from the PROWESS study because of the need for intensive heparin therapy and limited information on the medication half-life in this setting [1]. Patients enrolled in the study and who developed acute renal failure underwent hemofiltration or dialysis, when indicated, but heparin doses above 15,000 U/day were not allowed. In this group of patients there was no increase in the incidence of bleeding events [18]. In addition, pharmacokinetic and pharmacodynamic analyses performed in the PROWESS population have demonstrated that the serum concentration and drug half-life did not differ between patients with renal failure and the population overall [17]. Based on these data, patients with end-stage renal failure and chronic dialysis should not be excluded from this therapy.

Drotrecogin alfa (activated) has a molecular weight of 55 kDa and is not eliminated by hemofiltration or dialysis. Because pharmacodynamics and plasma concentrations of the drug are not significantly different in adult patients with renal failure, no dose adjustment is indicated in this population [17]. As a result of the anticoagulant properties of the drug, dialysis or hemofiltration may be performed without heparin or other forms of anticoagulation. In patients with severe sepsis and multiple organ dysfunction, PT and APTT are often moderately increased and platelet count may be reduced, limiting the dose of heparin required to maintain the extracorporeal circuit patent. It is suggested that hemofiltration or dialysis be started without concomitant heparin if the patient's baseline APTT is above 40 seconds or if the platelet count is below 100,000/mm$^3$. If clotting of the extracorporeal circuit occurs within the following hours then standard heparin may be added, but APTT (as determined within the circuit) should not be more than 70 seconds. After drotrecogin alfa (activated) infusion has been completed, anticoagulation should be conducted following standard practices.

## Selecting patients for drotrecogin alfa (activated) administration

Despite the US Food and Drug Administration and European Agency for the Evaluation of Medicinal Products indications for the drug, either for patients with severe sepsis at high risk for death or with multiple organ failure, when added to the best standard care, clinicians still often face difficulties in

**Figure 1**




Type of infection and proposed delay between infection source control and drotrecogin alfa (activated) administration. CAP, community-acquired pneumonia; H, hour; OD, organ dysfunction; UTI, urinary tract infection.

identifying patients to be treated with drotrecogin alfa (activated). First, severity scores such as Acute Physiology and Chronic Health Evaluation II score have been well correlated with outcome in large groups of patients, but they are of limited help for individuals and cannot be used to guide therapy. Second, after infection source control has been achieved, and failing organs supported, when are the effects of standard care to be expected? In other words, when should a patient, with severe sepsis and receiving appropriate care, be evaluated with regard to whether they should receive drotrecogin alfa (activated) as adjunctive therapy?

The indications for this drug should be guided by the type of infection and expected associated outcome, and the presence of comorbidities, which may influence the natural history of the disease. The indications for drotrecogin alfa (activated) may be divided into 'early' and 'delayed' indications, and are presented in Fig. 1.

## Early indications

The source of infection has been controlled and optimal standard care (including adequate antimicrobials and failing organ support) has been initiated, but the expected effects of this strategy are either delayed (>12–24 hours) or unpredictable. These situations include purpura fulminans, toxic shock syndrome, and meningitis with multiple organ failure. These patients could benefit from infusion of drotrecogin alfa (activated) within 3–6 hours after standard care has been initiated. Clinical evaluation and severity scores, determined at admission, are not able to predict individual outcome in these situations, and delaying the initiation of this adjunctive therapy may lead to irreversible tissue and organ damage. Other patients who are eligible for early treatment with this drug may include a subgroup of patients with severe community-acquired pneumonia admitted to the intensive care unit (i.e. *Streptococcus pneumoniae*). Community-acquired pneumonia with multiple organ failure, including hypotension, oliguria, and metabolic acidosis, are associated with an expected 28-day all-cause mortality in excess of 30%. If the clinical condition is not improving, or it is worsening, within 6–12 hours after adequate care has been provided, then the use of drotrecogin alfa (activated) could be considered.

## Delayed indications or 'resuscitate and reassess'

In various conditions, the infection source control and failing organ support is expected to be associated with a clinical improvement within 6–12 hours. Despite the initial clinical severity and the presence of multiple organ failure, surgery or drainage of the infectious focus is rapidly followed by control of or improvement in organ dysfunction. These situations include ascending cholangitis or pyelonephritis, secondary to obstruction, catheter-related sepsis, and intra-abdominal collections or abscesses drained surgically or percutaneously. If adequate infection source control has been achieved, and organ dysfunction is sustained or worsening in the following 6–12 hours, then drotrecogin alfa (activated) may be indicated as adjunctive therapy for severe sepsis. In patients in whom surgery is required to control infection, a 12-hour delay must be permitted before drug infusion is initiated. This period should be used to re-evaluate the adequacy of the surgical procedure and standard care before considering drotrecogin alfa (activated). This delay should also ensure

that adequate hemostasis has been achieved and should reduce the risk for bleeding during infusion of the drug.

In patients developing nosocomial pneumonia, the indication for the drug should be evaluated within 12 hours after adequate standard care has been initiated. In trauma patients developing nosocomial infections and sepsis-induced organ dysfunction, particular attention must be paid to bleeding risks. If the trauma involved solid organs or pelvis, or if flail chest is present, then the delay between the initial trauma and the development of sepsis must be taken into account before considering the use of drotrecogin alfa (activated). If no bleeding event has occurred during the week following trauma, then the drug may be administered if no other contraindication is present. In situations in which severe sepsis develops during the first few days after trauma, administration of the drug may be hazardous and should not be recommended if solid organs (i.e. liver, spleen) have been fractured or if the trauma was associated with retroperitoneal bleeding.

### 'Too late' indications

Because of the apparent increased benefit of the drug in patients at higher risk for death or with more than two organ failures, some clinicians may be tempted to postpone the consideration of drotrecogin alfa (activated) as adjunctive therapy for severe sepsis. In the PROWESS study, the time window between the development of the first organ dysfunction and the start of the infusion could reach 36 hours, with a mean of 17.5 hours. This implies that the benefit of the drug after this delay has not been evaluated. Prolonging the waiting period between initiating adequate standard care and evaluating whether the drug is indicated is not recommended. Tissue damage and organ dysfunction may be irreversible, and drotrecogin alfa (activated) should not be used as a rescue therapy for severe sepsis when all other strategies have failed to improve the patient's condition.

## Conclusion

Drotrecogin alfa (activated) is the first recognized adjunctive therapy to improve survival in patients with severe sepsis at high risk for death, when added to the best standard care. Because of its anticoagulant properties, the use of this drug is associated with an increased incidence of bleeding events. This reinforces the need to select patients adequately, to weigh risks and benefits of the therapy, and to follow the recommendations when procedures must be performed, in order to minimize the incidence of bleeding complications. The use of the drug should be evaluated when adequate infection source control has been achieved and appropriate supportive care has failed to improve the patient's condition significantly, after a period of time determined by the type of infection and associated comorbidities.

## Competing interests

P-FL is a consultant for Eli Lilly and Company.

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