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Drotrecogin Alfa (Activated)

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Contents

Abstract

▲ Drotrecogin alfa (activated), recombinant human activated protein C, inhibits coagulation and inflammation and promotes fibrinolysis in patients with severe sepsis.

▲ 850 patients with severe sepsis treated with intravenous drotrecogin alfa (activated) 24 μg/kg/h for 96 hours had a significantly greater reduction in 28-day all-cause mortality (24.7%) than 840 placebo recipients (30.8%) in a randomised, double-blind, placebo-controlled study. The drug was associated with a 19.4% reduction in the relative risk of death at 28 days compared with placebo.

▲ Baseline characteristics of and pre-existing conditions in patients with sepsis appeared to have no effect on the efficacy of drotrecogin alfa (activated).

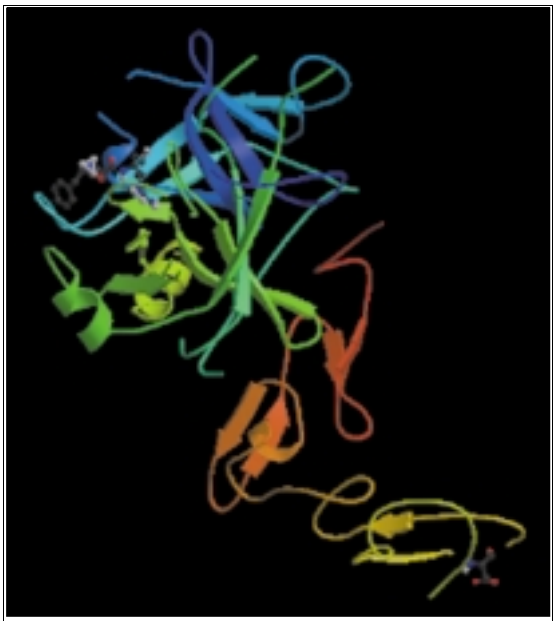
▲ A significantly greater reduction in median percentage change from baseline plasma D-dimer levels (a coagulation marker) was seen with drotrecogin alfa (activated) treatment than with placebo on study days 1 to 7 in patients with severe sepsis. On study days 1, 4, 5, 6 and 7, a significantly greater median reduction in interleukin-6 levels (an inflammation marker) from baseline was seen with drotrecogin alfa (activated) treatment than placebo.

▲ Drotrecogin alfa (activated) was associated with an increased incidence of serious bleeding events during the infusion period [2.4% *vs* 1.0% with placebo; p = 0.024] and the 28-day study period (3.5 *vs* 2.0%; p = 0.06) of the efficacy trial. This increase was primarily related to procedure-related events; there were no significant differences between the treatment groups in nonprocedure-related serious bleeding events. The most frequent site of bleeding was the gastrointestinal tract.

▲ With the exception of bleeding events, there were no clinically significant differences between treatment groups in the efficacy trial in the incidence of adverse events.

▲ Of the 210 deaths in patients with severe sepsis treated with drotrecogin alfa (activated) 24 μg/kg/h in the efficacy trial, four deaths due to haemorrhage and one due to cerebral oedema were possibly related to the study drug.

Features and properties of drotrecogin alfa (activated) [recombinant human activated protein C, rhAPC, activated protein C]	
Indication	
Severe sepsis	
Mechanism of action	
Pharmacological concentration of activated protein C	Antithrombotic, anti-inflammatory and profibrinolytic properties
Dosage and administration	
Dosage	24 μg/kg/h
Route of administration	Intravenous
Duration of administration	Continuous infusion for 96h
Pharmacokinetic profile (24 μg/kg/h in patients with severe sepsis)	
Median plasma concentration at steady state	44.9 μg/L
Median plasma clearance	40.1 L/h
Volume of distribution	17.6L
Serious adverse events	
Bleeding	



Human activated protein C

A systemic inflammatory and procoagulant response to infection may result in sepsis and, if associated with acute organ dysfunction, severe sepsis.[1,2] Recent estimates indicate approximately 750 000 patients with severe sepsis in the US every year with a mortality rate approaching 30% despite advances in supportive care.[3] In Europe, approximately 146 000 deaths annually are associated with severe sepsis.[4] The aging and increasingly immunocompromised population, increasing use of invasive devices and procedures, and increased rate of antibacterial resistance have led to an increase in the incidence of this syndrome.[5]

Severe sepsis involves a complex cascade of events associated with three integrated components: inflammation, coagulation and impaired fibrinolysis.[6-12] Infection leads to the stimulation of proinflammatory cytokines resulting in endothelial dysfunction and changes in the thrombogenicity of the endothelium of the vascular bed.[9-11,13] This triggers coagulation and thrombin formation which, in turn, amplify inflammation and coagulation, continuing the cycle of events.[10-12] The normal fibrinolytic response is decreased, and this contributes to the development of disseminated intravascular coagulation (DIC) and microvascular thrombosis.[6,10,12] Although the underlying infectious process may be controlled, coagulopathy and DIC can become increasingly more severe, which may lead to acute multiple organ dysfunction and death.[8,10,11]

Endogenous protein C is converted to activated protein C (see structure[14]), a modulator of inflammation, thrombosis and fibronolysis, in an attempt to restore homeostasis in patients with severe sepsis.[9-11,15] However, endogenous protein C is rapidly depleted and levels of protein C may be deficient preceding the clinical diagnosis of sepsis and may remain depleted throughout the course of the syndrome.[16-19] A deficiency of protein C is associated with increased morbidity and mortality and is seen in the majority of patients with severe sepsis.[18,20,21]

The presentation, type of causative pathogen, course and treatment of the illness is similar in adult and paediatric patients.[22] Symptoms that indicate a systemic inflammatory response, leading to coagulopathy, hypotension and ultimately organ failure and death, are seen in both adults and children. In children, age sensitive adjustments in vital signs such as heart and respiratory rate are required in the diagnostic criteria. Although the absolute amount of some blood factors differs in adults and children, baseline illness characteristics and abnormality of biomarker levels (e.g. D-dimer, protein C and antithrombin levels) are comparable.

Medical and surgical interventions to normalise physiology and eliminate infection are standard management approaches for patients with severe sepsis.[2,23-25] Antibacterial drugs, although essential, are not sufficient for the treatment of severe sepsis[2,26] and may even precipitate or accelerate the sepsis cascade by the release of microbial products.[27-29] Prompt antibacterial therapy for the causative pathogen is necessary; however, it is not received by ≈10% of patients.[2,30] Treatment is hampered by antibacterial resistant organisms, polymicrobial infections and occult infection

sites,[2,23] and by delayed diagnosis and inappropriate antibacterial therapy.[31]

Increased understanding of the pathogenesis of sepsis has led to numerous investigational approaches for the treatment of this serious condition [e.g. bacterial modulators, anticytokines, anti-inflammatory agents, nitric oxide inhibitors and haemostatic agents (including recombinant human activated protein C)]. These investigations have been previously reviewed.[5,32-34]

Drotrecogin alfa (activated) has been developed for the treatment of severe sepsis and its efficacy and tolerability have been evaluated in two randomised, double-blind, placebo-controlled multicentre clinical trials in adults.[20,35] The tolerability, pharmacokinetics and pharmacodynamics of the agent have been investigated in a noncomparative, multicentre trial in paediatric patients with severe sepsis. The results of the tolerability[35] and efficacy trials[20] have been published; however, most of the information in this article has been derived from the trials reported in the manufacturer's briefing document for drotrecogin alfa (activated).[22] Drotrecogin alfa (activated) is administered as a continuous intravenous infusion.

1. Pharmacodynamic Profile

Mechanism of Action

• Drotrecogin alfa (activated) acts in a similar manner as endogenous activated protein C, a serine protease.[15,22] It slows the coagulation process in the microvasculature by proteolytic inhibition of coagulation factors Va and VIIIa.[10] It reduces inflammation by indirectly inhibiting thrombin-mediated inflammatory activities[11] and perhaps by directly suppressing inflammatory cytokine production.[36,37] Fibrinolysis is enhanced by drotrecogin alfa (activated) by inhibiting thrombin production, thrombin-mediated inflammation, plasminogen activator inhibitor 1 (PAI-1) inhibition and release and thrombin-activatable fibrinolysis inhibitor activation, and by acceleration of clot lysis by tissue plasminogen activator.[8,10,11,15,16]

• The binding of endogenous protein C to thrombomodulin and endothelial protein C receptor is required to activate the protein.[11,38-40] In severe sepsis, the conversion of protein C to activated protein C may be impaired by generalised endothelial dysfunction and down-regulation of thrombomodulin by inflammatory cytokines; therefore, administration of activated protein C [drotrecogin alfa (activated)], may be more effective than administration of protein C.[19,41]

Animal Studies

• In a baboon model of *Escherichia coli* sepsis, all of the animals receiving high-concentration infusions of activated protein C plus a lethal concentration of *E. coli* survived, whereas all the control animals receiving the same infusions of *E. coli* died of sepsis-related complications.[42]

• The antithrombotic, anticoagulant and profibrinolytic activity of activated protein C has been demonstrated in experimental animal models. Fibrinolysis was enhanced by activated protein C through a direct inhibitory effect on PAI-1 in rats with DIC.[43] Activated protein C plus urokinase had additive effects in increasing clot lysis[44] and in preventing the accumulation of fibrin and platelets in animal models.[45]

• Platelet thrombosis was inhibited by infusion of activated protein C in baboon,[46] canine[47] and rabbit models of acute arterial thrombosis. [48] Activated protein C increased prothrombin time (PT) in rabbits with meningococcal endotoxin shock[49] and activated partial thromboplastin time (aPTT) in a canine model of thrombosis.[47] In *in vivo* animal studies, little or no prolongation of bleeding time was detected in association with activated protein C administration.[43,46,47,50,51]

Effects on Coagulation Markers in Patients with Sepsis

Change over time and percentage change from baseline in plasma D-dimer levels (normal range 0.0 to 0.39 mg/L) were measured in patients who participated in the two randomised, double-blind,

placebo-controlled trials of drotrecogin alfa (activated) [section 3].[20,22] D-dimer levels indicate coagulation has occurred in conjunction with fibrinolysis activation, forming fibrin breakdown products.[52] A reduction in plasma D-dimer levels, therefore, is evidence of a reduction in the procoagulant effects of sepsis. Other biomarkers of coagulation, thrombin generation and fibrinolysis, were also measured.

- During the 48- or 96-hour infusion of drotrecogin alfa (activated) in the dose-ranging trial (section 3),[22] the median percentage decrease in baseline D-dimer levels was greater in the drotrecogin alfa (activated) 24 and 30 μg/kg/h recipients than in the recipients of the lower doses of drotrecogin alfa (activated) or placebo ($p \leq 0.05$ among treatment groups at several timepoints).[22]

- At the end of infusion, a statistically significant ($p \leq 0.001$) dose response was seen in median changes in D-dimer levels of, respectively, –8.9, 4.4, –27.6, –45.9 and –0.4% from baseline for the drotrecogin alfa (activated) 12 μg/kg/h (n = 21), 18 μg/kg/h (n = 21), 24 μg/kg/h (n = 22), 30 μg/kg/h (n = 12) and placebo (n = 35) recipients (combination of 48- and 96-hour infusion duration groups).[22]

- In patients with severe sepsis in the randomised, placebo-controlled efficacy trial (section 3), recipients of drotrecogin alfa (activated) 24 μg/kg/h for 96 hours had a significantly greater reduction in median plasma D-dimer levels than placebo recipients on study days 1 to 7 ($p \leq 0.01$ for all evaluation timepoints; figure 1).[22] Baseline values were obtained for >90% of patients in the efficacy trial;[53] median baseline levels of D-dimer were 4.22 and 4.15 mg/L in the drotrecogin alfa (activated) 24 μg/kg/h for 96 hours (n = 792) and placebo recipients (n = 758), respectively.[20]

- Longer periods of infusion of drotrecogin alfa (activated) may need evaluation, as D-dimer levels rose after completion of the 96-hour infusion, indicating incomplete resolution of the procoagulant state.[20] Prothrombin F1.2 and thrombin-antithrombin complex levels decreased to a significantly greater extent in patients treated with drotrecogin alfa (activated) than in the placebo group on study days 1, 2 and 4 ($p < 0.001$).[22]

- 87.6% of patients with severe sepsis in the efficacy trial (section 3) had deficient baseline plasma protein C levels as defined by <81% plasma protein C activity (normal range 81 to 173%).[20,22] Although both treatment groups displayed increases from baseline in endogenous protein C levels, the increases were significantly greater in the drotrecogin alfa (activated) than in the placebo recipients over study days 1 to 7 ($p < 0.001$ on days 1 to 6; $p \leq 0.003$ on day 7).[22] Nevertheless, even with a median percentage increase of 43% in protein C levels, 57% of survivors receiving drotrecogin alfa (activated) 24 μg/kg/h remained protein C deficient on day 4 of the study.

- Median percentage increases from baseline in aPTT were greater in patients with severe sepsis treated with drotrecogin alfa (activated) than in those receiving placebo on study days 1 to 4 ($p < 0.001$ on each day) of the efficacy trial (section 3).[22] On study day 1, the median aPTT increase was ≈7 seconds, and aPTT decreased thereafter. On study days 5 to 7, there were no significant differences between the treatment groups in aPTT. This

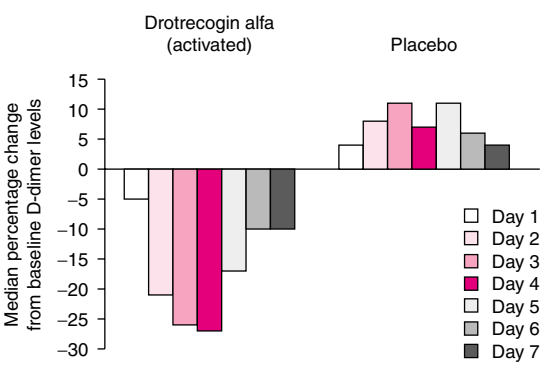


Fig. 1. Change from baseline in plasma D-dimer levels during treatment with drotrecogin alfa (activated). Median percentage change from baseline in D-dimer levels on study days 1 to 7 in patients with severe sepsis receiving intravenous drotrecogin alfa (activated) 24 mg/kg/h (n = 770) or placebo (n = 729) for 96 hours in a randomised, double-blind, multicentre trial (p â 0.01 vs placebo for each day).[22]

rise of aPTT during drotrecogin alfa (activated) administration is due to the anticoagulant pharmacodynamic effects of the drug. Improvement in coagulopathy and decreased consumption of clotting factors are indicated by the subsequent fall of aPTT.

• In healthy volunteers, whole blood aPTT prolongation strongly correlated with drotrecogin alfa (activated) concentrations.[22] The prolongation of aPTT may vary during infusion of the agent; therefore, the status of coagulopathy in the patient should not be monitored by aPTT during infusion of the agent.[54]

• In contrast, PT weakly correlated with drotrecogin alfa (activated) concentrations with differences of <3 seconds from baseline in healthy volunteers.[22] This minimal effect on PT is consistent with the anticoagulant pharmacodynamic effect of the agent;[22] therefore, PT may be used to assess the status of coagulopathy in patients with severe sepsis during drotrecogin alfa (activated) infusion.[54] Between the two groups in the efficacy trial, the magnitude of difference in median PTs was about 1 second.[22]

• Paediatric patients [0 to <1 year (n = 16), 1 to <8 years (n = 25) and 8 to <18 years (n = 15 or 16)] with severe sepsis treated with drotrecogin alfa (activated) 24 μg/kg/h for 96 hours showed similar changes in protein C activity, D-dimer and antithrombin activity levels in the nonblind trial to those observed in adults in the efficacy trial (section 3).[22]

Effects on Inflammation Markers in Patients with Sepsis

Levels of serum interleukin-6 (IL-6), a proinflammatory cytokine released during the systemic inflammatory response, were measured in the two randomised, double-blind, placebo-controlled clinical trials (section 3).[20,35] Normal levels of this inflammation marker range from 0.38 to 10.09 ng/L[20] and the risk of mortality increases with the increased level of IL-6 at the presentation of sepsis.[22] In patients with severe sepsis, a more rapid decrease in IL-6 levels with active treatment than with placebo is indicative of anti-inflammatory activity.

• During the 48-hour infusion of drotrecogin alfa (activated) in the dose-ranging trial (section 3), the median percentage decrease in IL-6 levels was greater in the drotrecogin alfa (activated) 30 mg/kg/h group on days 1 and 3 ($p = 0.04$ and $p = 0.02$, respectively) than in the other treatment groups.[22] No significant differences in IL-6 levels were observed during the 96-hour infusion. At the end of the infusion, a statistically significant dose response ($p = 0.021$) was demonstrated by the median percentage changes in IL-6 levels of –42.5, –57.4, –68.8, –86.4 and –45.9% from baseline for infusions of drotrecogin alfa (activated) 12, 18, 24 and 30 ug/kg/h and placebo, respectively (combination of the 48- and 96-hour infusion duration groups).

• In the randomised, double-blind, placebo-controlled efficacy trial (section 3), median IL-6 levels decreased from baseline significantly more rapidly with drotrecogin alfa (activated) 24 μg/kg/h for 96 hours than placebo on study day 1 ($p = 0.01$) and on days 4 to 7 ($p = 0.02$) in patients with severe sepsis (figure 2).[22] At entry into the study, IL-6 levels were elevated in 98.5% of patients with severe sepsis for whom values were obtained with median baseline levels of 497 and 484 ng/L in the drotrecogin alfa (activated) [n = 827] and placebo (n = 808) treatment groups, respectively.[20,22]

2. Pharmacokinetic Profile

Eight phase I studies evaluated the pharmacokinetics of intravenous drotrecogin alfa (activated) in healthy male and female individuals, healthy individuals pretreated with aspirin, women with low serum estrogen levels and patients with end-stage renal impairment undergoing dialysis.[22] In general, there were no significant differences in the pharmacokinetic profile of drotrecogin alfa (activated) between healthy individuals and those in other groups. Unless otherwise noted, values pertain to a homogeneous group of healthy volunteers

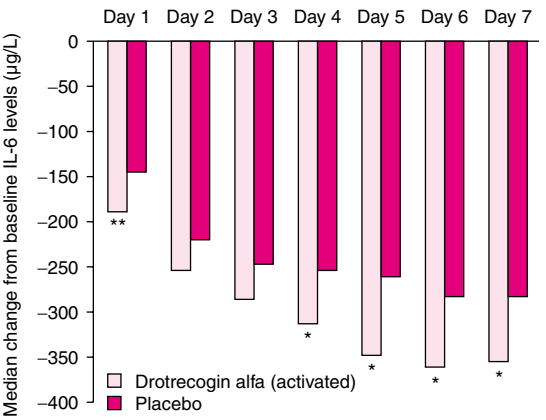


Fig. 2. Decrease in serum interleukin-6 (IL-6) levels during treatment with drotrecogin alfa (activated). Median change from baseline in IL-6 levels on study days 1 to 7 in patients with severe sepsis who received intravenous drotrecogin alfa (activated) 24 µg/kg/h (n = 803) or placebo (n = 774) for 96 hours in a randomised, double-blind, multicentre trial. * p = 0.02, ** p = 0.01 *vs* placebo.[22]

receiving infusions of drotrecogin alfa (activated) at a rate of 24 µg/kg/h for 24 hours (n = 78 doses).

Plasma concentrations at steady state (C^{ss}) and plasma clearance (CL) of drotrecogin alfa (activated) in patients with severe sepsis were evaluated in the phase II and III studies (section 3).[22] Preliminary pharmacokinetic data are available for paediatric patients (aged 1 day to 17 years) with severe sepsis who received drotrecogin alfa (activated) 24 µg/kg/h for 96 hours in an ongoing nonblind, noncomparative, multicentre trial.

- Because of its short hybrid plasma half-life ($t_{½}$) of 0.69 hours, drotrecogin alfa (activated) rapidly attains C^{ss} during constant-rate infusion in healthy volunteers.[22] Seventy-nine percent of the area under the plasma concentration-time curve is accounted for by the rapid initial half-life phase ($t_{½\alpha}$) of 13 minutes. The time involved to move from 90 to 100% of C^{ss} is controlled by the second phase ($t_{½\beta}$) of 1.6 hours. Within 40 minutes of starting a constant-rate infusion of drotrecogin alfa (activated), approximately 75% of C^{ss} is reached; within 1.8 hours, 90% of C^{ss} is reached.

- C^{ss} of drotrecogin alfa (activated) is proportional to infusion rate with an expected C^{ss} of 72.4 µg/L at an infusion rate of 24 µg/kg/h in healthy volunteers.[22] However, in patients with severe sepsis treated with drotrecogin alfa (activated) 24 µg/kg/h for 96 hours in the efficacy study (n = 843 samples for 326 patients), median C^{ss} was 44.9 µg/L.[22]

- The small volume of distribution of drotrecogin alfa (activated) at steady state (17.6L) approximates extracellular volume and is attributable to its high molecular weight and resultant inability to penetrate membranes.[22]

- The infusion rate or infusion duration of drotrecogin alfa (activated) does not alter its CL of 26.0 L/h in healthy volunteers. However, median CL of the drug was 40.1 L/h in patients with severe sepsis in the efficacy study. This increase in CL results in the lower C^{ss} seen in patients with severe sepsis than in healthy volunteers.

- In healthy volunteers, drotrecogin alfa (activated) is inhibited by several plasma serine protease inhibitors (e.g. protein C inhibitor, α_1-antitrypsin, α_2-antiplasmin, PAI-1) resulting in rapid elimination and a short $t_{½\alpha}$ (13 minutes).[19,55-57] The time required to eliminate the final 21% of drotrecogin alfa (activated) infused during treatment is governed by the $t_{½\beta}$ of 1.6 hours.[22] Within 40 minutes, 1.8 hours and 4.5 hours of stopping an infusion, approximately 75, 90 and 97%, respectively, of the drug is eliminated.

- Elimination of drotrecogin alfa (activated) in patients with severe sepsis was rapid and consistent with the $t_{½}$ in healthy individuals.[22]

- CL of drotrecogin alfa (activated) increases with increased bodyweight (section 5).[22] Covariates, including age, sex, estrogen status, disease severity or heparin coadministration, or multiple covariates did not alter CL of drotrecogin alfa (activated) to a clinically significant degree.

- The magnitude of difference in CL between patients with severe sepsis with and without renal or hepatic dysfunction was within the interquartile range of the observed weight-adjusted CL in all

patients in the efficacy trial (section 5).[22] Weight-adjusted CL of drotrecogin alfa (activated) was 23.7% lower in renally impaired patients on dialysis [Cockroft-Gault creatinine clearance (CL_{CR}) of <1.2 L/h (20 ml/min)] with severe sepsis than in patients with CL_{CR} >3.0 L/h (50 ml/min). Patients with baseline levels of AST or ALT >3 times the upper limit of normal had weight-adjusted CL of drotrecogin alfa (activated) that were 23.7 and 26.7% lower, respectively, than patients with normal baseline levels.

- The pharmacokinetics of drotrecogin alfa (activated) are not significantly influenced by baseline plasma levels of endogenous activated protein C in healthy individuals or patients with severe sepsis (section 5).[22] Similarly, baseline levels of coagulation markers [haematological Sequential Organ Failure Assessment (SOFA) scores, PT and whole blood aPTT] and IL-6 do not clinically affect the pharmacokinetic profile (section 5).

- Preliminary pharmacokinetic data in paediatric patients with severe sepsis treated with drotrecogin alfa (activated) are consistent with those in adult patients with severe sepsis.[22] In 43 paediatric patients (newborns to <18 years) treated with drotrecogin alfa (activated) 24 μg/kg/h for 96 hours, C^{ss} was 66.6 μg/L, CL was 0.49 L/h/kg and $t_{½}$ was 0.91h.

3. Therapeutic Trials

The efficacy of intravenous drotrecogin alfa (activated) in reducing the mortality rate of patients with severe sepsis has been evaluated in two randomised, double-blind, placebo-controlled, multicentre studies.[20,22,35] Based on the results of the dose-ranging phase II trial,[22,35] which showed trends towards improvements in mortality in patients treated with drotrecogin alfa (activated) [12 to 30 μg/kg/h for 48 or 96 hours], the large, adequately powered phase III efficacy trial was initiated.[20,22]

Adult patients with severe sepsis[1] were eligible for enrolment in the two trials.[20,22,35] Severe sepsis was defined as suspected or proven infection and, within a 24-hour period, three or more signs of the systemic inflammation response syndrome (SIRS: core temperature ≥38°C or ≤36°C, heart rate ≥90 beats/min, respiratory rate ≥20 breaths/min or arterial carbon dioxide tension ≤32mm Hg or mechanical ventilation for an acute process, white cell count $\geq 12 \times 10^9$/L or $\leq 4 \times 10^9$/L) and the sepsis-induced dysfunction of at least one organ or system.[20,22]

Patients were excluded from the studies if they had a condition or had taken medication which increased the risk of bleeding (with the exception of prophylactic heparin treatment <15 units/kg/h), chronic renal failure requiring dialysis, thrombocytopenia (platelet count $< 30 \times 10^9$/L), or a known hypercoagulable condition or if death was perceived to be going to occur within 28 days because of a pre-existing, non-sepsis related medical condition.[20,22] After patients met the inclusion criteria, treatment began within 24 hours in the phase III trial or 36 hours in the phase II trial.[22]

A nonblind trial in paediatric patients with severe sepsis determined the recommended infusion rate of the agent for these patients.[22] The efficacy of drotrecogin alfa (activated) in paediatric patients may be extrapolated from the results of the efficacy trial in adults. Inclusion criteria were more restrictive than those used in the adult studies and were age-specific for SIRS and organ failure. Consistent with the higher incidence of meningitis in children, the CNS was the site of infection in 16.9% of the paediatric patients.[22]

Dose-Ranging Trial

In the dose-ranging trial, 131 patients with severe sepsis were randomised to receive continuous infusions of low-dose drotrecogin alfa (activated) [12 or 18 μg/kg/h; n = 51] or high-dose drotrecogin alfa (activated) [24 or 30 μg/kg/h; n = 39] or placebo (n = 41) for 48 or 96 hours.[35] At enrolment, all patients had D-dimer levels above the upper limit of normal and 92% of the patients were protein C deficient.[35] The effect of drotrecogin alfa (activated) on coagulation markers was used to de-

termine the effective infusion rate and infusion duration (section 1).

- The effective infusion rate and duration for use of drotrecogin alfa (activated) in patients with severe sepsis was determined to be 24 μg/kg/h for 96 hours based on reductions in plasma D-dimer levels (section 1).[22,35] A large number of patients receiving drotrecogin alfa (activated) 30 μg/kg/h required a decrease in infusion rate; therefore, this infusion rate was not studied for longer than a 48-hour infusion duration.

- Patients with severe sepsis receiving high-dose drotrecogin alfa (activated) infusions exhibited a trend in reduction in the incidence of mortality and an improvement in the number of days free of SIRS, ventilator usage, shock, and stays in the intensive care unit and hospital.[35] The observed 28-day mortality rate was 21% in the high drotrecogin alfa (activated) dose group, 35% in the low-dose group and 34% in the placebo group. Compared with the results in the placebo recipients, the 40% relative risk reduction in 28 day all-cause mortality in the high drotrecogin alfa (activated) dose group and 15% reduction in all drotrecogin alfa (activated) groups were not statistically significant.[22,35]

Efficacy Trial

The second interim analysis of the randomised, placebo-controlled, double-blind efficacy study revealed a significantly greater reduction in the 28-day mortality rate of 768 patients treated with drotrecogin alfa (activated) 24 μg/kg/h for 96 hours (25.0%) than in 752 patients receiving placebo (31.4%; p = 0.0071); therefore, enrolment in the trial was suspended because it had met the a priori criteria for reduced mortality.[20,22]

Death from any cause was the primary endpoint of the trial and was assessed 28 days after the initiation of treatment.[20] Analysis of data included all patients who received the infusion for any length of time and was founded on three baseline covariates: disease severity, age (<60 or ≥60 years), and plasma protein C activity level.[20,22] The Acute Physiology and Chronic Health Evaluation II (APACHE II) quartile defined the severity of disease (3 to 19, 20 to 24, 25 to 29, 30 to 53) with higher scores indicative of more severe disease.

Data from patients with severe sepsis who were enrolled before second interim analysis was completed are included in the results for a total study population of 1690.[20,22] Similar baseline demographic and disease severity characteristics were seen in the placebo (n = 840) and drotrecogin alfa (activated) 24 μg/kg/h for 96 hours (n = 850) treatment groups. For example, in the drotrecogin alfa (activated) and placebo groups, mean APACHE II scores were 24.6 and 25.0, respectively, the percentage of patients aged ≥60 years were 55.9 and 56.4%, respectively, and protein C was deficient in 83.4 and 79.8% of patients, respectively. In both treatment groups, approximately 75% of patients had two or more organ failures.

Within 24 hours of the diagnosis of severe sepsis, 89.3% of patients in the drotrecogin alfa (activated) group and 89.1% of patients in the placebo group received appropriate antibacterial therapy, which was continued for at least 5 days or until death.[53] The most frequent sites of infection were the lungs (53.6% in each group) and abdomen [19.9% in the placebo group, 20.0% in the drotrecogin alfa (activated) group]. Likewise, within each group and between the two groups, the incidence of Gram-positive and Gram-negative organism cultures was similar. At least 90% of the intended infusion was received by 81.8% of the drotrecogin alfa (activated) group and 82.4% of the placebo group.[20]

- In patients with severe sepsis, a significantly greater reduction in 28-day all-cause mortality was seen in 850 drotrecogin alfa (activated) recipients (24.7%; n = 210) than in 840 placebo (30.8%; n = 259) recipients [absolute reduction in the risk of death 6.1%; 95% confidence interval (CI), 1.9 to 10.4%; figure 3].[20] In comparison with placebo, treatment with drotrecogin alfa (activated) produced a 19.4% reduction in the relative risk of death at 28 days (95% CI, 6.6 to 30.5%)[20] and a 27.6% reduction in the odds of death at 28 days (p = 0.005).[22]

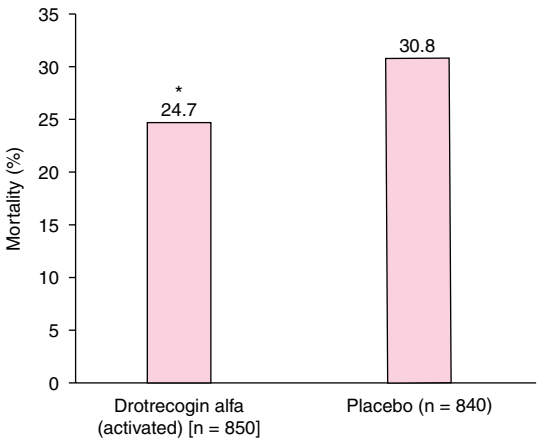


Fig. 3. Effect of drotrecogin alfa (activated) on mortality in patients with severe sepsis. All-cause mortality rates at 28 days in patients with severe sepsis who received intravenous drotrecogin alfa (activated) 24 μg/kg/h (n = 850) or placebo (n = 840) for 96 hours in a randomised, double-blind, multicentre trial. * p = 0.005 *vs* placebo.[22]

• This equates to a 38.1% increase in the odds of 28-day survival compared with the placebo group.[22] In other words, for every 16 patients treated with drotrecogin alfa (activated) 24 μg/kg/h for 96 hours in the population studied, one death would be prevented in the first 28 days.[20] To put this in perspective, a widely accepted standard of effective clinical practice is the treatment of 56 patients for intravenous thrombolysis in acute myocardial infarction to prevent one death within 35 days.[58,59]

• Analysis of >70 subgroups of patients stratified according to baseline characteristics [e.g. demographics (including age), disease severity, type and site of infection, and number of dysfunctional organs or systems] showed a consistent beneficial effect of treatment with drotrecogin alfa (activated) with similar p-values, relative risks and odds ratios compared with the primary analysis.[20,22,53] In patients treated with drotrecogin alfa (activated), the relative reduction in the risk of death was 42% (p = 0.06) in 90 patients who did not have a deficiency of protein C and 20% (p = 0.009) in 709 patients with a deficiency of protein C.[20]

• The relative reduction in the risk of death by 28 days in recipients of drotrecogin alfa (activated) was similar in patients with or without prior or pre-existing conditions (e.g. hypertension, myocardial infarction, diabetes mellitus, or chronic obstructive pulmonary disease).[20,53] In comparison with placebo, the overall relative reduction in the risk of death by 28 days was 19.4% (p = 0.005) in patients with severe sepsis treated with drotrecogin alfa (activated); the reduction in patients with severe sepsis plus congestive cardiomyopathy was 18.9% (p = 0.008), cancer 19.8% (p = 0.006), mechanical ventilation 18.5% (p = 0.009), shock 19.8% (p = 0.006) and the use of vasopressors 18.7% (p = 0.008).

• A significantly greater increase in the number of days alive without the need for vasopressor support was seen in drotrecogin alfa (activated) recipients compared with placebo recipients (20.1 *vs* 18.8 days; p = 0.014).[22,60] Likewise, drotrecogin alfa (activated) decreased the number of mechanical ventilator-free days by a significantly greater extent than placebo (14.3 *vs* 13.2 days; p = 0.049). Among survivors, the differences in total or organ-specific SOFA scores (mean and cumulative) were not significant between treatment arms.[60]

• The differences in the number of SIRS-, intensive care unit (ICU)- or hospital-free days were not statistically significant between the two treatment groups.[22] However, compared with placebo recipients, a slightly higher percentage of drotrecogin alfa (activated) recipients were alive and discharged from hospital or alive and out of the ICU from days 7 to 28 of the study.

• As measured using SOFA scores over days 1 to 28, drotrecogin alfa (activated) recipients had significantly lower (better) mean cardiovascular and respiratory morbidity (p = 0.009 and 0.023, respectively) compared with those of placebo recipients.[22] In addition, the time to the first resolution of cardiovascular and respiratory organ failure (days 1 to 7) was significantly more rapid with

drotrecogin alfa (activated) than with placebo treatment (p = 0.009 for both organ failures).

• Based on patient location (e.g. ICU, hospital, home) and activities of daily living (ADL) scores on study day 28, functional recovery was similar in the 640 survivors treated with drotrecogin alfa (activated) compared with the 581 survivors who received placebo.[22,60] On day 28 of the study, a similar proportion of survivors in each treatment arm were at home or were considered to be independent for each component of the ADL assessment.

4. Tolerability

• In the randomised, double-blind, placebo-controlled efficacy study (section 3), similar numbers of patients with severe sepsis receiving drotrecogin alfa (activated) 24 μg/kg/h (n = 850) or placebo (n = 840) for 96 hours had experienced at least one serious adverse event during the infusion period (6.8 and 6.5%, respectively) and during the 28-day study period (12.5 and 12.1%, respectively) [figure 4].[20,22] Except for bleeding adverse events, there were no clinically significant differences between treatment groups in the incidence of any adverse event of any degree of severity.[22,54]

• During the infusion period, the incidence of a bleeding event reported as a serious adverse event was more frequent in the drotrecogin alfa (activated) treatment group than in the placebo group (2.4 *vs* 1.0%; p = 0.024).[20,22] The definition of a serious bleeding event was any intracranial haemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of three units of packed red cells on 2 consecutive days. Gastrointestinal bleeding was the most frequently reported adverse bleeding event in both groups.

• During the 28-day study period, a bleeding event reported as a serious adverse event was seen in 30 drotrecogin alfa (activated) 24 μg/kg/h recipients (3.5%) compared with 17 placebo recipients (2.0%; p = 0.06) [figure 4].[20,22,54] The most frequent site of serious bleeding (1.1% of patients in each treatment group) was the gastrointestinal tract.[20]

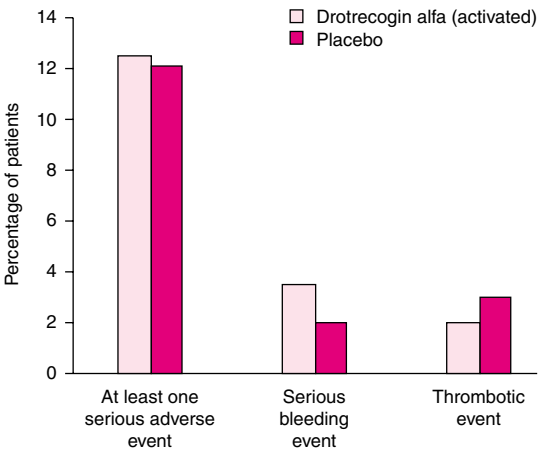


Fig. 4. Incidence of serious adverse events with drotrecogin alfa (activated). Serious adverse events during the 28-day study period experienced by patients with severe sepsis treated with intravenous drotrecogin alfa (activated) 24 μg/kg/h (n = 850) or placebo (n = 840) for 96 hours in a randomised, double-blind, multicentre trial. [20,22] Serious bleeding events were defined as any intracranial haemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of three units of packed red cells on 2 consecutive days.

• During the infusion and 28-day study periods, the increased proportion of patients with at least one serious bleeding event in the drotrecogin alfa (activated) group was associated with procedure-related events (e.g. instrumentation of a major blood vessel or highly vascular organ).[22] There were no significant differences between the treatment groups in serious bleeding events that were not procedure-related. Serious bleeding occurred mainly in patients with an identifiable predisposition to bleeding [e.g. gastrointestinal bleeding, aPTT >120 seconds, prolonged PT (international normalised ratio >3.0), or traumatic injury of a blood vessel or of a highly vascular organ] in both treatment groups.[20]

• During the infusion period and the 28-day study period, at least one treatment-emergent bleeding

event of any degree was experienced by significantly more drotrecogin alfa (activated) recipients than placebo recipients (18.8 *vs* 10.8% and 24.9 *vs* 17.7%, respectively; $p < 0.001$ for both).[22] The majority of these events were mild or moderate in severity for both groups. The most commonly reported bleeding events were cutaneous and gastrointestinal tract bleeding.

• Treatment-emergent adverse events with any degree of severity were reported in 68.6 and 81.8% of patients treated with drotrecogin alfa (activated) during the 96-hour infusion period and the 28-day period, respectively.[22] Similarly, 65.0 and 77.7% of placebo recipients experienced at least one adverse event during the infusion and study period, respectively.

• Patients with severe sepsis receiving drotrecogin alfa (activated) permanently discontinued treatment because of an adverse event by a significantly greater extent (6.4%) than patients receiving placebo (3.6%) in the efficacy trial ($p = 0.009$).[22] The most frequently reported adverse event that led to permanent withdrawal of the infusion was gastrointestinal haemorrhage [1.3% of drotrecogin alfa (activated) recipients *vs* 0.6% of placebo recipients; $p = 0.138$].

• There was no apparent difference in treatment effect on the relative risk or odds of treatment-emergent bleeding events of any severity across the 70 investigated subgroups of patients.[22] However, a robust assessment of serious bleeding risk by subgroup is precluded by the small absolute increase in the number of patients ($n = 13$) who experienced a serious bleeding event.

• Of the 210 deaths in patients with severe sepsis treated with drotrecogin alfa (activated) 24 μg/kg/h in the efficacy trial, five deaths were stated by the investigators to be possibly related to the study drug and four of these five were due to haemorrhage.[22] One additional death in a patient who experienced cerebral oedema was considered possibly related to drotrecogin alfa (activated) treatment. The remaining two haemorrhagic deaths in the drotrecogin alfa (activated) recipients, as well as two haemorrhagic deaths in the placebo group, were not considered by the investigators to be related to the bleeding event. Of the 259 deaths in the placebo group, the death of a patient who developed cerebral infarcts was possibly related to placebo treatment.

• The risk of serious bleeding did not increase with coadministration of a prophylactic dose of heparin as evidenced by the similar incidence of serious bleeding in patients who received drotrecogin alfa (activated) alone and those who also received heparin during the 96-hour infusion period (2.4 *vs* 2.3%) and 28-day study period (3.7 *vs* 3.5%) of the efficacy trial.[20,22] Therapeutic concentrations of other anticoagulants and fibrinolytic agents were not allowed during the trial.[22]

• In the efficacy trial, administration of drotrecogin alfa (activated) was not associated with an increase in the incidence of thrombotic events, which occurred in 17 patients (2.0%) in the drotrecogin alfa (activated) group and 25 patients (3.0%) in the placebo group (figure 4).[20,22] The development of antibodies against endogenous activated protein C may be indicated by the occurrence of thrombotic events.[22,61] Likewise, immunogenicity testing did not detect the presence of neutralising antibodies against activated protein C in any patient.[20]

• The incidence of new infections did not increase with the administration of drotrecogin alfa (activated).[20,22] 25.5 and 25.1% of the drotrecogin alfa (activated) and placebo recipients, respectively, had new infections during the efficacy trial.

• Assessments of organ dysfunction, vital signs, serum chemical data or haematological data in the efficacy trial did not reveal any additional safety concerns associated with administration of drotrecogin alfa (activated).[20]

• In the noncomparative, multicentre 14-day tolerability trial of drotrecogin alfa (activated) 24 μg/kg/h given for 96 hours to 83 paediatric patients with severe sepsis (aged newborn to <18 years), one of the 20 serious adverse events reported was considered to be possibly related to drotrecogin alfa (activated) and resulted in the death of the pa-

tient from cerebral haemorrhage and oedema.[22] Including this event, four patients (4.8%) had a serious bleeding event including nasopharyngeal haemorrhage, intracranial haemorrhage and petechial haemorrhage. The 14-day mortality rate was 9.6%; the other seven deaths reported were due to sepsis-related complications.

- At least one treatment-emergent adverse event was experienced by 94.0% of paediatric patients.[22] Fever (19.3%), generalised oedema (15.7%), agitation, lung oedema and thrombocytopenia (14.5% for each) were the most frequent adverse events reported.

5. Dosage and Administration

Drotreogin alfa (activated) should be administered by continuous intravenous infusion at a rate of 24μg/kg/h for a total infusion duration of 96 hours.[54] Infusion rates should be adjusted for bodyweight.[22,54] However, no adjustments are required for age, gender, estrogen status, disease severity, prophylactic heparin coadministration, renal or hepatic dysfunction, baseline haematological SOFA scores, or baseline plasma endogenous activated protein C, PT, whole blood aPPT or IL-6 levels (section 2).[22] The drug is contraindicated in patients with clinical conditions in which bleeding could be associated with significant morbidity or a high risk of death (e.g. active internal bleeding, recent haemorrhagic stroke, recent intracranial or intraspinal surgery, recent 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).

6. Drotrecogin Alfa (Activated): Current Status

Drotrecogin alfa (activated) is a recombinant form of human activated protein C approved in the US for the treatment of adult patients with sepsis associated with acute organ dysfunction (severe sepsis) at high risk of death.[54] Trials to date have demonstrated clinical efficacy with intravenous drotrecogin alfa (activated) 24 μg/kg/h for 96 hours in the reduction of mortality in adult patients with severe sepsis.[20,35]

Further data on the efficacy and tolerability of drotrecogin alfa (activated) in paediatric and adult patients with severe sepsis are being obtained in ongoing noncomparative, multicentre trials and in a compassionate use programme.[22]

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