REVIEW ARTICLE

Drug Safety 2007; 30 (11): 995-1010
0114-5916/07/0011-0995/$44.95/0



# Benefit-Risk Assessment of Drotrecogin Alfa (Activated) in the Treatment of Sepsis

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## Contents



## Abstract

Severe sepsis is a common cause of death in critically ill patients. Several mechanisms have been implicated in the development of organ dysfunction in patients with severe sepsis. Among these, activation of inflammation and coagulation, together with endothelial dysfunction, seem to be major contributors. Several anti-inflammatory agents have been tried for the treatment of sepsis, with limited success. Anticoagulant drugs have been shown to be of potential interest for the therapy of severe sepsis. Among these agents, a natural anticoagulant named activated protein C, which is manufactured as a recombinant human protein under the name of drotrecogin alfa (activated), has been a topic of intense interest. Drotrecogin alfa (activated) is an antithrombotic and profibinolytic agent that also possesses anti-inflammatory and antiapoptotic properties. Small trials have shown that drotrecogin alfa (activated) reduces the sepsis-induced alterations in endothelial and microcirculatory function.

In this review, the benefit-risk balance of drotrecogin alfa (activated) is assessed. The results of one phase II trial, two phase III trials (one including patients with high and low risk of death, the other restricted to patients with low risk of death) and several cohort studies have been published. The PROWESS (Recombinant human protein C Worldwide Evaluation in Severe Sepsis; phase III) trial showed that drotrecogin alfa (activated) is associated with a reduction in the risk of death in patients with severe sepsis, but this benefit seems to be greater in patients at high risk of death. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the number of failing organs have been proposed as means to identify patients with sepsis who are at a high risk of death, but these criteria may sometimes not make good indicators, especially as the APACHE II score has not been validated for this purpose.

Bleeding is more common in drotrecogin alfa (activated)-treated patients than in placebo recipients; however, many of the additional episodes of bleeding in drotrecogin alfa (activated) recipients are procedure related. Importantly, bleeding did not outweigh the benefits of drotrecogin alfa (activated), as there was an overall survival benefit, provided only patients at high risk of death from sepsis were treated with drotrecogin alfa (activated). The bleeding rate associated with drotrecogin alfa (activated) was slightly higher in cohort studies than in clinical trials, but this may be related to the higher severity of illness in these patients. Thus, in clinical practice, great caution should be taken in the selection of patients to be treated, and unnecessary invasive procedures should be avoided in order to preserve the survival benefit conferred by drotrecogin alfa (activated).

Sepsis is the leading cause of death in critically ill patients. In developed countries, it accounts for as many deaths as acute myocardial infarction.[1] It is estimated that the incidence of sepsis in the US is three cases per 1000 in the general population and 2.26 cases per 100 hospital discharges. Studies of several databases have shown that the incidence of sepsis has increased over the last 30 years;[2-6] however, it is difficult to distinguish between better recognition of sepsis (i.e. improved awareness, better definitions) and a true increase in incidence.

Half of the population of patients with sepsis receive intensive care and 17% receive intermediate care.[2] Depending on definition and local specifications, sepsis may account for 10[7] to 27%[5] of intensive care unit (ICU) admissions. Mortality from sepsis has decreased over time, from 30% in the early 1980s to 20% in 2000.[2,8] Recent database studies have shown similar trends in mortality associated with severe sepsis.[5,9] Importantly, the mortality rate associated with sepsis depends on its severity. In the absence of any organ dysfunction, mortality is approximately 15% and then increases with the number of organs that are dysfunctional: 21% for one, 44% for two, 64% for three and 74% for when four or more organs are dysfunctional.[1] Although mortality is very high in patients with multiple organ failure, it is important to recognise that the evolution of organ failure in the first 48 hours of admission is more relevant than the number of failing organs on admission. Ferreira et al.[9] reported that the mortality rate of patients with very high scores for organ dysfunction on admission whose sequential organ failure assessment (SOFA) score[10] decreased by at least 2 points over 48 hours, was similar to that of patients with very low SOFA scores on admission. Similar results were recently observed in a large database study of placebo recipients who had been included in interventional trials.[11] Although sepsis survivors usually recover well from organ dysfunction and long-term organ support is not commonly required,[12,13] all efforts

should be made to limit the development and severity of organ failure.

## 1. Sepsis, Severe Sepsis and Septic Shock

In response to an infection, various pro- and anti-inflammatory mediators are released. Although these mediators play an important role in the defence against infection, the uncontrolled activation of this cascade may, directly or by initiating a chain of events, lead to profound haemodynamic and cellular metabolic effects, which in turn may lead to organ dysfunction. Therefore, sepsis is considered to reflect the response of the host to an infection, and is usually accompanied by fever or hypothermia, tachycardia, tachypnea and leucocytosis or leucopenia. Severe sepsis reflects the disproportionate response of the host to an infection, and is defined as dysfunction of at least one organ in addition to signs of sepsis. Septic shock is severe sepsis featuring circulatory failure. Septic shock defines a state of inadequate supply of oxygen and nutrients to the cells, which may result in tissue hypoxia and lactic acidosis. Unless transient, this will lead to irreversible tissue damage, organ failure and death. As tissue necrosis is uncommon in patients with septic shock, adaptations of organ metabolism occur that shut down some of the less essential metabolic pathways in order to preserve vital functions.[14] These further contribute to the development of multiple organ failure. Direct cellular toxicity, as well as alterations in whole-body haemodynamics, regional bloodflow distribution and microvascular bloodflow, may play a crucial role in the development of multiple organ failure in patients with sepsis.

## 2. Pathophysiology of Sepsis

Several recent reviews have described in detail the pathophysiological mechanisms implicated in the development of sepsis and organ failure.[15-18]

In brief, the recognition of the pathogen or its byproducts by toll-like receptors activates signalling pathways, leading to the release of various pro- and anti-inflammatory cytokines and mediators. Some of these pathways require the transcription of nuclear factor-κB, whereas others do not. These chemokines and mediators activate the endothelium, white blood cells, dendritic cells and epithelial cells and contribute to the release of various vasoactive mediators (i.e. nitric oxide, endothelin, prostaglandins, thromboxane, free oxygen radicals), leading to a cascade of events. These mechanisms activate the coagulation cascade, inhibition of fibrinolysis and adhesion of white blood cells and platelets to the endothelium, and lead to increased vascular permeability and vasodilation. When moderate, these alterations facilitate the control of infection, allowing white blood cells to migrate to the site of the infection and preventing overt dissemination of the micro-organism. However, once initiated, this response is often auto-amplified and, when control mechanisms fail, may lead to diffuse endothelial lesions that are associated with altered vascular tone, increased vascular permeability and microvascular alterations that contribute to the development of organ damage.

Modulation of the inflammatory response and/or coagulation may appear attractive treatment modalities in patients with sepsis. However, interventions should aim to prevent the excessive expression of these responses, rather than to block one of the pathways, because the inflammatory response and coagulation cascade may be useful for the control of infections.

## 3. Rationale for Administration of Activated Protein C

Besides activation of the inflammatory response, pathogens also activate the coagulation pathway. Several recent reviews have covered this issue.[19-21] In this article, we mainly focus on the role of protein C, even though levels of protein S and antithrombin are also decreased in sepsis.

In sepsis, protein C levels are decreased.[22] Several studies[22-25] have shown that low protein C levels on admission are associated with poor outcomes, with outcomes deteriorating as protein C levels at admission decrease. In addition, the evolution of protein C levels over time is a factor that is independently associated with the outcome of sep-

sis.[22] In patients who are severely deficient in protein C at baseline (baseline levels ≤40% of maximal protein C levels), a failure to increase their protein C levels was associated with an increased risk of death compared with patients who increased their levels (odds ratio [OR] = 2.75; $p < 0.0001$), whereas an increase in these levels to >40% by day 1 was associated with a decreased risk of death compared with patients who did not achieve an increase of >40% at this timepoint (OR = 0.43; $p = 0.03$). If baseline protein C levels in placebo recipients were >40% but decreased by ≥10% on day 1, the risk of death for these patients increased compared with that for patients who did not experience a decrease of ≥10% (OR = 1.87; $p = 0.02$).

In addition to the decreased protein C levels, protein C activity is also reduced,[22] mostly as a result of a failure of the activation of protein C at the endothelium.[26,27] Accordingly, administration of exogenous activated protein C would theoretically be preferred to administration of protein C.

Protein C polymorphisms are frequent, but evidence for a functional impact of these polymorphisms has only been reported for the −1641 A/G and −1641 C/T polymorphisms, which are associated with decreased protein C levels.[28] Recently, Walley and Russell[29] evaluated the influence of these two polymorphisms in a large cohort of patients with septic shock, and they showed that the −1641 AA genotype, which has a deep penetration in the population as it was present in 35% of the patients, was associated with a higher incidence of organ dysfunction (hazard ratio close to 1.5 for all types of organ failure; 95% CI not provided) and a poor outcome (28-day survival of 58% vs 66% in patients with vs without this polymorphism; $p = 0.03$). Whether this polymorphism is associated with a different response to treatment with activated protein C remains to be determined.

## 4. Effects of Activated Protein C

The effects of activated protein C are multiple,[30] and this compound should not be viewed as a simple anticoagulant agent. Of course, activated protein C exhibits antithrombotic properties (inhibition of factors V and VII) and profibrinolytic properties (inhibition of plasminogen activator-inhibitor 1 and activation of thrombin activatable fibrinolysis inhibitor);[30,31] however, it also exhibits anti-inflammatory properties, which may either be mediated via decreased thrombin generation or by direct cellular effects due to inhibition of nuclear factor-κB.[32] In addition, activated protein C has anti-apoptotic properties.[33,34]

Activated protein C also interacts with endothelial cells, white blood cells and platelets.[30] Activated protein C decreases platelet and white blood cell rolling and adhesion to the endothelium,[35-38] which results in improved microvascular bloodflow.[35-37] In patients with septic shock, we recently demonstrated that activated protein C improves the sublingual microcirculation.[39] This effect is of great importance, as alterations in the microcirculation are more severe in individuals with severe sepsis and are associated with a poor outcome and organ dysfunction.[40-42]

This improved endothelial function due to increased levels of activated protein C is associated with an increased vasoreactivity[43,44] and an improved barrier function of the endothelium,[45] which leads to a reduction in vascular permeability.[46] In patients with septic shock, this translates into a more rapid reversal of hypotension.[39,47]

## 5. Large-Scale Studies of Drotrecogin Alfa (Activated)

To identify trials evaluating the potential beneficial effects and adverse events associated with drotrecogin alfa (activated) administration, the PubMed database was searched using the following keywords: 'drotecogin alfa activated', 'activated protein C', 'sepsis', 'severe sepsis', 'septic shock', 'outcome', 'adverse event' and 'bleeding'. Related articles and the reference lists of retrieved citations were also examined.

Large-scale, randomised studies were conducted with recombinant activated protein C, which is manufactured by Eli Lilly and has been released under the name of drotrecogin alfa (activated).

### 5.1 Phase II Trial

A phase II trial was conducted[48] in 131 adult patients with severe sepsis. This randomised, double-blind, placebo-controlled, dose-ranging clinical trial was conducted in 40 ICUs in the US and Canada. Severe sepsis was defined as dysfunction of one or more organs in patients with suspected or proven infection who had at least two signs of a systemic inflammatory response, such as fever, hypothermia, tachycardia, tachypnoea or the need for mechanical ventilation for the treatment of sepsis, leukocytosis or leucopenia. Organ dysfunction included cardiovascular dysfunction (hypotension or the need for vasopressor therapy), respiratory dysfunction (hypoxaemia defined as a ratio of the arterial partial pressure of oxygen [$PaO_2$] to fraction of inspired oxygen [$FiO_2$] of <300 or <200 if the lung was the source of sepsis) and renal impairment (oliguria urinary output of <0.5 mL/kg for at least 1 hour); this dysfunction had to have been present for <24 hours at time of inclusion. The exclusion criteria were mostly related to the risk of bleeding (patients with active bleeding, an increased partial thromboplastin time [APTT] or a platelet count <30 000/$mm^3$, those who had undergone major surgery within 12 hours or who had recently experienced a stroke or undergone cranial surgery, patients with a history of cerebral aneurysm or brain tumour, those with an epidural catheter, severe cirrhosis with portal hypertension or inherited coagulation disorders and patients receiving anticoagulant or anti-aggregant therapy) or to a too-severe underlying condition (patients not expected to survive >6 hours, patients not committed to full aggressive support, patients with a severe underlying condition and a life expectancy of <28 days, patients with end-stage renal failure, patients with advanced malignancies).

Patients were randomised, at a ratio of 1 : 2, to received either placebo or drotrecogin alfa (activated) 12, 18, 24 or 30 μg/kg/h for 48 hours (initial phase) and then 96 hours (second phase). As drotrecogin alfa (activated) affected coagulation in a dose-dependent manner, with marked effects at the higher dosages, frequent dosage adjustments were required in response to increased APTTs in patients treated with drotrecogin alfa (activated) 30 μg/kg/h in the initial phase of the study. Therefore, this dosage was not used in the second phase of the study.

Of the patients included in the study, 97% had decreased activated protein C levels at baseline and treatment with drotrecogin alfa (activated) increased activated protein C levels in a dose-dependent manner in these patients. Steady-state levels were achieved 2 hours after starting the infusion. Activated protein C levels declined rapidly after stopping drotrecogin alfa (activated) infusion, and were below the limit of detection 4.5 hours after treatment cessation.

Levels of D-dimer slowly and slightly decreased during the 96 hours of drotrecogin alfa (activated) administration. Low dosages of drotrecogin alfa (activated) [≤18 μg/kg/h] did not affect D-dimer levels, whereas higher dosages (≥24 μg/kg/h) rapidly decreased D-dimer levels. These favourable effects on disseminated intravascular coagulation (DIC) were accompanied by a dose-dependent decrease in interleukin 6 levels.

Mortality at 28 days did not differ between placebo- and drotrecogin alfa (activated)-treated patients (34.1% vs 28.8%; p = ns); however, there was a trend towards improved survival in patients treated with the higher dosages of drotrecogin alfa (activated) [OR 0.60; 95% CI 0.28, 1.27]. This phase II trial showed that drotrecogin alfa (activated) effectively blunted DIC and accelerated the decrease in interleukin 6 levels in patients with severe sepsis, and that these effects were associated with a satisfactory safety profile (see section 6 for further details).

### 5.2 PROWESS

The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) pivotal, phase III trial[49] commenced in July 1998 and was discontinued in June 2000 when efficacy was shown at the second interim analysis. This randomised, double-blind, placebo-controlled trial was conducted in 164 centres in 11 countries (USA, Canada, Belgium, France, Germany, The Nether-

lands, Spain, Brazil, Australia, New Zealand and South Africa) and included 1690 patients with severe sepsis. The inclusion criteria were the presence of two signs of a systemic inflammatory response in the presence of a known or suspected source of infection, and organ dysfunction as shown by at least one of the five following criteria: hypotension or need for vasopressor therapy (indicating cardiovascular dysfunction); hypoxemia defined as a $PaO_2/FiO_2$ ratio of <250 or <200 if the lung was the source of sepsis (indicating respiratory dysfunction); oliguria (indicating renal impairment); a platelet count <80000/mm$^3$ or a decrease in platelet count of 50% in the 3 days preceding enrollment (indicating haematological dysfunction); and lactic acidosis, defined as a blood pH <7.30 or a base deficit >5 mmol/L in association with lactate levels >1.5 × the upper normal limit in the local laboratory. A time window of a maximum of 48 hours was tolerated between the occurrence of first organ failure and the initiation of infusion of placebo or drotrecogin alfa (activated) 24 μg/kg/h for 96 hours. The exclusion criteria were globally the same as in the phase II trial, with the additional exclusion of HIV-infected patients who had low CD4 cell counts and patients with a history of organ transplantation, with the exception of renal transplant recipients. Patients with pancreatitis without proven infection were also excluded.

There were no differences in baseline characteristics between the placebo and drotrecogin alfa (activated)-treated groups and 90% of patients in both groups received adequate therapy with antibacterials within 48 hours of the diagnosis of infection. Of the included patients, 75% had dysfunction of at least two organ systems, 75% were receiving mechanical ventilation and 71% were receiving vasopressor support for the treatment of shock. Coagulation abnormalities were frequent in both groups at baseline, with elevation of D-dimer levels in 99.7% of patients. Protein C deficiency was present in 88% of the patients, with median protein C activity of approximately 50% in both groups.

Drotrecogin alfa (activated) effectively increased protein C levels in treated patients.[22] This resulted in a reduction in markers of thrombin generation and accelerated normalisation of anticoagulant and fibrinolytic factors.[50] As a result of all these effects, the prothrombin time and APTT were prolonged in drotrecogin alfa (activated)-treated patients but D-dimer levels decreased more rapidly.

Drotrecogin alfa (activated) administration was associated with a more rapid reversal of organ dysfunction, especially cardiovascular and respiratory dysfunction.[51] It also slowed the onset of haematological dysfunction. Renal and hepatic dysfunction were not affected by drotrecogin alfa (activated).

Twenty-eight day mortality was significantly lower in drotrecogin alfa (activated)-treated than placebo-treated patients (24.7% vs 30.8%; p = 0.005), representing a 19.4% (95% CI 6.6, 30.5) relative reduction in the risk of death. This benefit is associated with a number to treat of 16 (95% CI 9, 83), which is favourable compared with other successful interventions in sepsis and acute respiratory distress syndrome.[52] Kaplan-Meier analysis of survival yielded similarly positive results for drotrecogin alfa (activated) [p = 0.006], with a difference in cumulative survival curves occurring within 4–6 days of inclusion and then increasing throughout the follow-up period. A prospectively defined analysis that accounted for baseline differences in Acute Physiology and Chronic Health Evaluation (APACHE II) score, age and protein C activity produced similar results.[49]

#### 5.2.1 PROWESS: Subgroup Analyses

Further important information was gained from subgroup analyses of the PROWESS trial, although this should be treated with caution. First, there was no stratification according to predefined factors. Second, the study was not powered to detect significant differences among subgroups. Third, most analyses were generated *post hoc*. Fourth, the multiplicity of these analyses increases the risk of false-positive statistical significance. Nevertheless, these analyses may be helpful to ensure that the benefit was preserved in clinically relevant subgroups and to further elucidate the safety profile. Whenever possible (when equipoise exists for a specific situa-

tion), these analyses should be confirmed by a randomised trial.

The first subgroup analysis was prospectively defined and was based on the severity of sepsis.[49,53] After separation of patients into quartiles of APACHE II scores, it appeared that patients with the lowest severity of sepsis (APACHE II scores <25) may not benefit from drotrecogin alfa (activated) administration because the relative risk of death in drotrecogin alfa (activated) recipients compared with placebo recipients was close to 1 with large confidence intervals. Conversely, patients with a greater severity of sepsis (APACHE II scores ≥25) clearly had a better outcome with drotrecogin alfa (activated) treatment (relative risk of death was between 0.60 and 0.75, with the upper limit of the CI being <1). A similar analysis conducted for the number of organ failures revealed that the relative risk of death in drotrecogin alfa (activated) recipients versus placebo recipients was close to 1 for single organ failure, whereas it was <1.0 in patients with failure of two or more organs.

Using the data from placebo recipients, Ely et al.[53] calculated a risk of death score based on admission data. Applying this score in the drotrecogin alfa (activated)-treated patients, they were able to show that patients for whom the risk of death was predicted to be <30% did not benefit from drotrecogin alfa (activated) administration (i.e. mortality was similar or only slightly decreased with drotrecogin alfa [activated] compared with placebo), whereas in patients with a predicted risk of death >30%, the risk of death was significantly lower for drotrecogin alfa (activated)-treated patients than for placebo recipients. This risk reduction increased with the severity of sepsis. These analyses prompted the US FDA and the European regulatory agencies to license the drug for the treatment of patients with severe sepsis and an APACHE II score >24 (US) or failure of at least two organs (Europe).

Other subgroup analyses were also conducted. These essentially showed that there was no interaction between age, race, sex, type and source of infection and underlying disease and the drotrecogin alfa (activated)-associated reduction in the risk of death.[49,53] In particular, patients who had recently undergone surgery also experienced a decreased risk of death when treated with drotrecogin alfa (activated), even though this reduction was slightly lower than in medical patients.[53] Patients with overt DIC[54] had a greater risk reduction when treated with drotrecogin alfa (activated) than patients without overt DIC; however, the individual components of the DIC score (platelet count, APTT) and protein C deficiency did not influence the response to drotrecogin alfa (activated).[53]

Follow-up of 93% of the patients included in the PROWESS trial was obtained for up to 1 year.[55] The survival benefit was globally maintained over time, as survival curves were shown to be parallel after 3 months, but statistical significance was not achieved ($p = 0.10$). As expected from the effect on 28-day mortality, patients at high risk of death, as estimated by an APACHE II score ≥25, had the greatest survival advantage at 1 year (for patients with APACHE II scores ≥25, 1-year survival rate was 52.1% in drotrecogin alfa (activated) recipients vs 41.3% in placebo recipients; $p = 0.002$).

### 5.3 ENHANCE

The ENHANCE (Extended Evaluation of Recombinant Human Activated Protein C) study was a large (2434 patients in 25 countries, at 361 sites), observational, non-randomised open-label study conducted in adult patients with severe sepsis.[56] Entry criteria were similar to those of the PROWESS phase III trial; however, all patients were treated with drotrecogin alfa (activated) [2378 patients received drotrecogin alfa (activated) and were included in the analysis]. Mortality in ENHANCE was similar to that in PROWESS (25.3% vs 24.7%, respectively); however, important information was gained from subgroup analyses: patients receiving drotrecogin alfa (activated) within 24 hours of the onset of first organ failure had lower mortality than patients treated between 24 and 48 hours after the first organ dysfunction (22.9% vs 27.4%; $p = 0.01$). These results suggest that drotrecogin alfa (activated) is more effective when initiated early in severe sepsis, which is also the case for

other interventions such as haemodynamic resuscitation[57] and antibacterials.[58,59]

### 5.4 INDEPTH Database Study

The INDEPTH (International Integrated Database for the Evaluation of Severe Sepsis and Drotrecogin alfa [activated] Therapy) database[60] incorporated 4459 patients included in the phase II, PROWESS and ENHANCE trials, as well as patients from the placebo arm of two other trials evaluating another agent for the treatment of severe sepsis. The inclusion and exclusion criteria were relatively similar across the studies. In total, there were 1231 placebo recipients and 3228 drotrecogin alfa (activated)-treated patients. Data from this register confirmed the benefit of drotrecogin alfa (activated) and, more importantly, highlighted the need for minimal delay between the onset of organ failure and initiation of drotrecogin alfa (activated) therapy. As in the ENHANCE trial, patients treated within 24 hours of the onset of organ failure had the greatest survival advantage. Analysing the OR for mortality with drotrecogin alfa (activated) versus placebo according to the time to drotrecogin alfa (activated) administration, the authors showed that the OR was <1 (favouring drotrecogin alfa [activated]) up to 36 hours after initial organ failure and was >1 (favouring placebo) when the drug was initiated between 36 and 48 hours after the onset of organ failure.

Although interesting, these results should be evaluated cautiously because this was not a randomised study and there was no stratification for time to initiation of treatment from onset of organ failure. Thus, one cannot exclude imbalance in some unmeasured variables, even though most measured variables were similar in placebo and drotrecogin alfa (activated)-treated patients.

### 5.5 ADDRESS

The second phase III trial, ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis),[61] was requested by the FDA to evaluate the effects of drotrecogin alfa (activated) in patients with severe sepsis and a low risk of death. The same inclusion criteria were used as in the PROWESS trial. Patients estimated to be at high risk of death on the basis of an APACHE II score of ≥25 or multiple organ dysfunction were in principle excluded, although physicians were nevertheless allowed to include a patient meeting these severity criteria if they estimated that the patient was at low risk of death. In addition, the exclusion criteria from the PROWESS and ENHANCE trials were applied. Since some patients were expected to worsen and to meet severity criteria allowing for clinical use of drotrecogin alfa (activated), it was accepted that patients deteriorating within 48 hours of the onset of the first organ dysfunction may be switched to clinical treatment with drotrecogin alfa (activated). The study was projected to include >11 000 patients, but was stopped after the first interim analysis due to futility. At that time, 2640 patients had already been enrolled. Baseline data were similar in both groups, with the exception of a trend towards dysfunction of more organs in the drotrecogin alfa (activated)-treated patients (34.5% of drotrecogin alfa [activated] recipients had dysfunction of two or more organs compared with 31.5% in placebo group; $p = 0.08$). Forty-seven patients in the placebo group and 39 in the drotrecogin alfa (activated)-treated group switched to clinical drotrecogin alfa (activated) treatment.

There was no statistically significant difference in 28-day mortality between drotrecogin alfa (activated) and placebo recipients (18.5% vs 17.0%; $p = 0.34$). This difference remained insignificant after adjustment for APACHE II scores (which were similar in both groups at baseline); however, no adjustment was performed for organ failure.

The analysis of the predefined subgroups of patients with either APACHE II scores of ≥25 or with dysfunction of two or more organs was quite compelling because it somewhat replicated the results of the PROWESS trial. No survival benefit, in terms of 28-day mortality, was observed with drotrecogin alfa (activated) administration in patients with an APACHE II score of ≥25 (mortality 29.5% compared with 24.7% in placebo recipients; $n = 321$, $p = 0.81$) nor in patients with dysfunction of two or more organs (mortality 20.7% compared with

21.9% in placebo; n = 862, p = 0.38). However, these data should be interpreted with caution. First, this analysis is particularly dangerous because there was no stratification for these factors during the randomisation process; accordingly, important imbalances in confounding factors may have occurred. Second, the whole study was not powered to detect significant differences in outcomes in the entire population, because it was stopped early; therefore, analysis of subgroups would be even more delicate. Finally, patients were allowed to be included in this study even if they presented with a high APACHE II score or dysfunction of more than one organ, as long as they were judged to be at low risk of death by the attending physician. Accordingly, patients with either an APACHE II score of ≥25 or with dysfunction of two or more organs were less severely ill in the ADDRESS trial than the PROWESS trial. This is clearly illustrated by the mortality rates in the placebo arms of the two trials; the mortality rate in the placebo arm was much lower in the ADDRESS than the PROWESS trial (figure 1). Accordingly, the results of the ADDRESS trial cannot be used to contradict the results of the PROWESS trial; nevertheless, ADDRESS did determine that drotrecogin alfa (activated) should not be used in patients at low risk of death.

Follow-up of 90% of the patients included in the ADDRESS trial was obtained for up to 1 year.[62]

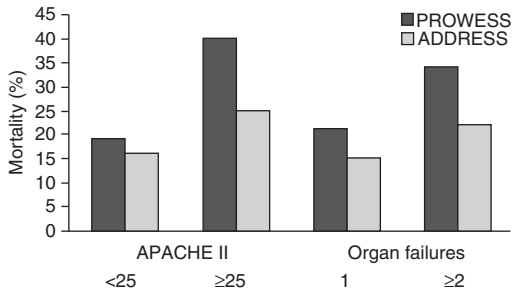


**Fig. 1.** Mortality rates in the placebo arm of the two phase III PROWESS[49] and ADDRESS[61] studies. This graph shows that the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the number of dysfunctional organs at inclusion cannot adequately predict the risk of death at baseline, since subgroups with expected similar severity of sepsis had marked differences in outcome in the two trials. The ADDRESS (phase III extension for indication) trial[61] included only patients at low risk of death.

The results were globally maintained over time because survival curves were superimposed for the drotrecogin alfa (activated) and placebo treatment groups over the entire period of observation. The non-significant trend towards a lower mortality rate with drotrecogin alfa (activated) versus placebo in patients with dysfunction of two or more organs was maintained (if not improved) at 1 year (drotrecogin alfa [activated] 36.2% vs placebo 39.9%; p = 0.29), whereas no between treatment difference was observed for patients with an APACHE II score of ≥25 (drotrecogin alfa [activated] 49.7% vs placebo 48.3%; p = 0.81).

### 5.6 RESOLVE

This third phase III trial, RESOLVE (Researching Severe Sepsis and Organ Dysfunction in Children: a Global Perspective) [phase III extension for indication] was requested by the FDA to evaluate the effects of drotrecogin alfa (activated) in paediatric patients with severe sepsis.[63] Since mortality is usually lower in paediatric patients (3000 patients would need to be included to show a 2% reduction in 28-day mortality), the primary endpoint was a composite score evaluating the time to resolution of organ dysfunction (mechanical ventilation, cardiovascular support and renal support) from inclusion to day 14. Accordingly, 600 patients had to be included to show a 15% reduction in this score; however, the study was stopped after second interim analysis due to futility.

A total of 496 children aged between 38 weeks of corrected gestational age and 17 years with suspected or proven infection and sepsis-induced cardiovascular or respiratory failure were randomised to receive either placebo (n = 250) or drotrecogin alfa (activated) [n = 246]. Exclusion criteria were an estimated high risk of intracranial bleeding, a life expectancy of <28 days and end-stage renal or liver failure. Drotrecogin alfa (activated) was administered at a dose of 24 μg/kg/h for 4 days, which had been shown in an exploratory study (open-label, sequential design) to have a similar pharmacokinetic profile in paediatric patients with severe sepsis as in adult patients.[64]

Overall, most of the patients were aged <5 years; 7% were aged 0–1 month and 25% aged 1–12 months.[63] There were more boys in the drotrecogin alfa (activated)-treated group than in the placebo group. In addition, the Pediatric Risk of Mortality score was slightly higher in the drotrecogin alfa (activated) group (16 vs 15; p = 0.07); however, the number of dysfunctional organs was similar in both groups. The outcomes were similar in both groups, with similar time to resolution of organ failure scores (placebo vs drotrecogin alfa [activated]: 6 vs 6 days; p = ns), proportions of patients receiving organ support at day 15 (19.3% vs 19.8%; p = ns) and 28-day mortality rates (17.5% vs 17.2%; p = ns). Adjustment for small differences in baseline characteristics did not modify the results. Looking at the different predefined subgroups, the authors identified an interaction between response to drotrecogin alfa (activated) treatment and the DIC score: patients with overt DIC, which represented close to half of the investigated population, derived a significant benefit from drotrecogin alfa (activated) administration (28-day mortality was 14% in drotrecogin alfa [activated] group vs 22% in placebo recipients); however, this was mirrored by an increased mortality in patients who did not present with overt DIC (18% in drotrecogin alfa [activated] recipients vs 11% in placebo recipients). Although this is consistent with the idea that only the patients with the most severe sepsis should be treated, the data from the subgroup analysis cannot be taken as a justification for treating paediatric patients with overt DIC with drotrecogin alfa (activated) outside of specifically designed trials.

### 5.7 A Meta-Analysis of the Published Trials

There have been three randomised trials comparing drotrecogin alfa (activated) with placebo in adult patients published. A meta-analysis of the three published, randomised trials comparing drotrecogin alfa (activated) with placebo in adult patients has recently been performed.[65] The results, summarised in table I, confirm the positive impact of drotrecogin alfa (activated) on outcomes in patients at high risk of death who present with dysfunction of two or more organs (with borderline statistical significance, as indicated by a value of 1.0 for the upper limit of the confidence interval for the OR for mortality associated with drotrecogin alfa [activated] vs placebo). No conclusions could be made in patients with an APACHE II score ≥25, because there was too much heterogeneity between the two studies that performed such an analysis. This meta-analysis also confirmed that patients with a low severity of sepsis (defined as having dysfunction of only one organ or an APACHE II score <25) do not benefit from drotrecogin alfa (activated) administration.

**Table I.** Meta-analysis of three published, placebo-controlled, randomised trials with drotrecogin alfa (activated) in patients with severe sepsis[65]

| Patient subgroup | Relative risk of death (95% CI)[a] |
|---|---|
| Low risk of death | |
| APACHE II score <25 (n = 3164) | 1.03 (0.89, 1.21) |
| single organ dysfunction (n = 2157) | 1.10 (0.89, 1.36) |
| High risk of death | |
| APACHE II ≥25 (n = 1138)[b] | 0.90 (0.54, 1.49) |
| multiple organ failure (n = 2133) | 0.84 (0.70, 1.00) |

a A relative risk value <1 denotes a survival benefit in favour of drotrecogin alfa (activated).

b Significant heterogeneity was shown between the studies.

**APACHE** = Acute Physiology and Chronic Health Evaluation.

## 6. Safety Profile of Drotrecogin Alfa (Activated)

Most of the data on the safety of drotrecogin alfa (activated) have come from the phase II trial, the PROWESS trial and the ADDRESS trial. Important information was also gained from the subgroup analyses of these trials, especially in patients with coagulation abnormalities and those undergoing surgery, from the observational ENHANCE study and from registries.

In the phase II trial,[48] 4% of patients receiving drotrecogin alfa (activated) and 5% receiving placebo experienced severe bleeding. In patients receiving drotrecogin alfa (activated), half of these events occurred during the infusion period and half were delayed. Serious adverse events occurred in similar proportions of patients in both groups (39% in dro-

trecogin alfa [activated] recipients and 46% in placebo recipients; p = ns).

In the PROWESS trial,[49] 12.5% of drotrecogin alfa (activated)-treated patients and 12.1% of placebo recipients experienced at least one predefined serious adverse event. Among these, serious bleeding events were more frequent in the drotrecogin alfa (activated) group (3.5% vs 2.0%; p = 0.06). This trend towards an increased rate of serious bleeding events was due to events occurring during infusion of drotrecogin alfa (activated) and these were, in many cases, related to procedures (insertion of catheters or chest tubes); the rates of serious bleeding events after cessation of infusion were similar in both groups (table II). There was no difference in the rate of thrombotic events between groups (2.0% in drotrecogin alfa [activated] recipients vs 3.0% in placebo recipients; p = 0.20). Subgroup analysis[53] was unable to identify patients who were at risk of bleeding. In particular, the slight increase in bleeding rates associated with drotrecogin alfa (activated) administration was similar in patients who had recently undergone surgery and in other patients (3.7% in drotrecogin alfa [activated] recipients vs 1.9% in placebo recipients for patients who had recently undergone surgery, compared with 3.5 vs 2.1% in medical patients). Similar bleeding rates were observed in the ADDRESS trial.[61]

In the open-label ENHANCE study,[56] bleeding was also the most commonly observed adverse event. The serious bleeding rate was higher than in the PROWESS trial (table II), with rates of serious bleeding both during and after infusion being higher than in the earlier study. The persistence of the increased bleeding rate after drotrecogin alfa (activated) infusion may suggest that the patients treated in this cohort were at higher risk of bleeding, independent of drotrecogin alfa (activated) administration. This is in line with the greater severity of sepsis in these patients, as suggested by failure of an increased number of organs and the greater number of patients receiving treatment with vasoactive agents.

In a subsequent analysis, Bernard et al.[66] focussed on intracranial haemorrhage in a large cohort of patients, collecting data from 2786 patients who

**Table II.** Incidence, type and time of adverse events associated with drotrecogin alfa (activated) administration in adult patients[a]

| Adverse events [n (%)] | Phase II[48] | | PROWESS[49] | | ADDRESS[61] | | ENHANCE[56] |
|---|---|---|---|---|---|---|---|
| | placebo (n = 41) | drotrecogin alfa [activated] (n = 90) | placebo (n = 840) | drotrecogin alfa [activated] (n = 850) | placebo (n = 1293) | drotrecogin alfa [activated] (n = 1317) | drotrecogin alfa [activated] (n = 2378) |
| At least one serious adverse event | | | 102 (12.1) | 106 (12.5) | 183 (14.2) | 182 (13.8) | |
| **Serious bleeding event** | 2 (4.9) | 4 (4.4) | 17 (2.0) | 30 (3.5) | 28 (2.2) | 51 (3.9)* | 155 (6.5) |
| Serious bleeding during infusion | 0 | 2 (2.2) | 8 (1.0) | 20 (2.4) | 15 (1.2) | 31 (2.4)** | 86 (3.6) |
| Serious bleeding after infusion | 2 (4.9) | 2 (2.2) | 9 (1.1) | 10 (1.2) | 13 (1.0) | 20 (1.5) | 76 (3.2) |
| **Source** | | | | | | | |
| Gastrointestinal | 2 (4.9) | 3 (3.3) | 9 (1.1) | 9 (1.1) | | | |
| Intra-abdominal | NR | 1 (1.1) | 4 (0.5) | 3 (0.4) | | | |
| Intrathoracic | | | 1 (0.1) | 6 (0.7) | | | |
| Retroperitoneal | | | 0 | 4 (0.5) | | | |
| Intracranial | | | 1 (0.1) | 2 (0.2) | 5 (0.4) | 6 (0.5) | 35 (1.5) |
| Skin or soft tissue | | | 0 | 2 (0.2) | | | |
| Other | | | 2 (0.2) | 4 (0.5) | | | |

a Some data were gathered in related papers.[53,66]

**NR** = not reported; * p < 0.01; ** p < 0.05 drotrecogin alfa (activated) vs placebo.

were included in phase II and phase III PROWESS trials and from 3991 patients receiving drotrecogin alfa (activated) in clinical use. Episodes of intracranial haemorrhage, which were considered as serious bleeding events in studies, were uncommon, but the incidence was slightly higher in drotrecogin alfa (activated)-treated patients than placebo recipients (1.1% vs 0.6%; p = ns). The majority of the intracranial haemorrhage episodes that occurred during drotrecogin alfa (activated) administration (10/16) were associated with severe thombocytaemia (≤30 000/mm$^3$) or meningitis, factors that were also associated with a higher risk of intracranial haemorrhage in placebo recipients. In another analysis, patients with meningitis, purpura fulminans and meningococcal disease were found to be the group most at risk for intracranial bleeding during drotrecogin alfa (activated) administration:[67] intracranial haemorrhage occurred in 2.5% (4.3% for 28-day study period) of the 163 patients with meningitis, purpura fulminans or meningococcal disease, whereas it occurred in only 0.4% (1.0% for the 28-day study period) in the other patients in the database. In the PROWESS study,[49] one of the 24 (4.2%) placebo recipients with purpura fulminans, meningitis or meningococcal disease experienced intracranial haemorrhage. Although the small number of placebo recipients with these risk factors does not allow precise evaluation of the increase in the risk of death due to drotrecogin alfa (activated) in this subpopulation, these data suggest that patients with meningitis, purpura fulminans or meningococcal disease are at an increased risk of intracranial bleeding and that indications for drotrecogin alfa (activated) should be more carefully considered in these patients.

Of note, paediatric patients may be more at risk of intracranial bleeding than adult patients, as these patients commonly present with meningitis or purpura fulminans. In the paediatric RESOLVE study,[63] serious bleeding events ascribed to the study drug occurred more frequently in the drotrecogin alfa (activated) than the placebo group (3.3% vs 0.4%, respectively, for bleeding occurring during days 0–6, and 4.2% vs 0.8%, respectively, for the entire 28-day observation period; $p < 0.05$ for both comparisons). Most of these bleeding events were intracranial haemorrhage, which also occurred more frequently in drotrecogin alfa (activated)-treated patients than in those receiving placebo, although this increase was not significant (2.1% vs 0.4%, respectively, for bleeding occurring during days 0–6, and 4.6% vs 2.1%, respectively, for bleeding occurring during the entire 28-day observation period; p = 0.22 and 0.13, respectively). Of note, patients aged <60 days were at the highest risk of bleeding, especially intracranial haemorrhage.

Interestingly, the occurrence of bleeding in drotrecogin alfa (activated)-treated patients was greater in the ENHANCE study and in cohort studies than it was in the randomised trials.[48,49,61] Several factors could be involved. First, the severity of sepsis in patients in the ENHANCE trial and cohort studies was greater than that in patients in the randomised trials, as evidenced by the number of failing organs, and the bleeding rate increased according to the underlying severity of sepsis. Patients in the ENHANCE study and in cohort studies had significantly higher numbers of failing organs, and this might be expected to increase the bleeding risk. Second, physicians are known to be less cautious in real life than during studies. It should be noted that important precautions were taken to prevent bleeding in the randomised trials: patients at high risk of bleeding were excluded and the infusion was stopped 1 hour before any percutaneous procedure or surgery and was resumed 1 hour and 12 hours later, respectively, in the absence of bleeding complications. These precautions should be also observed in clinical practice.

## 7. Benefit-Risk Balance for Drotrecogin Alfa (Activated)

As reported in the PROWESS trial[49] and subgroup analyses of that trial,[53] the administration of drotrecogin alfa (activated) at a dose of 24 μg/kg/h for 96 hours decreased mortality in patients with severe sepsis who were at high risk of death. Drotrecogin alfa (activated) treatment was accompanied by a moderate increase in the rate of severe bleed-

ing, including intracranial haemorrhage. The mortality associated with bleeding was obviously counterbalanced by the beneficial effects of the drug as the net result was a decrease in the risk of death. This beneficial benefit/risk balance is further highlighted by the fact that resource use is not increased in drotrecogin alfa (activated)-treated survivors of sepsis.[68] In patients with low risk of death as estimated, among other factors, by an APACHE II score <25 or dysfunction of only one organ, the benefit/risk was negligible because there was no effect of drotrecogin alfa (activated) on mortality.[61,65] The time between the onset of organ dysfunction and drotrecogin alfa (activated) administration is also a critical issue: drotrecogin alfa (activated) is more effective when administered early,[56,60] whereas the risk of bleeding is likely to be unaffected by time. Therefore, as represented in figure 2, drotrecogin alfa (activated) should ideally be implemented within a time window of 24 hours (or a maximum of 36 hours).[60] In patients with meningitis, purpura fulminans or meningococcal disease, the benefit/risk of drotrecogin alfa (activated) may not be satisfactory, as the risk of intracranial bleeding is increased in this population and the mortality rate in these patients was slightly lower than in the other patients treated with drotrecogin alfa (activated).[67] Finally, the risk/benefit is not favourable in paediatric patients, as these patients have a low risk of death and more frequently experience intracranial haemorrhage.[63]

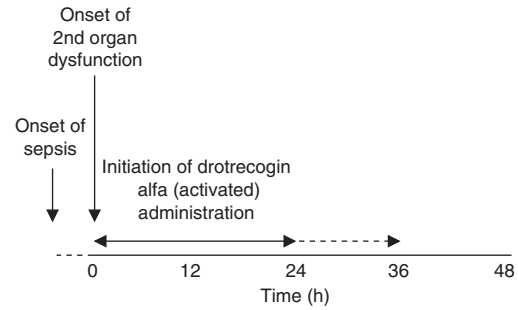


**Fig. 2.** The timeframe for drotrecogin alfa (activated) administration in patients with severe sepsis. Ideally, drotrecogin alfa (activated) should be initiated in patients at high risk of death within 24 hours of the onset of the first organ dysfunction. If necessary (i.e. in patients who underwent surgery within the time period 24 hours from first organ dysfunction), this timeframe may be extended up to 36 hours, but the benefits of drotrecogin alfa (activated) may be more limited.[60]

Taking into account that only patients at high risk of death should be treated, the contra-indications for the drug, and the time window allocated for drotrecogin alfa (activated) administration, it is usually considered that only one patient with severe sepsis out of 10–20 may benefit from drotrecogin alfa (activated) administration. Data extracted from the PROWESS study suggest that this strategy seems to be associated with a satisfactory cost-effectiveness ratio,[69] even when long-term mortality is taken into account.[68]

The mortality rate and bleeding rates were higher in the ENHANCE study[56] and the cohort series[70,71] than in the initial randomised studies. At first glance, one could rapidly conclude that the benefit risk is lower, or even negligible, in these patients,[72,73] casting some doubts on the results of the initial studies. However, it is quite usual that patients not included in randomised studies have higher mortality rates compared with patients included in studies. Similar results have been observed in patients with acute myocardial infarction, but cardiologists concluded differently. Gathering data form the Global Registry of Acute Coronary Events (GRACE registry), Steg et al.[74] recently reported that mortality was higher in patients screened but not included in randomised studies than in included patients. These differences were not totally explained by baseline estimation of risk of death or use or delay in reperfusion therapies. These findings have not been used to question the benefits of reperfusion therapy in acute myocardial infarction, but rather are used by the cardiology community to improve daily practice to reach the standard observed in clinical studies. In the case of drotrecogin alfa (activated), patients in cohort studies were definitively sicker, comprising older patients with dysfunction of more organs at baseline. As expected, mortality was higher in these patients than in the previous studies. This should not be used as a criterion to withhold drotrecogin alfa (activated) treatment, because subgroup analysis of randomised studies suggested that the patients with the most

severe disease were more likely to benefit from drotrecogin alfa (activated) administration.[53] In a Belgian registry study mandated by health authorities, all consecutive patients treated with drotrecogin alfa (activated) in Belgium from July 2003 until the end of September 2004 were recorded.[75] The patients included in this registry were older and had more severe sepsis (three-quarters of the cohort experienced failure of three or more organs) than in the PROWESS and ENHANCE studies; accordingly, hospital mortality was higher in the Belgian study than in the PROWESS and ENHANCE studies. Nevertheless, the mortality observed in drotrecogin alfa (activated) recipients in this study was lower than in patients not treated with drotrecogin alfa (activated) [according to data gathered from other registries and using a propensity score to account for most factors related to the outcome]. More than 90% of the surviving patients who had been treated with drotrecogin alfa (activated) were discharged home. These data suggest that drotrecogin alfa (activated) has a satisfactory risk-benefit profile in real world practice.

It is quite likely and greatly anticipated that a second phase III trial, focusing on the most severely ill patients, will be conducted, definitively answering many of the unresolved questions associated with drotrecogin alfa (activated) treatment. At the time of writing this manuscript, two phase III trials are actually under consideration: one sponsored by Eli Lilly, the other driven by independent French investigators. The details of these trials are not yet known as these are not yet registered in http://ClinicalTrials.gov. In the meantime, there should be no reason to refrain from administering drotrecogin alfa (activated) in patients with severe sepsis who are at high risk of death.

## 8. Conclusions

Drotrecogin alfa (activated) is associated with a reduction in the risk of death in adult patients with severe sepsis who are at high risk of death. APACHE II scores and the number of failing organs can be used to identify these patients; however, these criteria may sometimes not always be good indicators, especially as the APACHE II score has not been validated for this purpose. Bleeding has been shown to be more common in drotrecogin alfa (activated)-treated patients than in placebo recipients, but these bleeding episodes are often procedure related. Importantly, the increased rate of bleeding did not outweigh the potential benefits of drotrecogin alfa (activated), as there was an overall survival benefit, providing only patients at high risk of death from sepsis were treated with drotrecogin alfa (activated). The bleeding rate was slightly higher in cohort studies of patients treated with drotrecogin alfa (activated) than in randomised trials; however, this may be explained, at least in part, by the greater severity of illness in these patients. Thus, in daily practice, great caution should be taken to limit the risk of bleeding, by excluding patients at high risk of bleeding and avoiding unnecessary invasive procedures, in order to preserve the survival benefit conferred by drotrecogin alfa (activated).

## Acknowledgements

No sources of funding were used in the preparation of this article. The author participated as co-investigator in the PROWESS, ADDRESS and ENHANCE trials that were sponsored by Eli Lilly (manufacturing drotrecogin alfa [activated]), has received grants for studies from Eli Lilly and has received honoraria for lectures from Eli Lilly. He is also member of the advisory board of 'Advances in Sepsis' and 'About sepsis', a journal and a website sponsored at least in part by Eli Lilly.

The author has received honorarium from Talecris Biotherapeutics (manufacturing antithrombin) for participation in a round table on antithrombin and has also received grants and material for studies not related to the topic of the present article from other companies.

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