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Safety assessment of drotrecogin alfa (activated) in the treatment of adult patients with severe sepsis

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Abstract

Introduction Drotrecogin alfa (activated; recombinant activated protein C) was shown to reduce 28-day all-cause mortality in patients with severe sepsis and to have an acceptable safety profile in 1690 patients studied in the F1K-MC-EVAD (PROWESS) trial. We analyzed all available data on the safety of treatment with drotrecogin alfa (activated) in 2786 adult patients with severe sepsis enrolled in all phase 2 and 3 clinical trials, and in an estimated 3991 patients receiving the drug in commercial use.

Patients and method Mortality and safety analyses were performed on all available data from adult severe sepsis patients enrolled in seven clinical trials as of 12 April 2002. Trial-specific safety data and spontaneously reported serious adverse events from commercial use were extracted from a pharmacovigilance database.

Results The 28-day mortality rate for all adult patients who received active treatment in all clinical trials was 25.3% (704/2786). Serious bleeding events during the infusion period and 28-day study period occurred in 2.8% (79/2786) and 5.3% (148/2786) of patients, respectively. Of bleeding events during the infusion period, 43% (34/79) were procedure-related. Fatal serious bleeding events during the infusion period occurred in 0.4% (12/2786) of cases. Intracranial hemorrhage (ICH) events during the infusion period and 28-day study period occurred in 0.6% (16/2786) and 1.1% (32/2786) of patients, respectively. Ten out of the 16 ICH events occurring during the study drug infusion period were associated with severe thrombocytopenia ($\leq$30,000/mm^3) and/or meningitis. Serious bleeding and ICH events spontaneously reported from commercial use (n = 3991) occurred in 0.9% and 0.2% of patients, respectively.

Conclusion Drotrecogin alfa (activated) significantly reduces mortality in severe sepsis. The efficacy and safety profiles of drotrecogin alfa (activated) have remained consistent over the conduct of multiple clinical trials. The most important serious adverse event associated with drotrecogin alfa (activated) treatment is bleeding. Additional clinical experience indicates that invasive procedures are associated with a substantial percentage of serious bleeding events, particularly those occurring at the start of infusion of the drug. Severe thrombocytopenia (for all serious bleeding events, including ICH) and meningitis (for ICH only) may be risk factors for serious bleeding. However, patients with severe thrombocytopenia and/or meningitis may be at greater risk for bleeding or ICH in the absence of drug therapy.

Keywords activated protein C, drotrecogin alfa (activated), mortality, safety, severe sepsis

APACHE = Acute Physiology and Chornic Health Evaluation; CI = confidence interval; ICH = intracranial hemorrhage.

Introduction

Activated protein C, an endogenous plasma serine protease with antithrombotic, profibrinolytic and anti-inflammatory properties [1–3], is an important modulator of the host systemic response to severe infection [1]. Recently, recombinant human activated protein C (drotrecogin alfa [activated]) was approved for the treatment of adult patients with severe sepsis. Regulatory approvals were based on the results of a single pivotal phase 3 study, which demonstrated a statistically significantly reduction in 28-day all-cause mortality (absolute risk reduction compared with placebo 6.1%, relative risk reduction 19.4%; $P = 0.005$) [4], with supporting data from a single phase 2 study [5]. Consistent with its antithrombotic and profibrinolytic properties, the administration of drotrecogin alfa (activated), as compared with placebo, was associated with an increase in the percentage of patients experiencing a serious bleeding complication (3.5% versus 2.0%; $P = 0.06$) over 28 days in the phase 3 study [4]. Bleeding complications were the most important serious adverse events associated with the administration of drotrecogin alfa (activated) [4].

A total of 1821 adult patients with severe sepsis were enrolled in the randomized, placebo-controlled trials supporting the approval of drotrecogin alfa (activated); 940 patients received active treatment and 881 patients received placebo. Since completion of those controlled trials, further studies have been completed ($n = 2$) or are ongoing ($n = 3$), in which an additional 1846 patients have received drotrecogin alfa (activated). Furthermore, up to 12 April 2002, 3991 patients have received drotrecogin alfa (activated) in commercial use following approval in the USA.

The purpose of this report is to provide a comprehensive review of the safety of drotrecogin alfa (activated) for all adult patients with severe sepsis enrolled in clinical trials (completed and ongoing) since the start of phase 2 clinical development and up to 12 April 2002. Trials were grouped into three categories: controlled trials, open-label trials, and compassionate-use studies. In addition, safety data are presented for patients who received drotrecogin alfa (activated) from spontaneous reports in commercial use.

Patients and method

Patient populations

Table 1 lists the seven clinical studies that enrolled adult patients with severe sepsis and that were completed or ongoing as of 12 April 2002. Studies were classified as 'controlled' if they included a blinded placebo comparison with drotrecogin alfa (activated; Xigris®, Eli Lilly and Company, Indianapolis, IN, USA); 'open-label' if drotrecogin alfa (activated) was administered in a single arm study conducted at prospectively identified and trained investigative sites; or 'compassionate-use' if drotrecogin alfa (activated) was provided on emergent request to noninvestigator clinicians treating patients with severe sepsis.

All studies, except F1K-MC-EVAS, utilized inclusion and exclusion criteria similar to those in the phase 3 study F1K-MC-EVAD (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) [4]. Severe sepsis was defined in all protocols as the presence of known or suspected infection, the presence of a systemic response to infection (as evidenced by alterations in temperature, heart rate, respiratory rate, and white blood cell count), and the presence of one or more associated acute organ dysfunctions (cardiovascular, respiratory, renal, hematologic, or metabolic acidemia). Patients excluded from participation included those at high risk for bleeding, those with severe thrombocytopenia (platelet count $\leq 30{,}000/mm^3$), those taking a variety of antiplatelet agents, and those receiving systemic heparin anticoagulation. Study F1K-MC-EVAS required only the clinical diagnosis of purpura fulminans and did not have the presence of thrombocytopenia as an exclusion criterion.

Table 1

Clinical studies with drotrecogin alfa (activated) in adult patients with severe sepsis

Study ID	Study descriptor	Dosage and administration	Status
F1K-MC-EVAA ($n = 90$)	A phase 2 dose-ranging study	12, 18, 24, 30 μg/kg per hour for 48 hours; 12, 18, 24 μg/kg per hour for 96 hours	Completed
F1K-MC-EVAD ($n = 850$)	A phase 3 efficacy study (PROWESS)	24 μg/kg per hour for 96 hours (±1 hour).	Completed
F1K-MC-EVAS ($n = 28$)	A compassionate-use study in purpura fulminans	24 μg/kg per hour for a minimum of 96 hours	Completed
F1K-MC-EVBE ($n = 273$)	An open-label study (ENHANCE)	24 μg/kg per hour for 96 hours (±1 hour)	Completed
F1K-MC-EVBF ($n = 1189$)	An open-label study (ENHANCE)	24 μg/kg per hour for 96 hours (±1 hour)	Ongoing
F1K-MC-EVBG ($n = 116$)	An open-label study (ENHANCE)	24 μg/kg per hour for 96 hours (±1 hour)	Ongoing
F1K-MC-EVBC ($n = 240$)[1]	A compassionate-use study	24 μg/kg per hour for 96 hours (±1 hour)	Ongoing

Source: clinical study reports for completed studies and protocols for ongoing studies. [1]Mortality and safety monitored for 7 days in countries outside the USA. PROWESS, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis; ENHANCE, Extended Evaluation of Recombinant Human Activated Protein C.

Based on the approved recommendations for the USA, patients receiving drotrecogin alfa (activated) in commercial use would have been expected to have severe sepsis and have been at high risk for death (e.g. as assessed using the Acute Physiology and Chronic Health Evaluation [APACHE] II) [6]. The number of patients who received drotrecogin alfa (activated) in commercial use was estimated from the total number of courses of therapy sold in the USA using hospital-based stores information from 21 November 2001 until 12 April 2002.

Drug administration

Table 1 lists details of drug dose and durations of infusion for each clinical trial. Patients randomly assigned to placebo in the controlled clinical trials received either saline or 0.1% albumin in saline. Based on the approved recommendations for the USA [6], patients receiving drotrecogin alfa (activated) in commercial use would have been expected to receive an infusion rate of 24 μg/kg per hour for a total duration of 96 hours. Specific details regarding actual dose and duration of administration were not available for patients treated in commercial use.

Estimates of 28-day mortality rate

Mortality rates for completed clinical trials were obtained from validated clinical trial databases. Estimates of 28-day all-cause mortality rates for ongoing clinical studies were obtained from separate trial-specific databases created using trial-specific tracking tools. Twenty-eight-day all-cause mortality (i.e. 28 days after the start of infusion) was assessed for all studies, except study F1K-MC-EVBC, in which 7-day mortality was assessed for a subset of patients (non-US). For this subset, the number of additional deaths occurring between days 7 and 28 was estimated using the following method. Of the 240 adults in study F1K-MC-EVBC, 28-day follow-up data were available for 168 patients (40 deaths) and 7-day follow up data were available for 72 patients (12 deaths). It was determined from the result of F1K-MC-EVAD (PROWESS) that the 28-day mortality rate in 7-day survivors receiving drotrecogin alfa (activated) was 15.2%. Therefore, for the subset of 7-day survivors in study F1K-MC-EVBC, an additional nine deaths (15.2% of 60) were estimated to have occurred before study day 28. Thus, total 28-day mortality in study F1K-MC-EVBC was estimated at $(12 + 9 + 40)/240 = 0.254$.

At present, an estimate of the mortality rate for patients who have received drotrecogin alfa (activated) in commercial use is not available. For the placebo-controlled studies (F1K-MC-EVAA and F1K-MC-EVAD [PROWESS]), the cause of death was adjudicated by Lilly physicians, in a blinded manner, for all patients from death summaries provided by the investigators.

Serious bleeding event rate estimates

Bleeding complications meeting the regulatory definition of a serious adverse event were extracted from a validated pharmacovigilance database, which included events reported in clinical trials and in commercial use. For all clinical trials in this report, bleeding complications included, but were not limited to, any of the following: any intracranial hemorrhage (ICH); any life-threatening bleeding event; requirement for 3 units or more of packed red blood cell transfusion per day for 2 consecutive days; or meeting other criteria defining serious adverse events. For patients experiencing ICH, the following data were extracted from the serious adverse event report: type of ICH; most recent platelet count; and presence of meningitis.

The causal relationship of drotrecogin alfa (activated) to serious bleeding events was assessed by comparison with placebo event rates for controlled trials. For open-label and compassionate-use studies, causal relationship was assessed using investigator assignment of causality (related or not related) and by comparing events that occurred during the infusion period with events that occurred postinfusion. The study drug infusion period was defined as the actual duration of infusion plus 1 calendar day (study days 1–5). The 'postinfusion period' was defined as study days 6–28. All serious bleeding events were assessed as 'procedure-related' (if associated with an invasive procedure) or 'non-procedure-related'.

Serious bleeding events were recorded for up to 28 days following the start of study drug administration for all but one study (F1K-MC-EVBC). In study F1K-MC-EVBC, serious bleeding events were recorded for up to 28 days, except for a subset of patients ($n = 72$). For this subset, all serious bleeding events were recorded for 7 days following the start of infusion and study drug-related serious bleeding events were recorded for up to 28 days.

Statistical analysis

Because of the lack of final, validated baseline data for ongoing clinical trials, comparisons between clinical trial types were avoided. Accordingly, 95% confidence intervals (CIs) using exact methods are reported for event rate estimates. Hypothesis testing was not performed as part of the present study. All calculations were performed using SAS version 8.2 software (SAS Institute, Inc., Cary, NC, USA).

Results

Twenty-eight-day all-cause mortality

The administration of drotrecogin alfa (activated) was associated with a mortality rate in controlled trials of 25.1% (236/940; 95% CI 22.4–28.0%), in open-label studies of 25.2% (398/1578; 95% CI 23.1–27.4%), and in compassionate-use studies of 26.1% (70/268; 95% CI 21.0–31.8%). The mortality rate for all patients treated with drotrecogin alfa (activated) in clinical trials was 25.3% (704/2786; 95% CI 23.7–26.9%). The point estimate of the mortality rate with drotrecogin alfa (activated) for each trial category was less than the combined placebo mortality rate of 31.0% (273/881; 95% CI 28.0–34.2%). An estimate of

Table 2

Summary of causes of death in placebo-controlled clinical trials[1]

Cause of death category	Drotrecogin alfa (activated; *n* [%])	Placebo (*n* [%])
Sepsis-induced multiorgan failure	113 (47.9)	107 (39.2)
Refractory septic shock	49 (20.8)	65 (23.8)
Respiratory failure	32 (13.6)	51 (18.7)
Myocardial infarction	9 (3.8)	11 (4.0)
Primary cardiac arrhythmia	6 (2.5)	9 (3.3)
Hemorrhage	4 (1.7)	1 (0.4)
Intracranial hemorrhage	2 (0.8)	1 (0.4)
Stroke	2 (0.8)	7 (2.6)
Other	19 (8.1)	21 (7.7)
Total deaths	236 (100)	273 (100)

The drotrecogin alfa (activated) groups comprised 940 and the placebo groups 881, yielding a total of 1821 patients. [1]F1K-MC-EVAA and F1K-MC-EVAD (PROWESS).

the mortality rate for the population of patients who received drotrecogin alfa (activated) in commercial use is not available.

In controlled clinical trials, the leading causes of death were multiple organ failure, refractory septic shock, and respiratory failure (Table 2). There were numerically fewer deaths from refractory septic shock and respiratory failure in drotrecogin alfa (activated) treated patients than in placebo treated patients. There were fewer deaths from ICH and stroke combined in drotrecogin alfa (activated) treated patients than in placebo treated patients in controlled trials (Table 2).

Serious bleeding events

The overall rate of serious bleeding events for all patients treated with drotrecogin alfa (activated) in all clinical trials combined was 5.3% (148/2786) over the 28-day study period. The serious bleeding event rate associated with drotrecogin alfa (activated) was similar across classes of trials (controlled, open-label, and compassionate-use; Table 3).

The majority of serious bleeding events (58/79) that occurred during the infusion period in patients in all clinical trials (2.1%; 58/2786) were considered by the investigator to be related to drotrecogin alfa (activated). When assessed, thrombocytopenia (platelet counts $\leq$50,000/mm^3) was frequently present in drotrecogin alfa (activated) treated patients who experienced a serious bleeding event during the infusion period (22/53 patients for whom data were available; Table 4). Twenty-one serious bleeding events, which occurred during the infusion period (0.8% of all patients; 21/2786), were not considered to be related to drotrecogin alfa (activated). This incidence rate (0.8%) was similar to the serious bleeding event rate observed during the infusion period for placebo treated patients in controlled studies (0.7%; 6/881). In F1K-MC-EVAD (PROWESS), the incidence of serious bleeding events during the postinfusion period was similar between drotrecogin alfa (activated) (12/850) and placebo patients (11/840; both approximately 1%). For all drotrecogin alfa (activated) treated patients, only a small minority of serious bleeding events that occurred during the postinfusion period (8/69 events; 0.3% of all patients) were considered to be related to drotrecogin alfa (activated).

A relatively high proportion of all serious bleeding events was found to be related to invasive procedures, as shown in Table 5. In the phase 3 trial (study F1K-MC-EVAD [PROWESS]), 53.3% (16/30) of serious bleeding events in drotrecogin alfa (activated) treated patients and 23.5% (4/17) in placebo treated patients were associated with invasive procedures during the 28-day study period. These procedures typically involved the instrumentation of large blood vessels or highly vascular organs. The incidence of non-pro-

Table 3

Rates of serious bleeding events classified as during the infusion period and postinfusion period in all clinical trials

	SBE during infusion period		SBE postinfusion period	
Population	Patients (*n*)	% (95% CI)	Patients (*n*)	% (95% CI)
Placebo (*n* = 881)	6	0.7 (0.3–1.5)	14	1.6 (0.8–2.7)
Drotrecogin alfa (activated)				
All controlled trials (*n* = 940)	20	2.0 (1.3–3.3)	15	1.6 (0.9–2.6)
All open-label studies (*n* = 1578)	49	3.1 (2.3–4.1)	45	2.9 (2.1–3.8)
All compassionate-use studies (*n* = 268)	10	3.7 (1.8–6.8)	9	3.4 (1.6–6.3)
All treated patients (*n* = 2786)	79	2.8 (2.3–3.5)	69	2.5 (1.9–3.1)

CI, confidence interval; SBE, serious bleeding event.

Table 4

Classification by platelet counts of all serious bleeding events during infusion period in all clinical trials

	SBEs during infusion period	
Platelets ($\times 10^3/mm^3$)[1]	Events (*n*)	Cumulative %
≤20	5	9.4
>20 to ≤30	6	20.8
>30 to ≤50	11	41.5
>50 to ≤100	12	64.2
>100	19	100.0
Not available	26	
Total	79	

A total of 2786 patients treated with drotrecogin alfa (activated) infusion were included in this analysis. [1]Platelet counts were recorded within the preceding 24 hours of a serious bleeding event (SBE).

cedure-related serious bleeding events (i.e. spontaneous bleeding events) was similar between active treatment and placebo groups in that trial. In all patients receiving drotrecogin alfa (activated) in clinical trials, serious bleeding events associated with invasive procedures accounted for 39.2% (58/148) of the total number of events (Table 5).

The incidence of serious bleeding events was highest during the first day of therapy and decreased thereafter for all drotrecogin alfa (activated) treated patients. Of serious bleeding events on day 1 of therapy, 56% (15/27) were procedure-related. On day 1 there were 12 patients with non-procedure-related serious bleeding events. Platelet counts were not available for three of these 12 patients. Of the remaining nine patients, three had severe thrombocytopenia (platelets ≤30,000/mm^3) and three had an elevated international normalized ratio greater than 2.0.

In commercial use, 3991 patients received treatment with drotrecogin alfa (activated) in the USA. There have been 34 serious bleeding events spontaneously reported to the pharmacovigilance database, for a rate of 0.9% (34/3991). If one assumes that many of those patients had APACHE II scores greater than 25, then comparison with PROWESS (F1K-MC-EVAD) patients who had APACHE II scores greater than 25 is possible. PROWESS (F1K-MC-EVAD) patients with APACHE II scores greater than or equal to 25, who received drotrecogin alfa (activated) and suffered serious bleeding events during the infusion period, amounted to 9/414 (2.2%) and those with scores below 25 amounted to 9/436 (2.1%).

In PROWESS (F1K-MC-EVAD), 75% (634/850) of patients who received drotrecogin alfa (activated) and a similar percentage (76%; 637/840) of patients who received placebo were exposed to heparin during the infusion period. PROWESS (F1K-MC-EVAD) patients who had serious bleeding events during the infusion period and were exposed to heparin amounted to 11/18 (61.1%). For comparison, 14/49 (28.6%) of patients in open-label trials and 3/10 (30.0%) patients in compassionate-use trials who had

Table 5

Number of procedure-related 28-day serious bleeding events by site of hemorrhage sorted from largest to smallest percentage of serious bleeding events that were procedure-related in all clinical trials

	Procedure-related events				
Site of hemorrhage	During infusion period	Postinfusion period	Total procedure-related	All SBEs[1]	% Procedure-related
Vascular	5	2	7	7	100.0
Retroperitoneal	2	1	3	3	100.0
Intra-abdominal	5	4	9	10	90.0
Skin/soft tissue	9	3	12	15	80.0
Intrathoracic	8	3	11	20	55.0
Other/undetermined	2	5	7	14	50.0
Spleen	0	1	1	3	33.3
Gastrointestinal	3	5	8	44	18.2
ICH	0	0	0	32	0.0
Total	34	24	58	148	39.2%

A total of 2786 patients treated with drotrecogin alfa (activated) infusion were included in this analysis. [1]All serious bleeding events (SBEs) combines both procedure-related and non-procedure-related events during the 28-day period. ICH, intracerebral hemorrhage.

Table 6

Intracranial hemorrhages classified according to type during infusion period, postinfusion period, and for the total 28 days after initiation of infusion in all clinical trials

Intracranial hemorrhage type	During infusion period	During postinfusion period	Total
Parenchymal[1]	14	6	20
Subarachnoid	1	1	2
Subdural	0	1	1
Other/undetermined	1	1	2
Stroke with hemorrhagic transformation	0	7	7
Total	16	16	32

A total of 2786 patients treated with drotrecogin alfa (activated) infusion were included in this analysis. [1]Spontaneously occurring parenchymal hemorrhage.

serious bleeding events during the infusion period were exposed to heparin.

Serious bleeding events – intracranial hemorrhage subset

In controlled clinical trials, two patients receiving drotrecogin alfa (activated; 0.2%; 2/940) and one patient receiving placebo (0.1%; 1/881) experienced ICH (all reported as parenchymal). Both events in the drotrecogin alfa (activated) group occurred during the study drug infusion period and were associated with severe thrombocytopenia (platelet count $\leq$30,000/mm^3). All three events were associated with a fatal outcome. In open-label studies, 11 and 10 patients receiving drotrecogin alfa (activated) experienced ICH during the infusion period (0.7%) and postinfusion period (0.6%), respectively. Three and six patients receiving drotrecogin alfa (activated) in compassionate-use studies experienced ICH during the infusion period (1.1%) and postinfusion period (2.2%), respectively.

For all patients receiving drotrecogin alfa (activated) in clinical trials, the ICH rate was 0.6% (16/2786) during the study drug infusion period and 0.6% (16/2786) during the postinfusion period. The overall 28-day ICH event rate was 1.1% (32/2786).

Parenchymal hemorrhage ($n = 14$) was the most common site of ICH event during the infusion period (Table 6). Nine ICH events that occurred during the infusion period were fatal, of which seven were considered related to drotrecogin alfa (activated) (Table 7). Five of these seven events, which were considered to be related to drotrecogin alfa (activated), were associated with thrombocytopenia (platelets $\leq$50,000/mm^3; range 17,000–49,000/mm^3). Meningitis was present in two of those five events, and severe thrombocytopenia (platelets $\leq$30,000/mm^3) was present in four of those five events. Ten of the 16 events (62.5%) had one or both potential risk factors (Table 8). Eight fatal ICH events occurred during the postinfusion period, of which only one was considered related to drotrecogin alfa (activated). The other seven fatal ICH events considered not related to drotrecogin alfa (activated) occurred between study days 8 and 28 – well after the infusion period.

In commercial use, 0.2% (8/3991) patients receiving drotrecogin alfa (activated) were reported to have experienced an ICH.

Non-ICH serious bleeding events associated with fatal outcome

In controlled clinical trials, four drotrecogin alfa (activated) patients and one placebo patient experienced non-ICH serious bleeding events associated with a fatal outcome based on adjudicated cause of death. Fatal non-ICH serious bleeding events that were reported as serious adverse events for drotrecogin alfa (activated) patients in all clinical trials combined are presented in Table 8. Three patients experienced non-ICH serious bleeding events associated with a fatal outcome. All three events occurred during the infusion period and all were considered related to drotrecogin alfa (activated). One of these involved thrombocytopenia (platelets 19,000/mm^3) with severe coagulopathy (partial thromboplastin time $\geq$150 s).

Discussion

The observed mortality rates for patients receiving drotrecogin alfa (activated) were consistent across controlled, open-label and compassionate-use trials, ranging from 25.1% to 26.1%. These results are similar to, and supportive of, the observed mortality rate of 24.7% associated with drotrecogin alfa (activated) use reported in the pivotal, phase 3 trial F1K-MC-EVAD (PROWESS) [4]. These mortality rates are lower than recent mortality rate estimates for severe sepsis, which ranged between 30% and 50% [7] and lower than the combined placebo rate from controlled clinical trials of 31.0%. The consistency of treatment effects in drotrecogin

Table 7

Summary of all fatal bleeding events related and unrelated to drotrecogin alfa (activated) in all clinical trials

	During infusion period		Post-infusion period	
Type of event	Drug related (*n* [%])	Not related (*n* [%])	Drug related (*n* [%])	Not related (*n* [%])
All ICH bleeding	12 (0.4)	4 (0.1)	6 (0.2)	10 (0.4)
Fatal ICH bleeding	7 (0.3)	2 (0.07)	1 (0.04)	7 (0.3)
Fatal non-ICH bleeding	3 (0.1)	0 (0)	0 (0)	0 (0)

A total of 2786 patients treated with drotrecogin alfa (activated) infusion were included in this analysis. ICH, intracranial hemorrhage.

Table 8

Classification by platelet counts of intracranial hemorrhages during infusion period and cross-classification with presence of meningitis in all clinical trials

	ICH during infusion period		
Platelets ($\times 10^3/mm^3$)[1]	Events[2]	Cumulative % of patients	Meningitis
≤20	3/5	20.0% (3/15)	1/3
>20 to ≤30	3/6	40.0% (6/15)	1/3
>30 to ≤50	2/11	53.3% (8/15)	0/2
>50 to ≤100	3/12	73.3% (11/15)	2/3
>100	4/19	100.0% (15/15)	2/4
Not available	1/26		
Total	16/79		6/16

A total of 2786 patients treated with drotrecogin alfa (activated) infusion were included in this analysis. [1]Platelet counts were recorded within the preceding 24 hours of an intracerebral hemorrhage (ICH). [2]Patients with an ICH/all patients with a serious bleeding event.

alfa (activated) patients might have been expected given that, for the most part, inclusion and exclusion criteria were similar across trials.

The survival benefit associated with drotrecogin alfa (activated) appears to be related to a reduction in the number of deaths from refractory septic shock and respiratory failure. These observations are consistent with the observed more rapid improvement in cardiovascular and respiratory function for drotrecogin alfa (activated) patients as compared with placebo patients in study F1K-MC-EVAD (PROWESS) [8].

Consistent with its antithrombotic and profibrinolytic properties, drotrecogin alfa (activated) increased the risk for serious bleeding. The overall serious bleeding event rate (5.3%) includes compassionate-use trials, in which investigators had limited experience using drotrecogin alfa (activated). The percentage of patients experiencing an event probably related to drotrecogin alfa (activated) appears to range between 2.1% and 2.8%, as assessed by the investigator or by whether the event occurred during the infusion period, respectively. Approximately 2.0% of placebo patients enrolled in controlled trials experienced a serious bleeding event over the 28-day period. Neither APACHE II score (<25 or ≥25) nor concomitant heparin use appear to alter serious bleeding event rates associated with drotrecogin alfa (activated) substantially. Underreporting of baseline heparin exposure in the open-label and compassionate-use trials is likely, given that medication listings for the safety database were only collected on the day of the event.

Serious bleeding event rates for both active treatment and placebo patients enrolled in clinical trials of drotrecogin alfa (activated) probably underestimate the bleeding risk for all patients with severe sepsis. In these trials, patients at increased risk for bleeding (e.g. some patients with multiple trauma) or patients with severe thrombocytopenia (i.e. platelet count ≤30,000/mm^3) were excluded from participation. Clinical trials of treatment of severe sepsis with other novel therapeutics that have antithrombotic properties also excluded a similar patient population. Estimates of serious bleeding complications in these latter trials ranged between 6.0% [9] and 12.8% [10] for placebo treated patients. Exclusion criteria related to bleeding risk similar to those used in all of these trials should be employed in developing guidelines for the use of drotrecogin alfa (activated).

Severe thrombocytopenia is included as a 'warning' in the US Package Insert and as a 'contraindication' in the European Summary of Product Characteristics. In the former instance, the recommendation is for physicians to weigh potential benefit of drotrecogin alfa (activated) against a potentially increased risk associated with its use. In the European Summary of Product Characteristics, the recommendation is that physicians not administer drotrecogin alfa (activated) to patients with platelet counts of 30,000/mm^3 or less. Indeed, serious bleeding events in drotrecogin alfa (activated) patients appear to be associated with severe thrombocytopenia, suggesting that this characteristic may be a risk factor for bleeding complications. Therefore, maintaining a platelet count above 30,000/mm^3 and discontinuing the drotrecogin alfa (activated) infusion if the platelet count falls below this level are reasonable recommendations to guide its use.

A large percentage of bleeding events associated with drotrecogin alfa (activated) were also related to procedures performed either before or during the infusion period. The types of procedures associated with bleeding complications were frequently those in which adequate control of bleeding vessels could not be obtained. In controlled trials, the percentage of patients experiencing non-procedure-related bleeding complications was similar between drotrecogin alfa (activated) and placebo patients. Therefore, limiting invasive procedures before and during infusion of drotrecogin alfa (activated), as well as minimizing risks associated with procedures (e.g. instrumentation of blood vessels in which direct compression might be expected to control bleeding), could improve the safety profile of the drug.

Additionally, approved product labels recommend stopping the drotrecogin alfa (activated) infusion 2 hours before invasive procedures and waiting 12 hours after major surgical procedures to restart the infusion after ensuring adequate hemostasis [6]. The infusion may be restarted immediately after uncomplicated, less invasive procedures after ensuring adequate hemostasis. These recommendations are based on the observation that the concentration of drotrecogin alfa (activated) in plasma is below the assay level of detection in a large majority of patients within 2 hours of discontinuing the infusion [11].

The difference between ICH events occurring during the infusion period (0.6%) or considered related to drug, and the ICH event rate in all clinical trials combined (1.1%) was similar to the background rate for ICH reported for patients with severe sepsis. In a recent large sepsis trial of antithrombin III, 0.4% of placebo treated patients experienced ICH during the study [10]. Oppenheim-Eden *et al.* [12] also reported an ICH event rate of 0.4% for all intensive care unit patients who did not have an admitting diagnosis of stroke or stroke syndrome. However, all patients experiencing ICH had a diagnosis of severe sepsis and a platelet count of 30,000/mm^3 or less, suggesting that the event rate for the severe sepsis population overall may exceed 0.4% [12]. In a recently completed phase 2 trial of platelet activating factor-ase, an ICH event rate of 2.3% (1/43) was reported in placebo-treated sepsis patients (Opal S, personal communication).

Approximately 0.4% of drotrecogin alfa (activated) patients experienced a serious bleeding event associated with a fatal outcome that was considered related to its use during the infusion period. These events were most frequently ICH events. These data suggest that, although use of drotrecogin alfa (activated) reduces sepsis-induced mortality, its anticoagulant effects may increase the risk for life-threatening bleeding complications. Patients that appear to be at risk for such a complication are those with severe coagulopathy (i.e. low platelet counts, high international normalized ratio). Risk for sepsis-related death in these patients may be greater than that in the overall population of severe sepsis patients with no coagulopathy.

In controlled trials, although drotrecogin alfa (activated) treated patients experienced more hemorrhage-related deaths, there were fewer deaths from stroke in drotrecogin alfa (activated) patients than in placebo patients (two versus seven patients). The composite end-point of any fatal ICH and any fatal stroke favored drotrecogin alfa (activated) as compared with placebo (four versus eight patients). The number of patients experiencing any fatal bleeding event or any fatal stroke was similar between the drotrecogin alfa (activated) and placebo groups (nine versus eight patients, respectively). These data suggest that the 28-day all-cause mortality rates reported for drotrecogin alfa (activated) represent a composite end-point of less sepsis-induced death, potentially less thrombotic-related deaths, as well as any fatal complications associated with the use of drotrecogin alfa (activated).

The primary limitation of these analyses was the lack of placebo treatment groups for five of the seven studies reported, and no comparison group for patients administered drotrecogin alfa (activated) under commercial use. Additionally, baseline data describing the patient population was unavailable for patients enrolled in ongoing trials or receiving drotrecogin alfa (activated) commercially. There were also notable differences in the inclusion criteria used to enroll patients in the compassionate-use study F1K-MC-EVAS (i.e. that study enrolled only patients with purpura fulminans). This inclusion criterion may explain, in part, the higher bleeding rates seen in compassionate-use trials.

Conclusion

Drotrecogin alfa (activated) significantly reduces mortality in severe sepsis. The treatment efficacy and safety profiles of drotrecogin alfa (activated) have remained consistent over multiple clinical trials. The only significant serious adverse event associated with drotrecogin alfa (activated) treatment is bleeding. Additional clinical experience indicates that invasive procedures are associated with a substantial percentage of

Key messages

- Mortality rates in drotrecogin alfa (activated) treated patients remained consistent across trials
- The most important serious adverse event associated with drotrecogin alfa (activated) treatment is bleeding
- Serious bleeding events are most frequent on day 1 of therapy with drotrecogin alfa (activated) and rapidly decline on subsequent days
- Serious bleeding events were frequently procedure-associated
- ICH during infusion period of drotrecogin alfa (activated) was frequently associated with severe thrombocytopenia and/or meningitis

these serious bleeding events. Severe thrombocytopenia (for all serious bleeding events) and meningitis (for ICH only) may be risk factors for serious bleeding. Mitigating the risk for serious bleeding by maintaining adequate platelets (e.g. >30,000/mm^3) during drotrecogin alfa (activated) infusion may reduce risk for both bleeding and ICH.

Competing interests

Gordon R Bernard received grant support from Eli Lilly and Company and serves as an occasional consultant; Jean-Louis Vincent is a consultant to Eli Lilly and Company; and William L Macias, David E Joyce, Mark D Williams, and Joan Bailey are employees of Eli Lilly and Company.

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