

OUTCOMES AFTER ADMINISTRATION OF DROTRECOGIN ALFA IN PATIENTS WITH SEVERE SEPSIS AT AN URBAN SAFETY NET HOSPITAL

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ABSTRACT

Drotrecogin alfa was introduced in 2001 as a treatment for severe sepsis following the results of the PROWESS trial; however, in October of 2011 drotrecogin alfa was removed worldwide due to a lack of survival benefit demonstrated in the PROWESS-SHOCK trial. There is limited literature describing the outcomes seen outside of the controlled research environment with drotrecogin alfa. **Objective:** The purpose of this study was to describe the outcomes of patients treated with drotrecogin alfa in clinical practice at an urban safety net hospital. **Methods:** A retrospective analysis was conducted on all patients that received drotrecogin alfa from January 2002 to April 2008. The primary outcome was 28-day mortality in all patients. Baseline patient characteristics and 28-day mortality were compared to those found in the PROWESS trial. **Results:** In the current study, 59.5% expired before 28 days which was significantly higher than the 24.7% mortality rate found in PROWESS ($p < 0.0001$). However, patients in the current study were more ill than those found in PROWESS as shown by the average APACHE II score in the current study being 28.2 versus 24.6 in PROWESS ($p < 0.0001$). Patients with HIV had the highest 28-day mortality rate of 77% while patients that were obese had the lowest 28-day mortality rate of 33.3%. **Conclusions:** Patients treated with drotrecogin alfa in clinical practice tended to have a higher mortality rate than those patients treated in the PROWESS study. However, patients in the current study tended to be more ill than those in PROWESS.

INTRODUCTION

Sepsis, defined as the systemic inflammatory response syndrome (SIRS) secondary to infection, is a pathologic process that is often lethal and results in an annual economic burden of approximately 17 billion dollars in the United States (Martin, et al. 2003; Angus, et al. 2001). A rise in the incidence of sepsis has also been reported of approximately 8.7 percent annually (Martin, et al. 2003). Severe sepsis, defined as sepsis that results in organ dysfunction, carries a mortality rate of 30-50 percent (Levy, et al., 2003; Bernard, et al. 2001). Patients with severe sepsis display a generalized inflammatory and pro-coagulant response to infection through various inflammatory cytokines that activate coagulation and inhibit fibrinolysis (Bernard, et al. 2001). This state

can progress to endovascular injury, organ dysfunction, and ultimately death. Until 2001, management of sepsis consisted solely of supportive measures. Research demonstrated that depletion of protein C is a key factor to regulating the unabated inflammatory and pro-coagulant responses in severe sepsis. In 2001, the FDA approved drotrecogin alfa activated or recombinant human activated protein C (rhAPC, Xigris[®]) based on the results of the landmark trial, PROWESS (Protein C Worldwide Evaluation in Severe Sepsis), which demonstrated a 6.1 percent absolute reduction in 28-day mortality (Levy, et al 2003; Xigris[®] package insert, 2001). This was the first time any drug had demonstrated a positive impact on mortality related to severe sepsis. The PROWESS trial concluded that one life would be

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saved for every 16 patients treated. Bleeding was the most common adverse event of drotrecogin alfa and occurred more frequently in patients with predisposing conditions than in placebo. The PROWESS trial also concluded that one additional serious bleeding event would occur for every 66 patients treated with drotrecogin alfa. However in a subgroup analysis of patients enrolled in PROWESS with single organ dysfunction and recent surgery, the all-cause mortality rate was higher when compared to placebo (Bernard, et al. 2001). Consequently, the FDA required a study to evaluate the use of drotrecogin alfa in severe sepsis and a low risk of death.

The ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) trial was conducted and examined the use of drotrecogin alfa in severe sepsis and a low risk of death (Abraham, et al. 2005). The results demonstrated no impact on mortality and an increased incidence of serious bleeding in patients with severe sepsis and a low risk of death, such as in patients with an APACHE II less than 25 or only one organ failure, hence the Surviving Sepsis Campaign guidelines were modified recommending drotrecogin alfa only “in patients with high risk of death (APACHE II \geq 25 or multiple organ failure).”

In October of 2011, Eli Lilly and Company (manufacturer of drotrecogin alfa) announced a worldwide withdrawal of drotrecogin alfa due to no survival benefit demonstrated in the recently completed PROWESS-SHOCK trial (FDA drug safety communication).

Studies in the controlled research environment have arrived at conflicting conclusions about the efficacy of drotrecogin alfa. Additional studies are warranted that examine the efficacy and safety of drotrecogin alfa in the setting of clinical practice.

Grady Memorial Hospital is a level 1 trauma center in downtown Atlanta that serves a patient population of

primarily uninsured or underinsured patients.

The purpose of this study is to evaluate the outcomes in patients who were treated with drotrecogin alfa at Grady Memorial Hospital.

METHODS

A retrospective analysis of patients who received drotrecogin alfa from January 1st 2002 to April 30th 2008 was conducted using an institutional pharmacy prescription database. A chart review was conducted for all patients with missing information within the database. Outcomes were assessed in all patients as well as in the following predefined patient subgroups: end stage renal disease (ESRD), APACHE II score of \geq 25 or $<$ 25, HIV, HIV and a CD4 count \leq 50, burn injury, obesity as defined by a weight $>$ 135 kg, and treatment with stress dose corticosteroids (treatment with \geq 200 mg of hydrocortisone or equivalents per day). Bleeding events were prospectively assessed in all patients during drotrecogin alfa administration. A severe bleed was defined as any intracranial hemorrhage, any bleeding that required the administration of 3 units or more of packed red blood cells on two consecutive days, or any life-threatening bleed. Any bleeding that occurred during treatment with drotrecogin alfa that was not classified as severe bleed was classified as a bleeding event. The primary outcome measured was 28-day mortality in all patients as well as in the predefined patient subgroups. Secondary outcomes included ICU and hospital length of stay (LOS) in all patients as well as in the predefined patient subgroups and bleeding events. Some baseline characteristics, 28-day mortality, and incidence of severe bleeding in the study population were compared to those reported in the PROWESS study. Descriptive and inferential statistics were used for data analysis on study outcomes. A p-value of $<$ 0.05 was considered statistically significant.

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RESULTS

A total of 133 patients were identified during the study period; however, 17 patients were excluded due to incomplete data. Base-line demographics for the study sample are shown in Table 1. The majority of patients were severely ill as demonstrated by approximately 70% of patients having an APACHE II score of 25 or greater and 88% of patients presenting with shock. In addition, 30.2% of patients were treated with corticosteroids, and 14.6% of patients had a baseline precaution or relative contraindication to drotrecogin alfa prior to therapy. Eighty four percent of patients had two or more organ failures and most patients had infections of the lung or abdomen. Other sites of infection in the current study that comprised the other category were the blood, cerebrospinal fluid, and skin.

Table 1. Baseline characteristics of patients

N = 116	n (%)
Mean age, yrs (range)	51 (17-91)
Male	76 (65.5)
APACHE II \geq 25	81 (69.8)
Mechanical ventilation	74 (63.3)
Presence of shock	103 (88.0)
Obese	9 (7.8)
HIV	13 (11.2)
HIV with CD4 \leq 50	5 (4.3)
ESRD	2 (1.7)
Service type	
Surgical	54 (46.6)
Medical	56 (48.2)
Burn	6 (5.2)
Receipt of corticosteroids	35 (30.2)
Baseline drotrecogin alfa precaution	13 (11.2)
Baseline drotrecogin alfa contraindication	4 (3.4)
No. of organ failures	

0	1 (0.9)
1	18 (15.5)
2	21 (18.1)
3	41 (35.3)
4	27 (23.3)
5	8 (6.9)
Site of infection	
Lung	66 (42.9)
Abdomen	22 (14.3)
Urinary tract	15 (9.7)
Other	51 (33.1)

Table 2 shows the results for the primary outcome. For the overall study population the 28 day mortality rate was 59.5%. Compared to patients without HIV, those with HIV had a trend towards a higher 28-day mortality (76.9% vs. 57.3%). Patients who were obese or had an APACHE II score of $<$ 25 had a lower 28-day mortality rate of 33% and 45.7%, respectively.

Table 2. 28-day mortality

Category	n (%)
Overall, N=116	69 (59.5)
HIV, n=13	10 (76.9)
HIV CD4 \leq 50, n=5	3 (60)
ESRD, n=2	1 (50)
Steroids, n=35	20 (57.1)
Burn, n=6	3 (50)
Obese, n=9	3 (33.3)
APACHE II \geq 25, n=81	52 (64.2)
APACHE II $<$ 25, n=35	16 (45.7)

* Numbers reported are frequency counts (percentage)

Table 3 reports the median LOS seen in the study. Overall, patients had a median ICU LOS of 19 days and hospital LOS of 23 days. However, patients with

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burns and obesity had the longest LOS with a median ICU LOS of 59 and 58 days and hospital LOS of 65 and 58 days, respectively.

Table 3. Lengths of stay in the hospital in days

Category	ICU LOS	Hospital LOS
Overall, N = 116 (IQR)	19 (8.0-34.3)	23 (11.8-53.0)
HIV, n=13	8 (6-14)	15 (8-34)
HIV CD4 ≤ 50, n=5	6 (6-8)	12 (10-30)
ESRD, n=2 (IQR)	18 (13-23)	24 (22-26)
Steroids, n=35	18 (8.0-28.5)	22 (13.5-52.0)
Burn, n=6	59 (35.5-72.0)	65 (35.5-113.3)
Obese, n=9	58 (23-60)	58 (23-60)
APACHE ≥ 25		
Survivors	36 (14.5-58)	50 (27-67.5)
Non-survivors	14.5 (4-22)	17.5 (5.25-29)
APACHE < 25		
Survivors	19 (8.5-39.25)	28.5 (16.75-78.75)
Non-survivors	21 (11-29)	22 (15-34)

* Numbers reported are median (interquartile range)

Twenty-five non-severe bleeding events (21.6%) occurred with 5 (20%) occurring in patients with a baseline bleeding precaution and 2 (8%) occurring in patients with a baseline contraindication to drotrecogin alfa. Four severe bleeds occurred in the study group, with 1 occurring in a patient with a baseline precaution and 1 occurring in a patient with a baseline relative contraindication. Conversely, 3 patients with a baseline relative contraindication and 12 patients with a baseline precaution did not have a severe bleed following receipt of drotrecogin alfa.

Table 4 depicts the comparison of current patient

population and outcomes with those seen in the PROWESS trial. Patients in the current study were younger, more likely to be male and had more organ failure when compared to the patients in the PROWESS trial. The rate of severe bleeds was similar between these groups although 28-day mortality was significantly higher compared to PROWESS (59.5% vs. 24.7% p<0.0001).

Table 4. PROWESS comparison

Characteristic	PROWESS, N=850	Current Study, N=116	p-value
Age (years)	60.5 (17.2)	51 (16.9)	<0.0001
Male sex	56.1	65.5	0.05
APACHE II score	24.6 (7.6)	28.2 (7.4)	<0.0001
Mechanical ventilation	73.3	63.8	0.02
Shock	70.4	88.0	0.0001
Site of infection			
Lung	53.6	42.9	0.01
Abdomen	20.0	14.3	0.09
Urinary tract	10.0	9.7	0.92
Other	16.4	33.5	0.007
No. of organ failures			
0	0.1	0.9	0.84
1	25.3	15.4	0.02
2	31.8	17.9	0.002
3	25.2	35.0	0.02
4	14	23.9	0.005
5	3.6	6.8	0.10
Recent surgery	26.5	52	<0.0001
Serious bleed	3.5	3.4	0.95
28-day mortality	24.7	59.5	<0.0001

* Data presented are means +/- standard deviation, or percents

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DISCUSSION

The overall 28-day mortality in patients treated with drotrecogin alfa in this study was 59.5%. Patients with HIV or an APACHE II score ≥ 25 appeared to have a higher 28-day mortality rate of 76.9 and 64.2%, respectively, possibly due to the presence of additional comorbidities. Patients with burns and obesity had a higher median LOS in the ICU (59 and 58 days, respectively) as compared to the overall ICU length of stay (19 days), possibly due to their underlying disease states.

Patients with a baseline precaution or relative contraindication received drotrecogin alfa in our clinical practice when the treating team determined that the benefits of therapy outweighed the bleeding risks.

Differences at baseline were observed between the current study and PROWESS in regards to age (50.6 vs. 60.5, $p < 0.0001$), mechanical ventilation (63.8% vs. 73.3%, $p < 0.02$), shock (88% vs. 70.4%, $p < 0.0001$), and recent surgery (52% vs. 26.5%, $p < 0.0001$), respectively. The 59.5% 28-day mortality rate observed in this study is considerably higher than the 24.7% seen in PROWESS ($p < 0.0001$). However, 34% of the patients in this study would have been excluded from PROWESS due to comorbidities or baseline bleeding risk. In addition, 65% of patients in this study had 3 or more organ failures as compared to 42.8% of patients in PROWESS. Regardless, current patients had a higher severity of illness compared to those evaluated in PROWESS as evident by higher APACHE II score (28.2 vs. 24.6, $p < 0.0001$). Another possible explanation for the disparity in mortality found between the current study and PROWESS is that patients in the PROWESS trial had a predicted mortality of about 40-48% for an APACHE II score of approximately 25, yet the mortality for the control group was much lower than predicted at around 30%. A final possible explanation is the increased mortality

resulted from the receipt of an agent in a more critical population that does not affect mortality and confers an increased bleeding risk.

It is important to study the safety and efficacy of medications after their initial approval for this reason so as to provide additional information outside of the controlled research environment. Patients that receive drug therapies outside of the clinical trial setting may not exactly resemble those patients that approval for the medication was based. Those patients that would have been excluded from PROWESS formed the basis for the analysis for most of the predetermined patient subgroups.

One limitation for this study is that it was a retrospective chart review. Moreover, any differences in outcomes seen in the subgroups cannot be definitively attributed to the subgroup. Another limitation for this study is the absence of a control group at our institution with which to compare outcomes between those who received drotrecogin alfa and those who did not. The small sample size in the subgroups also limited the interpretation of the study outcomes.

CONCLUSIONS

Patients treated with drotrecogin alfa in our clinical practice tended to have a higher mortality rate than those patients treated in the PROWESS study. However, patients examined in the current study had a higher severity of illness compared to those in PROWESS. Patients with HIV or an APACHE II score ≥ 25 appeared to have an increased mortality rate when compared to the overall mortality rate, and patients with burns and obesity tended to have a longer LOS. Given the recent findings of the PROWESS-SHOCK trial, drotrecogin alfa is an agent of historical significance that ultimately provides no benefit to septic patients. The current study highlights the clinical outcomes and types of patients

that were treated with drotrecogin alfa at Grady Memorial Hospital from January 1st 2002 to April 30th 2008.

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