ADDRESS (ADministration of DRotrecogin alfa [activated] in Early stage Severe Sepsis) long-term follow-up: One-year safety and efficacy evaluation*

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Objective: **To demonstrate that drotrecogin alfa (activated) has an acceptable safety profile 1 yr from randomization.**

Design: **One-year follow-up of patients participating in a placebo-controlled clinical study of drotrecogin alfa (activated) in severe sepsis patients at low risk of death (the ADDRESS study).**

Setting: **The study was conducted at 516 hospitals in 34 countries.**

Patients: **The study included 2,640 patients.**

Interventions: **One-year follow-up was performed as an addendum to the placebo-controlled ADDRESS study. Treatment groups were compared using the chi-square test and Kaplan-Meier estimates.**

Measurements and Main Results: **Survival status at 1 yr was obtained for 90% of patients enrolled in the study (n = 2,376). The difference in mortality rate between drotrecogin alfa (activated) and placebo patients was numerically smaller at 1 yr (34.2% and 34.0%, respectively, $p = .94$) than at 28 days (18.5% and 17.0%, respectively, $p = .34$). In the subgroups defined by organ dysfunction class (single or multiple) and Acute Physiology and Chronic Health Evaluation II score (<25 or ≥25), the differences in mortality rate between treatment groups at 1 yr were consistent with those observed at 28 days; no significant differences in mortality rates between treatment groups were observed. No additional serious adverse events were reported during the period between hospital discharge and 1 yr.**

Conclusions: **No increased risk of death or evidence of harm at 1 yr was associated with drotrecogin alfa (activated) administration in patients with severe sepsis at lower risk of death. (Crit Care Med 2007; 35:1457–1463)**

KEY WORDS: severe sepsis; drotrecogin; activated protein C; Xigris; survival; clinical trial

Drotrecogin alfa (activated) (DrotAA), a recombinant human activated protein C, has been shown to reduce all-cause mortality in patients with severe sepsis. In the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) study, administration of DrotAA yielded a highly statistically significant reduction in 28-day all-cause mortality (1). However, subgroup analyses of mortality by disease severity showed that the observed absolute mortality benefit was larger in patients at high risk of death. As a result, regulatory authorities who have granted approval of DrotAA have recommended its use in patients with severe sepsis and a high level of disease severity and risk of death. At the time of approval of DrotAA for treatment of severe sepsis, the U.S. Food and Drug Administration (FDA) requested that the efficacy and safety of DrotAA be further evaluated in the non-indicated population of patients with "less severe" sepsis who are at lower risk of death. Therefore, an international, multicenter, randomized, placebo-controlled study (ADDRESS) was initiated to evaluate the efficacy and safety of DrotAA in patients with severe sepsis at low risk of death (e.g., patients with a baseline Acute Physiology and Chronic Health Evaluation [APACHE] II score <25 or only one organ dysfunction at baseline). Enrollment in the study was terminated on the recommendation of the study Data Monitoring Committee after the second interim analysis when it was determined that there was a low likelihood of meeting the prospectively defined objective of demonstrating a significant reduction in 28-day mortality with DrotAA. The 28-day and in-hospital efficacy and safety results from the ADDRESS study have recently been published (2).

*See also p. 1609.

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The study was conducted at 516 sites in 34 countries. A list of the participating institutions was published online in the full text article Abraham et al. *N Engl J Med* 2005; 353:1331–1342.

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The ADDRESS study was already underway when the long-term follow-up study of PROWESS was completed. The PROWESS long-term follow-up showed that the long-term survival benefit of DrotAA continued to be evident at 1 yr after study entry in patients at high risk of death (3). Thus, the U.S. FDA requested that information on the effect of DrotAA administration in patients at lower risk of death also be evaluated at 1 yr postrandomization. The objective of the long-term follow-up portion of the ADDRESS study was to demonstrate that DrotAA had an acceptable safety profile in adult patients at lower risk of death from severe sepsis at 1 yr postrandomization.

METHODS

Patients. ADDRESS was a randomized double-blind, placebo-controlled study evaluating the efficacy of DrotAA (Xigris, Eli Lilly and Company, Indianapolis, IN) in patients with severe sepsis at lower risk of death. Entry criteria have been reported previously (2). Briefly, the study enrolled patients with severe sepsis at low risk of death, that is, patients not indicated for treatment with DrotAA under the applicable label in the county in which they were enrolled. Because the label varied from country to country, this imposed some geographic variation on eligibility, but eligible patients were generally defined as those patients with severe sepsis with single organ dysfunction and/or an APACHE II score <25.

The ADDRESS protocol did not include 1-yr follow-up. After patient recruitment had begun, the U.S. FDA requested that 1-yr survival status be collected. An addendum to the protocol was implemented to collect the requested information. Patients were enrolled in the study from September 2002 to February 2004. One-year follow-up was conducted between March 2004 and February 2005. Each investigative site obtained ethical review board approval for the addendum. Where permitted by national and institutional ethical guidelines, information was obtained from review of public vital statistics data. For all other patients, written informed consent was obtained from the patients or their authorized representatives.

Study Procedures. In the initial ADDRESS study, all patients enrolled in the study were followed for 28 days from randomization. Patients who remained in the study hospital at day 28 were followed until hospital discharge or day 90. In the follow-up study reported in this article, 1-yr follow-up was performed for all patients who were alive at the end of the 28 day/in-hospital phase of the study, that is, patients who were alive at day 28, were discharged from the study hospital after day 28, or remained in the study hospital and were alive at day 90. Data collected in the long-term follow-up portion of the study were then combined with the mortality data collected in the 28-day/90-day portion of the study to produce the overall survival analyses (hereafter referred to as the *long-term follow-up population*). Survival status, cause of death, the investigator's opinion of whether the death was predictable given the patient's underlying medical condition and risk factors at randomization, and patient location at 1 yr were collected; date of discharge was collected for patients who remained in the study hospital at day 90. Information on serious adverse events that occurred after the 28-day study period and that were considered by the investigator to be study drug related was sought. Site personnel contacted the patient by mail or telephone or obtained survival status from medical records or public records according to local laws and regulations. If the patient had died or was unable to respond, site personnel requested information from a proxy respondent, such as a family member.

Statistical Analyses. The statistical analysis plan for the study was prospectively defined. Analyses were performed on the intention-to-treat population. The intention-to-treat population was defined as all patients who were randomly assigned to treatment, even if they did not receive treatment, did not receive the correct treatment, or did not follow the protocol. A 1-yr mortality analysis comparing mortality rates in the DrotAA and placebo treatment groups was performed using chi-square tests. Kaplan-Meier estimates of mortality are presented to complement the landmark mortality analysis with comparisons using log-rank tests. In addition, other prospectively defined subgroup analyses of 1-yr mortality were performed.

Data for qualitative variables are presented as incidence rates; treatment groups are compared using chi-square tests for comparisons of DrotAA and placebo, Cochran-Mantel-Haenszel tests for comparisons of DrotAA and placebo stratified by prespecified covariates, and Breslow-Day tests for significant interactions of treatment with prespecified covariates. Two-sided 5% significance levels are used for all analyses. No adjustments to p values for multiple comparisons were made as this was a safety-centered study in which restricting significance would hinder detection of safety issues. Analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC).

RESULTS

Patients. Figure 1 shows the patient disposition for the 1-yr follow-up portion of the ADDRESS study. Of the 2,640 patients enrolled in the study, 1-yr survival status was obtained for 2,376 patients (90% of patients enrolled in the study). Among patients with known 1-yr survival status, although not statistically significant, a greater percentage of DrotAA patients had multiple organ dysfunction, had been transferred to the study hospital from another acute care hospital, had respiratory dysfunction, had pure Gram-negative infections, and were female compared with placebo patients (Table 1). These imbalances were also noted among the entire randomized patient population (2). The baseline characteristics of the long-term follow-up population and the non-long-term follow-up population

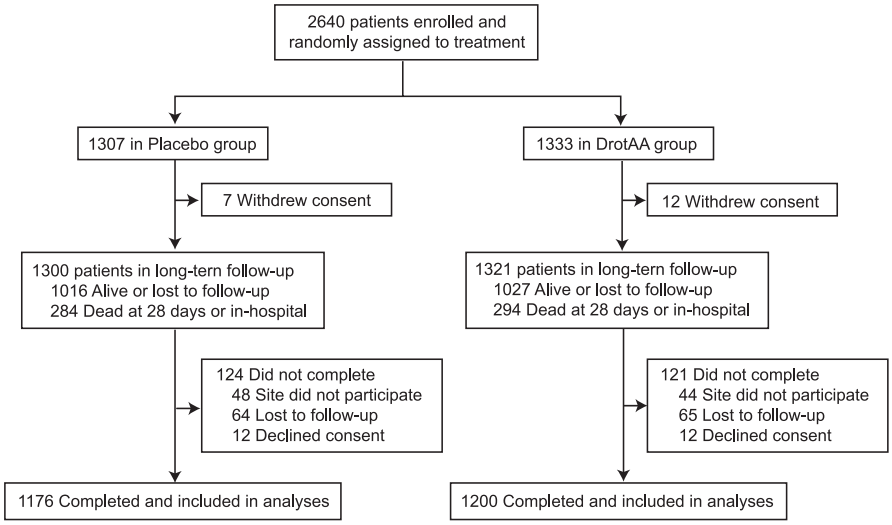

Figure 1. Disposition of drotrecogin alfa (activated) (*DrotAA*) and placebo patients in the 1-yr follow-up portion of the ADDRESS study. Sites that did not participate in the 1-yr follow-up did so for one of the following reasons: site decision (8 sites, 28 patients), site was closed before implementation of the addendum and was not reopened (12 sites, 26 patients), and site could not obtain ethics review board approval of the addendum or informed consent document within 1 yr of the implementation of the addendum (14 sites, 34 patients).

Table 1. Baseline characteristics of long-term follow-up population and patients not participating in long-term follow-up

	Long-Term Follow-Up Population		Non-Long-Term Follow-Up Population	
	DrotAA n = 1200	Placebo n = 1176	DrotAA n = 133	Placebo n = 131
Male, n (%)	677 (56.4)	689 (58.6)	74 (55.6)	76 (58.0)
Age, yrs, ±SD	59.4 ± 16.6	58.9 ± 16.6	52.9 ± 16.8	55.7 ± 16.9
Ethnicity, n (%)				
White	878 (73.2)	855 (72.7)	86 (64.7)	96 (73.3)
African descent	77 (6.4)	66 (5.6)	16 (12.0)	6 (4.6)
Hispanic	84 (7.0)	91 (7.7)	10 (7.5)	16 (12.2)
Asian	106 (8.9)	108 (9.1)	11 (8.3)	5 (3.8)
Other	55 (4.6)	56 (4.8)	10 (7.5)	8 (6.1)
Region, n (%)				
Europe	413 (34.4)	377 (32.1)	21 (15.8)	35 (26.7)
United States/Canada	483 (40.3)	507 (43.1)	95 (71.4)	76 (58.0)
Other	304 (25.3)	292 (24.8)	17 (12.8)	20 (15.3)
Patient location prior to hospital, n (%)				
Acute care hospital	231 (19.3)	196 (16.7)	20 (15.0)	30 (22.9)
Home	882 (73.5)	902 (76.7)	105 (78.9)	91 (69.5)
Skilled nursing facility	64 (5.3)	61 (5.2)	4 (3.0)	6 (4.6)
Other	23 (1.9)	17 (1.4)	4 (3.0)	4 (3.1)
Recent surgery (within 7 days), n (%)	458 (38.2)	454 (38.6)	46 (34.6)	44 (33.6)
No. of organ dysfunctions, n (%)				
0	5 (0.4)	3 (0.3)	4 (3.0)	1 (0.8)
1	786 (65.5)	807 (68.6)	78 (58.7)	84 (64.1)
2	318 (26.5)	269 (22.9)	38 (28.6)	33 (25.2)
3	72 (6.0)	76 (6.5)	10 (7.5)	13 (9.9)
4	17 (1.4)	20 (1.7)	3 (2.3)	0
5	2 (0.2)	1 (0.1)	0	0
Organ dysfunction class, n (%)				
Single	786 (65.5)	807 (68.6)	78 (58.7)	84 (64.1)
Multiple	409 (34.1)	366 (31.1)	51 (38.4)	46 (35.1)
Cardiovascular dysfunction, n (%)	590 (49.2)	575 (48.9)	70 (52.6)	68 (51.9)
Respiratory dysfunction, n (%)	738 (61.5)	698 (59.4)	78 (58.7)	76 (58.0)
Hematologic dysfunction, n (%)	106 (8.8)	89 (7.6)	12 (9.0)	11 (8.4)
Renal dysfunction, n (%)	207 (17.3)	209 (17.8)	28 (21.1)	27 (20.6)
Metabolic acidosis, n (%)	75 (6.3)	87 (7.4)	8 (6.0)	7 (5.3)
Time from first organ dysfunction, hrs ±SD	22.3 ± 13.5	22.6 ± 13.9	24.4 ± 14.6	23.3 ± 11.9
Mechanical ventilation, n (%)	681 (56.8)	659 (56.0)	70 (52.6)	70 (54.3)
Vasopressor support, n (%)	577 (48.1)	560 (47.6)	61 (45.9)	61 (47.3)
Renal replacement therapy, n (%)	45 (3.8)	38 (3.2)	2 (1.5)	2 (1.6)
APACHE II score ±SD	18.2 ± 5.8	18.2 ± 5.8	17.9 ± 6.2	17.8 ± 6.3
APACHE II class, n (%)				
<25	1051 (87.6)	1030 (87.6)	117 (88.0)	117 (89.3)
≥25	149 (12.4)	145 (12.3)	16 (12.0)	14 (10.7)
Site of infection, n (%)				
Lung	618 (51.5)	605 (51.4)	67 (50.4)	73 (55.7)
Intra-abdominal	252 (21.0)	234 (19.9)	23 (17.3)	21 (16.0)
Urinary tract	115 (9.6)	120 (10.2)	18 (13.5)	15 (11.5)
Other	215 (17.9)	217 (18.5)	25 (18.8)	22 (16.8)
Type of infection, n (%)				
Mixed Gram	127 (10.9)	148 (13.1)	20 (15.6)	12 (9.4)
No Gram	418 (35.8)	403 (35.6)	39 (30.5)	56 (43.8)
Pure Gram-negative	287 (24.6)	255 (22.5)	30 (23.4)	31 (24.2)
Pure Gram-positive	337 (28.8)	326 (28.8)	39 (30.5)	29 (22.7)

DrotAA, drotrecogin alfa (activated); APACHE, Acute Physiology and Chronic Health Evaluation.

comparison were generally similar. Patients in the non-long-term follow-up population were younger than patients in the long-term follow-up population. There was geographical variation in the percentage of patients from whom follow-up was obtained: A greater percentage of patients enrolled in the United States/Canada were not followed up vs. patients enrolled in Europe or in other countries.

Mortality. The 1-yr mortality rates for patients receiving DrotAA and placebo were similar: 34.2% for DrotAA patients and 34.0% for placebo patients ($p = .94$). Twenty-eight-day mortality was 18.5% DrotAA and 17.0% placebo ($p = .34$). Figure 2 shows the Kaplan-Meier mortality curves for DrotAA and placebo patients. The mortality rates increased rapidly through day 60 and increased more slowly thereafter. There was no difference between DrotAA and placebo patients in patient location at 1 yr: 92% of DrotAA and 93% of placebo patients who were alive at 1 yr were at home; approximately 5% of patients in both treatment groups were in an extended care facility.

Subgroups. All patients enrolled in the ADDRESS study were considered by the enrolling investigator to be at low risk of death and not indicated for treatment with DrotAA. However, because of the

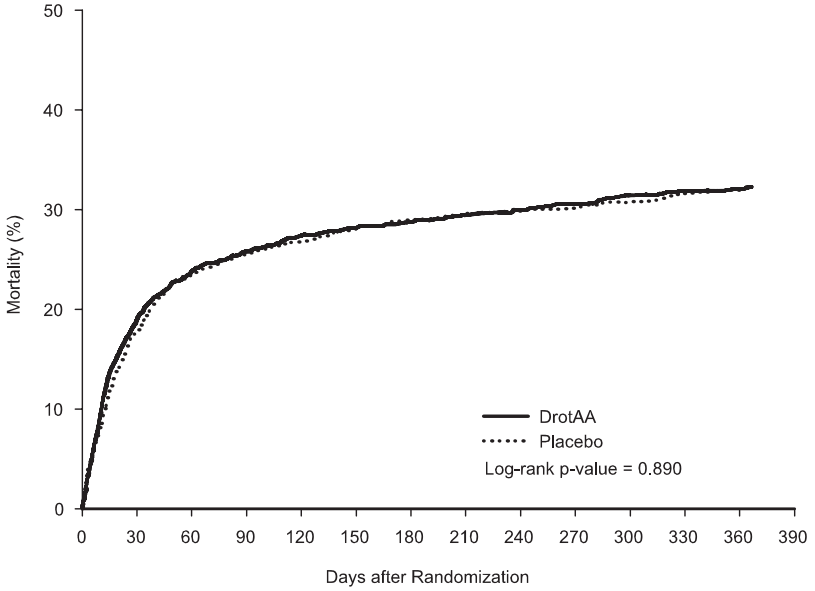

Figure 2. Kaplan-Meier estimates of survival for drotrecogin alfa (activated) (*DrotAA*) (n = 1,333) and placebo patients (n = 1,307) in the long-term follow-up portion of the ADDRESS study. There was no significant difference between the two treatment groups in 1-yr mortality (p = .890, log-rank test).

Table 2. Mortality in subgroups defined by Acute Physiology and Chronic Health Evaluation (APACHE) II score or organ dysfunction class[a]

	1-Yr Mortality			28-Day Mortality		
Patient Population	DrotAA	Placebo	p Value	DrotAA	Placebo	p Value
Baseline APACHE II score <25						
No. of patients	1,051	1,030	.97[b]	1,153	1,138	.55[b]
Dead, n (%)	336 (32.0)	330 (32.0)		195 (16.9)	182 (16.0)	
Baseline APACHE II score ≥25						
No. of patients	149	145	.81[b]	163	158	.34[c]
Dead, n (%)	74 (49.7)	70 (48.3)		48 (29.5)	39 (24.7)	
Single organ dysfunction						
No. of patients	786	807	.43[b]	853	886	.15[c]
Dead, n (%)	261 (33.2)	253 (31.4)		148 (17.4)	131 (14.8)	
Multiple organ dysfunction						
No. of patients	409	366	.29[b]	455	407	.67[c]
Dead, n (%)	148 (36.2)	146 (39.9)		94 (20.7)	89 (21.9)	

DrotAA, drotrecogin alfa (activated).

[a]One placebo patient had a missing APACHE II score and was excluded from analyses of mortality by APACHE II score; five DrotAA and three placebo patients had no organ dysfunctions and are excluded from analyses of mortality by organ dysfunction class; [b]frequencies were analyzed using a chi-square test; [c]two-sided p value from the Cochran-Mantel-Haenszel general association test.

varying definitions of high risk of death used in the applicable labels in the countries where patients were enrolled, there was not a single definition of low risk of death used in the study. High risk of death was most commonly defined as an APACHE II score >25 or the presence of multiple organ dysfunction. However, because of the differing labels in participating countries, patients with multiple organ dysfunction or an APACHE II score ≥25 could be enrolled in the study.

In the subgroups defined by baseline APACHE II score or organ dysfunction class (single or multiple), there were no statistically significant differences in 1-yr mortality between the DrotAA and placebo treatment groups (Table 2). Figure 3 shows the Kaplan-Meier mortality curves for DrotAA and placebo patients in the subgroups of APACHE II score <25 (Fig. 3*A*), APACHE II score ≥25 (Fig. 3*B*), single organ dysfunction (Fig. 3*C*), and multiple organ dysfunction (Fig. 3*D*). In both the APACHE II subgroups, the DrotAA and placebo curves are similar and there is considerable overlap. In both organ dysfunction class subgroups, the curves separate about day 15–20 and remain separated through 1 yr, although no significant differences are observed (Fig. 3*C* and 3*D*).

Cause of Death. Cause of death and the investigator's opinion of whether the death was predictable given the patient's underlying medical condition and risk factors at randomization were recorded for the 232 patients who died during the long-term follow-up portion of the study (Table 3). Information on deaths came from medical records or public records for approximately half of the patients who died and from the family or other source for the other half. Only four patients died of the severe sepsis episode that was present at enrollment. However, 53 patients died of a new episode of severe sepsis. The most common nonsepsis cause of death was cancer/malignancy (34 patients; 23 DrotAA and 11 placebo). An examination of the other causes of death revealed an additional two patients who died of cancer (one DrotAA and one placebo). One patient who died of cancer was randomly assigned to DrotAA but did not receive study drug. For all but six of the remaining patients (four DrotAA and two placebo), the investigator considered the cancer death to have been predictable given the patient's underlying condition and risk factors at randomization (Fig. 4).

Given the imbalance in cancer deaths observed at 1 yr, the cause of death was examined for patients who were dead at day 28 or who died while hospitalized in the study hospital (up to day 90). Seven patients died of cancer, two DrotAA and five placebo (Fig. 4). Three of these patients were diagnosed with cancer before study entry (one DrotAA and two placebo), three patients were diagnosed after study entry (one DrotAA and two placebo), and no information was available for the remaining patient (placebo). Death occurred 2–6 wks after study entry, making it likely that cancer was present at study entry.

During the entire study, 42 patients who received study drug (25 DrotAA and 17 placebo; one patient did not receive study drug) died of cancer. For 39 of these patients, the cancer was present or likely to have been present at study entry or their deaths were predictable given their underlying conditions and risk factors at randomization. Three patients, one DrotAA and two placebo, were diag-

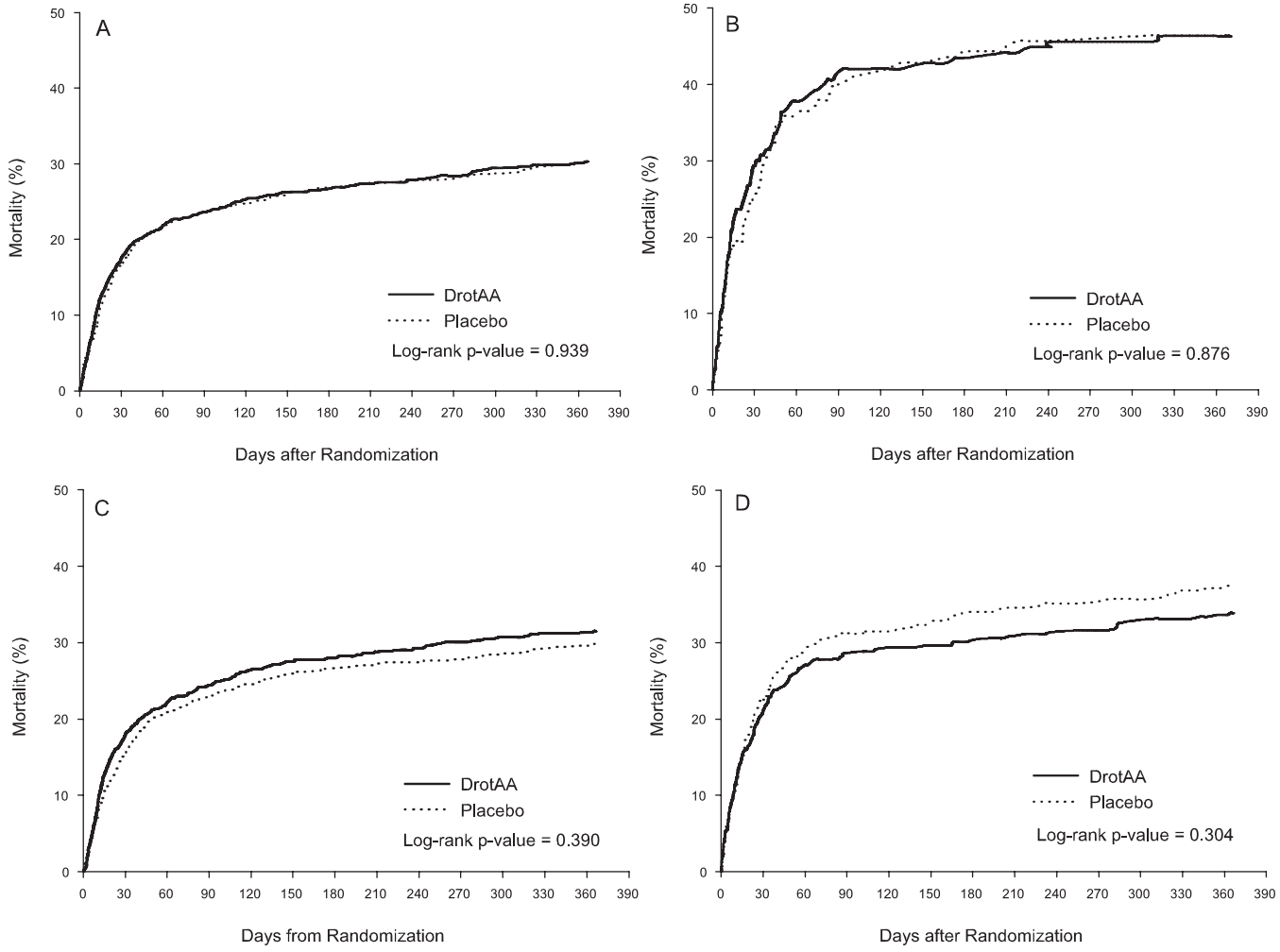

Figure 3. Kaplan-Meier estimates of survival for drotrecogin alfa (activated) (*DrotAA*) and placebo patients in subgroups defined by baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score (<25 or ≥25) or organ dysfunction class (single or multiple). There were no significant differences between the two treatment groups in 1-yr mortality in any of the subgroups. *A*, baseline APACHE II score <25 (DrotAA n = 1,168, placebo n = 1,147). *B*, baseline APACHE II score ≥25 (DrotAA n = 165, placebo n = 159). *C*, single organ dysfunction (DrotAA n = 864, placebo n = 891). *D*, multiple organ dysfunction (DrotAA n = 460, placebo n = 412).

nosed with cancer after study entry, and information on their cancer diagnosis, treatment, and disease progression is limited. It was not required that the type of cancer be recorded; however, where this information was available, there did not appear to be any pattern related to the type of cancers reported.

Safety. No additional serious adverse events were reported during the follow-up period between hospital discharge and 1 yr, and none of the deaths were considered by the investigator to be related to study drug.

DISCUSSION

We believe that the ADDRESS study represents the largest prospective long-term follow-up cohort of severe sepsis patients following treatment in the intensive care unit. However, in view of the selective nature of clinical studies in general, and the focus on this study in particular on patients at lower risk of death, the mortality rates at 1 yr will be lower than nonselective cohorts. In a cohort of 153 patients with sepsis, Sasse et al. (4) found 72% mortality at 1 yr, and in a cohort of 100 patients with Gram-negative sepsis, Perl et al. (5) found 47% mortality at 1 yr.

The purposes of conducting a long-term follow-up study are to investigate whether efficacy is sustained in the long term and whether there is harm associated with drug administration that is manifested in the long term. In the ADDRESS study, no beneficial treatment effect associated with DrotAA was observed in the overall population at 28 days and, as expected, no beneficial treatment effect was observed at 1 yr.

There was also no apparent harm associated with DrotAA administration at 1 yr in this population at lower risk of death. In the overall population, the 1-yr mortality rates in the two treatment groups were nearly identical. In the subgroups examined, the differences between the two treatment groups in 1-yr mortality rates were consistent with or were smaller than the differences observed at 28 days. No additional serious adverse events were reported during the long-term follow-up, and none of the deaths were considered by the investigator to be study drug related.

The majority of deaths that occurred in-hospital were sepsis related, whereas the majority of deaths that occurred after

Table 3. Cause of death for patients who died during long-term follow-up

	DrotAA	Placebo	*p* Value[a]
No. of patients	116	116	.66
Severe sepsis episode at enrollment, n (%)	3 (2.6)	1 (0.9)	
New episode of severe sepsis, n (%)	24 (20.7)	29 (25.0)	
Non-sepsis-related cause, n (%)	68 (58.6)	67 (57.8)	
Cancer/malignancy, n	23	11	
Ischemic heart disease, n	9	9	
End-stage lung disease, n	9	8	
Congestive heart disease, n	5	7	
End-stage renal disease, n	4	5	
Infection, n	2	6	
Cerebrovascular disease or stroke, n	3	1	
Pulmonary embolism, n	2	2	
Trauma, n	0	4	
End-stage liver disease, n	1	2	
Noncoronary, non-CNS arterial thrombosis, n	1	0	
Unknown cause, n (%)	21 (18.1)	19 (16.4)	
Other, n (%)	9 (13.2)	12 (17.9)	
Was death predictable?			
No. of patients	68	66	.21
No, n (%)	16 (23.5)	22 (33.3)	
Yes, n (%)	52 (76.5)	44 (66.7)	
Source of 1-yr death information			
No. of patients	116	116	.12
Investigator, n (%)	5 (4.3)	0 (0.0)	
Medical records, n (%)	50 (43.1)	61 (52.6)	
Other, n (%)	10 (8.6)	10 (8.6)	
Patient representative/family member, n (%)	48 (41.4)	40 (34.5)	
Public records, n (%)	3 (2.6)	5 (4.3)	

DrotAA, drotrecogin alfa (activated); CNS, central nervous system.
[a]Frequencies were analyzed using a chi-square test.

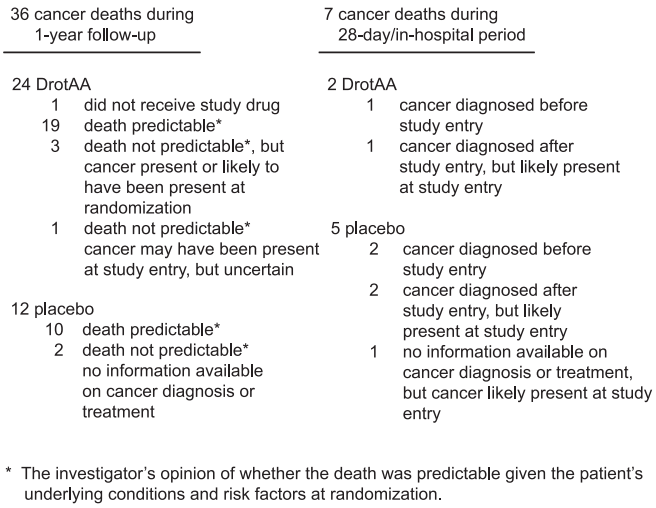

Figure 4. Cancer deaths that occurred during the 1-yr follow-up and 28-day/in-hospital study periods. For all but three of the deaths, cancer was present or likely to have been present at study entry or the deaths were predictable given the patients' underlying conditions and risk factors at randomization. *DrotAA*, drotrecogin alfa (activated).

hospital discharge were not sepsis related. There was an imbalance in the number of patients who died of cancer/malignancy: Twice as many DrotAA patients died of cancer than placebo patients. Most of the cancer deaths were assessed as predictable by the investigator given the patient's underlying medical condition and risk factors at randomization. The difference in cancer deaths between the two treatment groups may reflect an imbalance in the presence of cancer at baseline. However, since information on medical history and preexisting conditions was not collected in the ADDRESS study, this cannot be confirmed. Also, information on cause of death was obtained from a family member or other source for approximately half of the patients who died, and the accuracy of the information cannot be confirmed. In the PROWESS long-term follow-up study, cause of death was not recorded; however, patient history of cancer was recorded at baseline. More than 300 patients had cancer at study entry, and among these patients, lower mortality was observed with DrotAA at 28 days, at 1 yr, and at 30 months compared with placebo (6). Given that most of the deaths at 1 yr due to cancer in the ADDRESS study were predictable and that there was an apparent survival advantage among cancer patients who received DrotAA in the PROWESS study, it seems probable that the excess cancer deaths among DrotAA patients may have been related to a greater number of DrotAA patients having a diagnosis of cancer at the time of randomization compared with placebo patients. There is no known mechanism by which 4-day treatment of drotrecogin alfa (activated) would promote the initiation or spread of cancer.

Despite being conducted as an addendum, the study obtained 1-yr survival status for 90% of patients enrolled in the study, and, in many cases, lack of follow-up was related to a site's inability to participate in the addendum rather than inability to obtain patient follow-up. Analysis of baseline characteristics of patients with known 1-yr survival status showed some imbalances between the two treatment groups; however, they were similar to those noted in the overall population.

Comparisons of the PROWESS and ADDRESS long-term follow-up data are somewhat difficult because of the differing entry criteria. The PROWESS study enrolled patients with severe sepsis regardless of the severity of disease. The ADDRESS study enrolled patients with severe sepsis at low risk of death who were not indicated for treatment with DrotAA under the applicable label in the country in which the patient was enrolled. Because the indication for DrotAA varies from country to country and there were not universally fixed entry criteria, patient eligibility for the study depended on the investigator's interpretation of the applicable label. Thus, although patients with an APACHE II score $\geq$25 or multiple organ dysfunction were enrolled in the ADDRESS study, they were still considered at low risk of death, as is evident by their lower mortality compared with the PROWESS study.

In PROWESS, analysis of mortality in the subgroup with an APACHE II score <25 showed similar mortality in DrotAA and placebo patients at 28 days and numerically higher mortality in DrotAA patients at 1 yr (3). However, imbalances in the predictors of long-term outcome were noted between the two treatment groups: A higher percentage of DrotAA 28-day survivors were >75 yrs of age (18.1% vs. 11.0%). Importantly, in the ADDRESS long-term follow-up, there was no evidence of excess mortality at 1-yr in the APACHE II <25 subgroup.

Although 28-day all-cause mortality has been the standard end point for regulatory purposes in studies of severe sepsis, there is also interest in understanding if potential treatment effects are maintained in the longer term. However, there is currently no consensus as to how long such follow-up should be. Cohen et al. (7) suggested that patients should be followed for ≥90 days. Analysis of the ADDRESS data and the overall data from PROWESS suggest that follow-up >90 days would not alter the direction of any efficacy conclusion.

One of the conclusions made based on the PROWESS long-term follow-up results was that the results supported the recommendation by the U.S. FDA to restrict the use of DrotAA to more severely ill patients, such as those with higher APACHE II scores (3). The ADDRESS long-term follow-up results also support the use of DrotAA in sicker patients; however, this study could be interpreted as supporting more the recommendation by the European Medicines Agency to restrict the use of DrotAA to those patients with multiple organ dysfunction. However, this also illustrates the difficulty of trying to draw such conclusions from underpowered subgroup analyses.

CONCLUSIONS

DrotAA appears to have an acceptable safety profile through 1 yr in severe sepsis patients at low risk of death. There was no increased risk of death or evidence of harm associated with DrotAA in the ADDRESS long-term follow-up study.

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