

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

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ABSTRACT

BACKGROUND

In November 2001, the Food and Drug Administration (FDA) approved drotrecogin alfa (activated) (DrotAA) for adults who had severe sepsis and a high risk of death. The FDA required a study to evaluate the efficacy of DrotAA for adults who had severe sepsis and a low risk of death.

METHODS

We randomly assigned adult patients with severe sepsis and a low risk of death (defined by an Acute Physiology and Chronic Health Evaluation [APACHE II] score <25 or single-organ failure) to receive an intravenous infusion of placebo or DrotAA (24 µg per kilogram of body weight per hour) for 96 hours in a double-blind, placebo-controlled, multicenter trial. The prospectively defined primary end point was death from any cause and was assessed 28 days after the start of the infusion. In-hospital mortality within 90 days after the start of the infusion was measured, and safety information was collected.

RESULTS

Enrollment in the trial was terminated early because of a low likelihood of meeting the prospectively defined objective of demonstrating a significant reduction in the 28-day mortality rate with the use of DrotAA. The study enrolled 2640 patients and collected data on 2613 (1297 in the placebo group and 1316 in the DrotAA group) at the 28-day follow-up. There were no statistically significant differences between the placebo group and the DrotAA group in 28-day mortality (17.0 percent in the placebo group vs. 18.5 percent in the DrotAA group; $P=0.34$; relative risk, 1.08; 95 percent confidence interval, 0.92 to 1.28) or in in-hospital mortality (20.5 percent vs. 20.6 percent; $P=0.98$; relative risk, 1.00; 95 percent confidence interval, 0.86 to 1.16). The rate of serious bleeding was greater in the DrotAA group than in the placebo group during both the infusion (2.4 percent vs. 1.2 percent, $P=0.02$) and the 28-day study period (3.9 percent vs. 2.2 percent, $P=0.01$).

CONCLUSIONS

The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25.

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SEVERE SEPSIS CONTRIBUTES TO APPROXIMATELY 10 percent of admissions to the intensive care unit worldwide, with resultant in-hospital mortality of 20 to 52 percent.¹⁻⁹ The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, involving adult patients with severe sepsis, showed a 19.4 percent reduction in the relative risk of death from all causes and an absolute reduction of 6.1 percent at 28 days among patients treated with drotrecogin alfa (activated) (DrotAA; Xigris, Eli Lilly) as compared with placebo.¹⁰ Exploratory analyses of subgroups in the PROWESS trial indicated a consistent treatment effect in the majority of clinically relevant subgroups.^{10,11} On the basis of subgroup analyses, regulatory agencies approved the use of DrotAA for patients at high risk for death (as defined, for example, by an Acute Physiology and Chronic Health Evaluation [APACHE II] score¹² ≥ 25 or multiorgan failure), a population in which the risk-benefit profile appeared most favorable.

Approval of DrotAA by the Food and Drug Administration (FDA) required the sponsor to conduct a trial to evaluate the effects of DrotAA in the population of patients with severe sepsis who had a low risk of death. A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DrotAA in adult patients with severe sepsis and a low risk of death, indicated primarily by APACHE II scores of less than 25 or single-organ failure, was initiated.

METHODS

PATIENTS

From September 2002 to February 2004, we enrolled eligible adult patients in this randomized, double-blind, placebo-controlled, multicenter trial, which was conducted at 516 centers in 34 countries. Patients were eligible for the trial if they had severe sepsis, which was defined as the presence of a suspected or known infection and sepsis-induced dysfunction of at least one organ (cardiovascular, renal, respiratory, hematologic, or unexplained metabolic acidosis) (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org), and a low risk of death. The institutional review board at each investigative site approved the study protocol, and all patients or their authorized representatives gave written informed consent.

TREATMENT ASSIGNMENTS

Multiple lots of DrotAA were manufactured from clones of a single cell. Patients were randomly assigned to receive a 96-hour intravenous infusion of placebo (0.9 percent sodium chloride) or DrotAA at a dose of 24 μg per kilogram of body weight per hour. We used block randomization stratified according to investigative site and within a site in terms of whether the patient received or was intended to receive low-dose heparin for prophylaxis against deep-vein thrombosis at the start of infusion of the study drug (see Fig. 1 of Supplementary Appendix 1). Patients had to begin treatment with the study drug within 48 hours of documentation of the first organ dysfunction. All other patient care was at the discretion of the investigators and was not specified in the study protocol. Patients, investigators, and all others involved in conducting the study remained blinded to the treatment assignments for the duration of the study. All delivery systems for the study drug were covered to ensure blinding.

EXCLUSION CRITERIA

Patients were excluded from the study if DrotAA was indicated or contraindicated according to the applicable label in the country in which they were enrolled. The population for which DrotAA is indicated varies from country to country but is generally defined as one or both of the following: patients with multiorgan dysfunction (European Union label) or patients at high risk for death as defined, for example, by an APACHE II score of 25 or more (U.S. label). Since a degree of variability exists in label indications worldwide, if an investigator thought that the patient was at low risk for death despite a high APACHE II score or multiorgan failure, the protocol permitted enrollment of the patient.

Patients also were excluded if they had an increased risk of bleeding, if they were in a moribund state or were not expected to survive for 28 days, given their preexisting, uncorrectable medical condition, or if there was no commitment to aggressive management. If the patient's disease progressed and the investigator determined that it was in the best interest of the patient to initiate treatment with commercial DrotAA, treatment assignment was unblinded and the study drug was discontinued, but follow-up of the patient continued. Unblinding was required to permit the investigator to treat the patient appropriately for the indicated duration of ther-

apy (i.e., 96 hours). Patients assigned to placebo who received commercial DrotAA were evaluated in the intention-to-treat analyses as members of the placebo population.

EVALUATION OF PATIENTS

Baseline characteristics were assessed. APACHE II scores were based on variables assessed in the 24-hour period immediately before randomization. All patients (including those who did not receive the study drug or who discontinued it) were followed for the 28-day study period. If they were still in the hospital at day 28, they were followed to hospital discharge or day 90, whichever occurred first. Follow-up for survival at one year is continuing. We also assessed serious adverse events, including serious bleeding events; nonserious bleeding events that occurred during the treatment period (day 0 through day 6) and led to or contributed to the need for the transfusion of packed red cells; nonserious adverse events related to the study drug; and adverse events that led to permanent discontinuation of infusion of the study drug.

STATISTICAL ANALYSIS

Data were analyzed according to a prospectively defined plan. The primary efficacy end point (death from any cause, assessed 28 days after the initiation of the infusion) was analyzed in the intention-to-treat population, defined as all patients who were randomly assigned to treatment, even if the patient did not receive the assigned or correct treatment, did not follow the protocol, or received commercial DrotAA as a result of the investigator's decision.

The projected sample size of 11,444 patients ensured at least 90 percent power to detect a statistically significant difference between placebo and DrotAA with a two-sided P value of 0.05. The sample size was based on an assumed underlying mortality rate of 20 percent in the placebo group and 16 percent in the DrotAA group. The calculation of sample size also took into account the estimated 20 percent of patients assigned to the placebo group who had disease progression and for whom therapy with commercial DrotAA would be initiated during the study period.

Three planned interim analyses by an independent, external data-monitoring committee occurred after the 28-day follow-up for 1000, 3816, and 7632 patients, respectively. The committee, which could also request additional unplanned interim analy-

ses, agreed on prospectively defined statistical guidelines for stopping the trial for reasons of efficacy, safety, and futility before the first interim analyses. Statistical guidelines for efficacy were determined with the use of the O'Brien–Fleming spending function, according to the method of DeMets.¹³ Guidelines for futility ensured that at each interim analysis there would be at least a 5 percent chance of demonstrating a significant difference between the groups in the primary end point by the completion of the trial, in order to continue. Safety analyses were performed for all patients who received the study drug for any length of time.

In-hospital mortality was analyzed as a secondary end point. In addition, analyses of 28-day mortality, in-hospital mortality, and serious bleeding events were performed in multiple prospectively defined subgroups.

The data for categorical variables are presented as incidence rates, and the treatment groups were compared with the use of chi-square, Fisher's exact, Cochran–Mantel–Haenszel, or Breslow–Day tests. Data for continuous variables are summarized with the use of means \pm SD. Statistical tests for continuous variables were performed with the use of analysis of variance of ranked data. Kaplan–Meier estimates were used for time-to-event analyses, and log-rank tests for comparisons. Two-sided 5 percent significance levels and 95 percent confidence intervals were used for all efficacy and safety analyses. We made no adjustments to P values for multiple comparisons. Computations were performed with the use of SAS software (version 8.2).

This study was designed by the sponsor, Eli Lilly, with the external executive and steering committees of the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) study group. The data were collected and analyzed by the sponsor. The academic authors had full access to and vouch for the accuracy and completeness of the data and the analysis. One academic author wrote the paper with the input and critical review of all the authors.

RESULTS

At the first interim analysis (1000 patients), the data-monitoring committee recommended continuing the trial and requested a subsequent unplanned analysis of approximately 1500 patients. At the time of that analysis, the data-monitoring committee

recommended early termination of enrollment in accordance with the futility guidelines, owing to the fact that there was a less than 5 percent chance of success of meeting the prospectively defined objective of a significant reduction in the risk of death from any cause, assessed 28 days after the initiation of the infusion of DrotAA. The expected increase in the risk of bleeding with the use of DrotAA, along with the low likelihood of efficacy, also contributed to the recommendation to terminate the trial. At the time of termination, 2640 patients had enrolled in the study. Because some patients withdrew consent or were lost to follow-up, 28-day mortality rates were available for 2613 patients, 1297 in the placebo group and 1316 in the DrotAA group (Fig. 1). Owing to a progression of their disease, 3.3 percent of patients received commercial DrotAA (47 [3.6 percent] in the placebo group and 39 [3.0 percent] in the DrotAA group, $P=0.33$).

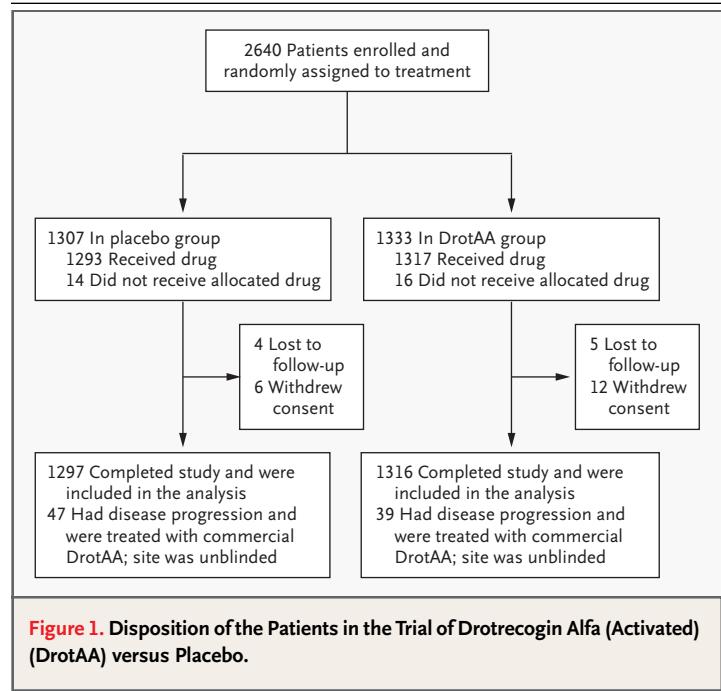
CHARACTERISTICS OF THE PATIENTS

Small numerical imbalances at baseline were observed between the treatment groups (Table 1). Respiratory and cardiovascular organs or systems were the most common sites of single-organ dysfunction at study entry, occurring in 35.2 percent and 21.8 percent of the patients, respectively. The distribution of APACHE II scores in the present trial as compared with those in the PROWESS trial is shown in Figure 2 of Supplementary Appendix 1.

EFFICACY

There was no statistical difference between the placebo and DrotAA groups in 28-day mortality (17.0 percent vs. 18.5 percent, respectively; $P=0.34$; relative risk, 1.08; 95 percent confidence interval, 0.92 to 1.28), and the difference remained nonsignificant after adjustment for the APACHE II score before infusion of the study drug. Figure 2 shows Kaplan–Meier survival curves for the placebo group and the DrotAA group ($P=0.31$). In-hospital mortality rates were nearly identical in the placebo group and the DrotAA group (20.5 percent vs. 20.6 percent; $P=0.98$; relative risk, 1.00; 95 percent confidence interval, 0.86 to 1.16).

Approximately 77 percent of the deaths were attributed to a sepsis-related cause (sepsis-induced multiorgan failure, respiratory failure, or refractory septic shock) as determined by the investigators. Although the differences in the causes of death between the groups were not statistically significant,



hemorrhage accounted for two deaths (0.9 percent) among patients in the placebo group as compared with seven deaths (2.9 percent) among patients in the DrotAA group ($P=0.12$).

The location of the patients was similar between treatment groups at day 28 and at hospital discharge or day 90. At day 28, 52.3 percent of survivors were at home, and at hospital discharge or day 90, 65.2 percent of survivors were at home.

SUBGROUP ANALYSES

Mortality rates among prespecified subgroups of patients are shown in Table 2. Of the 2640 patients enrolled in the study, 2315 (87.7 percent) had an APACHE II score of less than 25 (see Fig. 2 of Supplementary Appendix 1). In this group, there were no statistically significant differences between the placebo group and the DrotAA group in 28-day mortality (16.0 percent vs. 16.9 percent, $P=0.55$) or in in-hospital mortality (18.7 percent vs. 18.9 percent, $P=0.97$).

Post hoc exploratory analyses of the subgroup of patients who had undergone recent surgery (i.e., within 30 days before enrollment) and had single-organ dysfunction (314 patients in the placebo group and 321 in the DrotAA group) indicated that surgical patients with single-organ dysfunction receiving DrotAA had higher 28-day mortality rates

Table 1. Baseline Characteristics of All Patients Enrolled and Randomly Assigned to Treatment.*

| Characteristic | Placebo (N=1307) | DrotAA (N=1333) | P Value |
|--|------------------|-----------------|---------|
| Male sex — no. (%) | 765 (58.5) | 751 (56.3) | 0.26 |
| White race — no. (%)† | 951 (72.8) | 964 (72.3) | 0.64 |
| Age — yr | 58.6±16.7 | 58.8±16.8 | 0.84 |
| Region — %‡ | | | 0.79 |
| United States and Canada | 583 (44.6) | 578 (43.4) | |
| Europe | 412 (31.5) | 434 (32.6) | |
| Intercontinental | 312 (23.9) | 321 (24.1) | |
| Patient location before hospitalization — no. (%) | | | 0.60 |
| Home | 993 (76.0) | 987 (74.0) | |
| Acute care hospital | 226 (17.3) | 251 (18.8) | |
| Skilled nursing home | 67 (5.1) | 68 (5.1) | |
| Rehabilitation center | 11 (0.8) | 11 (0.8) | |
| Other | 10 (0.8) | 16 (1.2) | |
| Time from first organ dysfunction to start of drug infusion — hr | 22.6±13.8 | 22.5±13.6 | 0.74 |
| Mean APACHE II score§ | 18.2±5.9 | 18.2±5.8 | 0.72 |
| APACHE II score — no. (%)§ | | | 0.99 |
| <25 | 1147 (87.8) | 1168 (87.6) | |
| ≥25 | 159 (12.2) | 165 (12.4) | |
| Other indicators of disease severity — no. (%) | | | |
| Mechanical ventilation | 729 (55.8) | 751 (56.3) | 0.80 |
| Use of vasopressors | 621 (47.5) | 638 (47.9) | 0.89 |
| Recent surgery¶ | 498 (38.1) | 504 (37.8) | 0.99 |
| Use of heparin | 776 (59.4) | 775 (58.1) | 0.52 |
| Use of steroids | 191 (14.6) | 214 (16.1) | 0.31 |
| Number of dysfunctional organs or systems — no. (%) | | | 0.08 |
| 0 | 4 (0.3) | 9 (0.7) | |
| 1 | 891 (68.2) | 864 (64.8) | |
| 2 | 302 (23.1) | 356 (26.7) | |
| ≥3 | 110 (8.4) | 104 (7.8) | |
| Type of organ dysfunction — no. (%) | | | |
| Cardiovascular | 643 (49.2) | 660 (49.5) | 0.87 |
| Respiratory | 774 (59.2) | 816 (61.2) | 0.30 |
| Hematologic | 100 (7.7) | 118 (8.9) | 0.26 |
| Renal | 236 (18.1) | 235 (17.6) | 0.77 |
| Metabolic acidosis | 94 (7.2) | 83 (6.2) | 0.32 |

than did those patients receiving placebo (20.7 percent vs. 14.1 percent, $P=0.03$). Likewise, surgical patients with single-organ dysfunction receiving DrotAA had higher in-hospital mortality rates than did those patients receiving placebo (23.4 percent vs. 19.8 percent, $P=0.26$). The primary cause of death in this subgroup was sepsis-related. In the surgical patients with single-organ dysfunction, there were significantly more bleeding events in the DrotAA group than in the placebo group, both dur-

ing infusion (10.3 percent vs. 5.1 percent, $P=0.01$) and during the 28-day study period (10.9 percent vs. 6.1 percent, $P=0.03$). In the surgical patients with single-organ dysfunction who had a bleeding event, more patients in the DrotAA group than in the placebo group died of sepsis-induced multi-organ dysfunction (11 vs. 2) or of a hemorrhage (4 versus 0). The rates of serious bleeding events in the treatment groups were similar during infusion, as well as during the 28-day study period.

Table 1. (Continued.)

| Characteristic | Placebo (N=1307) | DrotAA (N=1333) | P Value |
|---|------------------|-----------------|---------|
| Site of infection — no. (%) | | | 0.81 |
| Lung | 678 (51.9) | 685 (51.4) | |
| Intraabdominal | 255 (19.5) | 275 (20.6) | |
| Urinary tract | 135 (10.3) | 133 (10.0) | |
| Other | 239 (18.3) | 240 (18.0) | |
| Source of infection — no. (%) | | | 0.99 |
| Community-acquired | 952 (72.8) | 971 (72.8) | |
| Nosocomial | 355 (27.2) | 362 (27.2) | |
| Type of infection — no. (%) | | | 0.79 |
| Pure gram-positive | 378 (28.9) | 397 (29.8) | |
| Pure gram-negative | 308 (23.6) | 331 (24.8) | |
| Mixed gram-positive and gram-negative | 160 (12.2) | 146 (11.0) | |
| Neither gram-positive nor gram-negative | 68 (5.2) | 68 (5.1) | |
| No organism identified | 393 (30.1) | 391 (29.3) | |

* DrotAA denotes drotrecogin alfa (activated). Plus-minus values are means \pm SD. Because of rounding, not all percentages sum to 100.

† Race was determined by study personnel.

‡ Europe includes Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Romania, Russia, the Slovak Republic, Spain, Sweden, Switzerland, and the United Kingdom, and Intercontinental includes Argentina, Australia, Brazil, Chile, Egypt, India, Mexico, New Zealand, the Philippines, Saudi Arabia, Singapore, South Africa, Taiwan, and Thailand.

§ Acute Physiology and Chronic Health Evaluation (APACHE II) scores can range from 0 to 71, with higher scores indicating more severe illness. The APACHE II score was missing for one patient in the placebo group.

¶ Recent surgery denotes surgery within 30 days before study enrollment.

SAFETY

The most important serious adverse event was bleeding (Table 3). In both treatment groups, approximately two thirds of the serious bleeding events were spontaneous and one third were related to a procedure during the infusion period.

The number of bleeding events involving the central nervous system was similar in the placebo group and the DrotAA group during infusion (three vs. four patients, $P=0.72$) and during the 28-day study period (five vs. six patients, $P=0.79$). Three deaths were considered to be related to the study drug — a cerebral hemorrhage in a patient in the placebo group, and hemorrhagic shock and an upper gastrointestinal hemorrhage in two patients in the DrotAA group.

DISCUSSION

In this study of adult patients with severe sepsis and a low risk of death, no statistically significant

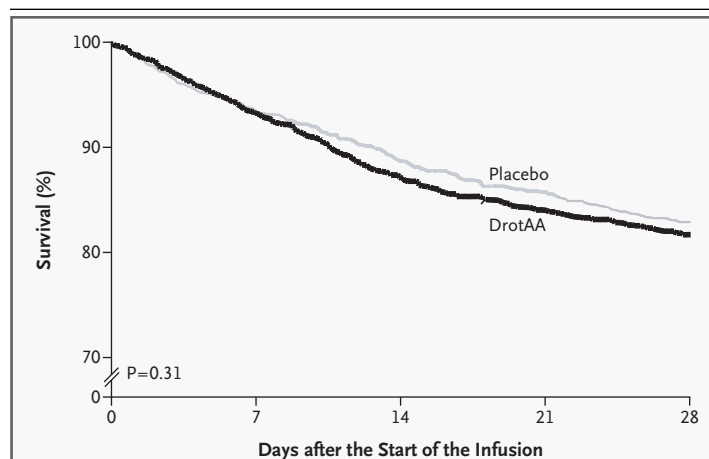


Figure 2. Kaplan–Meier Estimates of Survival among 1316 Patients with Severe Sepsis in the Drotrecogin Alfa (Activated) (DrotAA) Group and 1297 Patients in the Placebo Group.

There was no significant difference between the treatment groups in survival at 28 days ($P=0.31$ by the log-rank test).

Table 2. Mortality in Prespecified Subgroups.*

| Variable | 28-Day Mortality | | | | In-Hospital Mortality | | | |
|----------------------------|------------------|--------------|-------------|---------|-----------------------|--------------|-------------|---------|
| | No. of Patients | Placebo % | DrotAA % | P Value | No. of Patients | Placebo % | DrotAA % | P Value |
| Overall | 2613 | 17.0 | 18.5 | | 2624 | 20.5 | 20.6 | |
| APACHE II score† | | | | 0.81 | | | | 0.64 |
| <20 | 1554 | 13.3 | 14.3 | | 1563 | 15.5 | 16.6 | |
| 20–24 | 737 | 21.6 | 22.4 | | 737 | 26.0 | 23.7 | |
| >24 | 321 | 24.7 | 29.5 | | 323 | 32.7 | 32.3 | |
| Organ dysfunction | | | | 0.38 | | | | 0.59 |
| Single | 1739 | 14.8 | 17.4 | | 1746 | 18.3 | 19.3 | |
| Multiple | 862 | 21.9 | 20.7 | | 866 | 25.3 | 23.1 | |
| Recent surgery‡ | | | | 0.41 | | | | 0.88 |
| Yes | 993 | 16.4 | 20.4 | | 997 | 22.0 | 23.1 | |
| No | 1614 | 17.4 | 17.2 | | 1621 | 19.6 | 19.0 | |
| First patient enrolled§ | | | | 0.04 | | | | 0.22 |
| Yes | 509 | 14.5 | 22.3 | | 511 | 19.7 | 23.7 | |
| No | 2104 | 17.7 | 17.5 | | 2113 | 20.7 | 19.8 | |
| Use of heparin at baseline | | | | 0.91 | | | | 0.84 |
| Yes | 1536 | 16.9 | 18.2 | | 1540 | 21.3 | 21.1 | |
| No | 1077 | 17.3 | 18.9 | | 1084 | 19.4 | 19.9 | |

* DrotAA denotes drotrecogin alfa (activated). The number of patients refers to the total number of patients who completed the study and were included in the analysis. P values were calculated with the use of the Breslow–Day test.

† Acute Physiology and Chronic Health Evaluation (APACHE II) scores can range from 0 to 71, with higher scores indicating more severe illness. APACHE II class was prospectively defined for the ADDRESS trial. The prospectively defined subgroups of patients with an APACHE II score below 20 and those with an APACHE II score of 20 to 24 were combined to obtain the subgroup of patients with an APACHE II score below 25. At 28 days, mortality rates among the 2291 patients with APACHE II scores below 25 were 16.0 percent in the placebo group versus 16.9 percent in the DrotAA group (P=0.55). In-hospital mortality rates among the 2300 patients with APACHE II scores below 25 were 18.7 percent in the placebo group versus 18.9 percent in the DrotAA group (P=0.97). The APACHE II score was missing for one patient in the placebo group.

‡ Recent surgery denotes surgery within 30 days before enrollment. The surgical status was unknown for six patients.

§ The number of first patients enrolled does not equal the number of centers in the trial owing to patients lost to follow-up at 28 days or to hospital discharge.

difference was demonstrated in 28-day or in in-hospital mortality between the placebo and the DrotAA groups. These results are consistent with those previously described from a post hoc analysis of the subgroups of patients with APACHE II scores of less than 25 enrolled in the original PROWESS study of DrotAA.^{11,14,15}

In PROWESS, the 28-day mortality rates were significantly lower with DrotAA treatment than with placebo among patients whose APACHE II scores were 25 or higher (30.9 percent vs. 43.7 percent)¹⁵ or who had two or more sepsis-induced organ failures (26.5 percent vs. 33.9 percent).¹¹ No such effects were observed in the present study; however, only 324 patients (12.3 percent) enrolled in this

clinical trial had APACHE II scores of 25 or more, a number too small to permit the detection of statistically significant survival differences associated with DrotAA therapy.

The 95 percent confidence interval for the relative risk of death in the subgroup of patients with APACHE II scores of 25 or more in the present study (relative risk, 1.19; 95 percent confidence interval, 0.83 to 1.71) overlaps with that in the PROWESS study (relative risk, 0.71; 95 percent confidence interval, 0.59 to 0.84). Furthermore, the mean (\pm SD) APACHE II score in this subgroup was lower in our study than in the PROWESS study (28.1 \pm 3.3 vs. 31.1 \pm 3.3). In addition, 28-day mortality among patients in the placebo group who had APACHE II

scores of 25 or more was 24.7 percent in the present study, a rate significantly lower than the 43.7 percent observed in the placebo group of the PROWESS study, indicating that less severely ill patients were enrolled in the present study. Improvements in the care of patients with severe sepsis may have contributed to the lower mortality rates in the placebo group in the present study. The relatively low mortality observed may also reflect the trial design and entry criteria, which were aimed at enrolling patients who had sepsis and a low risk of death.

Although APACHE II scores are an indication of the severity of illness in populations of patients, they may be less useful in predicting the outcome of individual patients. Approximately one third of the patients in this study had multiorgan dysfunction, and small reductions in mortality among patients treated with DrotAA were observed in this subgroup; however, the number enrolled was too small for us to detect a statistically significant difference.

Since this study was originally designed to enroll more than 11,000 patients, we anticipated that approximately 1000 clinical sites would be needed for the recruitment of patients. A total of 516 centers in 34 countries enrolled patients. Many of these centers and countries had not previously participated in critical care trials. Although there were no clear differences in the clinical characteristics of patients enrolled by inexperienced sites as compared with experienced sites, the inclusion of large numbers of centers new to critical care trials may have affected the patient population included in this study, making it difficult to compare the results of this clinical trial directly with those of other studies of DrotAA, such as PROWESS. Although the entry criteria in this study were designed to be simple, the complexity of diagnosing and managing severe sepsis in patients and the variability in the local indications for the use of DrotAA as part of routine clinical care are likely to have introduced uncontrolled variables that may have affected the outcome of patients and their response to treatment with DrotAA or placebo.¹⁶

We performed a post hoc analysis of the small subgroup of patients in the present study who had had recent surgery (i.e., within 30 days before enrollment). We found that the subgroup of surgical patients who had single-organ dysfunction and were treated with DrotAA had a higher rate of 28-day and in-hospital mortality than the surgical patients with single-organ dysfunction who received placebo.

Table 3. Adverse Events.*

| Event | Placebo (N=1293) | DrotAA (N=1317) | P Value |
|---|---------------------|--------------------|---------|
| | no. (%) | | |
| Days 0–6 (infusion period) | | | |
| Any serious adverse event | 78 (6.0) | 75 (5.7) | 0.71 |
| Serious bleeding events | 15 (1.2) | 31 (2.4) | 0.02 |
| Bleeding involving the central nervous system | 3 (0.2) | 4 (0.3) | 0.72 |
| Serious nonbleeding events | 66 (5.1) | 46 (3.5) | 0.04 |
| Days 0–28 | | | |
| Any serious adverse event | 183 (14.2) | 182 (13.8) | 0.81 |
| Serious bleeding events | 28 (2.2) | 51 (3.9) | 0.01 |
| Bleeding involving the central nervous system | 5 (0.4) | 6 (0.5) | 0.79 |
| Any bleeding event leading to transfusion | 44 (3.4) | 90 (6.8) | <0.001 |
| Serious nonbleeding events | 168 (13.0) | 143 (10.9) | 0.09 |

* DrotAA denotes drotrecogin alfa (activated). Only patients who received the assigned study drug are included in this analysis.

This observation triggered an analysis of the same subgroup in the PROWESS study, and a similar effect was noted.

In the PROWESS study, in the subgroup of 98 surgical patients with single-organ dysfunction, those patients receiving DrotAA had a higher 28-day mortality rate than the surgical patients with single-organ dysfunction receiving placebo (20.4 percent vs. 16.3 percent, $P=0.60$), as well as a higher in-hospital mortality rate (29.2 percent vs. 17.0 percent, $P=0.16$). Because the response to surgery may mimic many of the early signs of sepsis and organ dysfunction, it may be difficult, especially in the surgical patients with single-organ dysfunction, to distinguish between a patient with a surgery-induced inflammatory state and one with severe sepsis. It is also possible that increased postoperative bleeding contributed to sepsis-induced tissue ischemia, worsening organ failure, and a higher mortality rate. An additional contributing factor, if time-to-treatment is important, may have been the requirement to wait 12 hours after surgery before the administration of the study drug. These hypotheses are difficult to confirm because data on surgery and its relationship to the diagnosis of severe sepsis are limited.

DrotAA has anticoagulant effects that result in increased bleeding episodes in patients treated with this agent.^{10,17,18} In the present study, serious bleeding events occurred in 2.2 percent of pa-

tients who received placebo and in 3.9 percent of patients who received DrotAA. These rates of serious bleeding events are similar to those found in the PROWESS study (2.0 percent in the placebo group vs. 3.5 percent in the DrotAA group during the 28-day study period). The similarity in bleeding rates between the placebo groups in the two trials may reflect the expected bleeding rate among patients with severe sepsis. Bleeding events involving the central nervous system are of particular concern among patients receiving anticoagulant therapies but did not occur with higher frequency among patients treated with DrotAA in the present study. Such results confirm that bleeding events occur in patients treated with DrotAA but that the incremental incidence is low in critically ill patients with sepsis who already have a risk of serious bleeding.

The ADDRESS study did not enroll a sufficient number of patients to yield a precise estimate of the effect of DrotAA in patients with sepsis and a low risk of death. However, for the population of patients enrolled, no beneficial treatment effect associated with the administration of DrotAA was observed. The results of this trial are consistent with the post hoc subgroup analyses in PROWESS that found little or no benefit of DrotAA in patients at

low risk for sepsis-induced mortality. However, the present results cannot be used to draw any conclusions about the effects of DrotAA treatment in other patient groups, including high-risk patients with severe sepsis.

An open-label study that examined the use of DrotAA in patients with sepsis and a greater severity of illness than the patients in the present clinical trial suggested that the reduction in the mortality rate was similar to that found in the PROWESS study.¹⁹ The absence of an observed beneficial treatment effect in patients receiving DrotAA in the current study, coupled with the increased incidence of serious bleeding complications among such patients, supports the conclusion that the risk-benefit ratio for the administration of DrotAA in patients with severe sepsis who are at low risk for death is not favorable. These results indicate that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score of less than 25.

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APPENDIX

Members of the Data Monitoring, Executive, and Steering Committees for the ADDRESS trial are as follows: **Data Monitoring Committee:** S. Opal (chair), Memorial Hospital of Rhode Island, Pawtucket; E. Davis, University of North Carolina, Chapel Hill; J.F. Dhainaut, Groupe Hôpitalier Cochin, Paris; M. Matthay, University of California, San Francisco; C. Sprung, Hadassah Hebrew University Medical Center, Jerusalem, Israel; J. Whitehead, MPS Research Unit, University of Reading, Reading, United Kingdom; **Executive Committee:** E. Abraham, University of Colorado Health Sciences Center, Denver; P.F. Laterre, St. Luc University Hospital, UCL, Brussels; D. Angus, University of Pittsburgh School of Medicine, Pittsburgh; G. Bernard, Vanderbilt University Medical Center, Nashville; R. Califf, Duke Clinical Research Institute, Durham, N.C.; D. Maki, University of Wisconsin, Madison; J.A. Russell, St. Paul's Hospital, Vancouver, B.C., Canada; J.L. Vincent, Erasme University Hospital, Brussels; **Steering Committee Members:** D. Cook, St. Joseph's Hospital, Hamilton, Ont., Canada; J. Carlet, Hospital Saint Joseph, Paris; D. Payen, Hospital Lariboisiere-Fernand, Vidal, France; K. Reinhart, Friedrich Schiller-Universität, Jena, Germany; R. Rossaint, Universitätsklinikum Aachen Klinik für Anästhesiologie, Aachen, Germany; A. Pesenti, Istituto di Anestesia e Rianimazione, Milan; G. Ramsay, Hospital Apeldoorn, Apeldoorn, the Netherlands; A. Artigas, Hospital de Sabadell, Sabadell, Spain; D. Wyncoll, St. Thomas' Hospital, London; T. Buchman, Barnes Jewish Hospital, Washington University, St. Louis; T.B. Thompson, Massachusetts General Hospital, Boston. Supplementary Appendix 2 (available with the full text of this article at www.nejm.org) includes a complete list of the investigators and institutions participating in the ADDRESS trial.

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