MAJOR ARTICLE

Drotrecogin Alfa (Activated) Treatment of Older Patients with Severe Sepsis

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(See the Editorial Commentary by High on pages 196–200)

The incidence of severe sepsis increases dramatically with advanced age, with a mortality rate that approaches 50%. The main purpose of this investigation was to determine both short- and long-term survival outcomes among 386 patients aged ⩾75 years who were enrolled in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial. Subjects who were treated with drotrecogin alfa (activated; DAA) had absolute risk reductions in 28-day and in-hospital mortality of 15.5% and 15.6%, respectively ($P = .002$ for both), compared with placebo recipients. The relative risk (RR) for 28-day mortality was 0.68 (95% confidence interval [CI], 0.54–0.87), and the in-hospital RR was 0.70 (95% CI, 0.56–0.88). Resource use and patient disposition for DAA-treated patients compared favorably with those for placebo recipients. In addition, long-term follow-up data were available for 375 subjects (97.2%), and survival rates for DAA recipients were significantly higher over a 2-year period ($P = .02$). The incidences of serious adverse bleeding during the 28-day study period in the DAA and placebo groups were 3.9% and 2.2%, respectively ($P = .34$). There was no interaction between age and bleeding rates ($P = .97$). In conclusion, older patients with severe sepsis have higher short- and long-term survival rates when treated with DAA than when treated with placebo but an increased risk of serious bleeding that is not aged related.

Severe sepsis, defined as sepsis associated with acute organ dysfunction, involves excessive systemic inflammation and coagulopathy [1] and has an associated mortality rate of 30%–50% [2–4]. Severe sepsis has been called a disease of the elderly population, because increased age has been shown to be an independent predictor of the incidence of and mortality associated with this disease [4, 5]. Indeed, a recent epidemiological study by Angus et al. [4] estimated that, in the United States, ~750,000 patients develop sepsis annually, of whom nearly two-thirds are >65 years of age. Although the estimated incidence of severe sepsis in this study was 3 cases per 1000 population, among older patients the incidence was nearly 10-fold higher, at 26.2 cases per 1000 population. Of importance, this study also reported that the costs of care for patients aged >65 years and >75 years were $8.7 billion and $5.1 billion, respectively, or 52.3% and 30.8% of the total national hospital cost associated with severe sepsis.

Recently, the Committee on Manpower for Pulmonary and Critical Care Societies reported that 56% of all days in the intensive care unit (ICU) are incurred by patients aged >65 years [6]. This study also demonstrated that the number of days per year spent in

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the ICU (per 1000 person-years) is 7-fold higher for patients aged >75 years than for those aged <65 years. This is of particular concern, because the population of older persons and the associated health care expenditures are expected to double by the year 2030.

Recombinant human activated protein C, also called "drotrecogin alfa (activated)" (DAA; Xigris; Eli Lilly), is an anti-inflammatory, antithrombotic, profibrinolytic treatment for the specific pathophysiologic derangements that occur in severe sepsis. When used to treat severe sepsis, DAA therapy has demonstrated a significant absolute reduction in the mortality rate of 6.1% (relative risk reduction, 19.4%; $P = .005$), which led to its approval by the US Food and Drug Administration in November 2001 [7, 8] and, subsequently, by the European Agency for Evaluation of Medicinal Products. Multiple subgroup analyses were prospectively defined in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial, and the treatment effect was consistent across most subgroups [9]. Interestingly, the treatment effect was consistent across infection types due to different microorganisms (gram-positive organisms, gram-negative organisms, mixed organisms, and fungi) and different sites of infection (e.g., lung, abdomen, and urinary tract). The only safety issue of concern was an increased risk of adverse bleeding; 28-day serious bleeding rates were 3.5% and 2.0% for DAA and placebo recipients, respectively.

The purpose of this investigation was to evaluate the short- and long-term outcomes for older patients with severe sepsis treated with DAA. We hypothesized that DAA treatment of patients aged ⩾75 years with severe sepsis would be associated with a significant mortality benefit, compared with placebo. Potentially, DAA could increase the duration of survival in older patients but lead to more serious adverse events, greater resource consumption, or less-desirable patient disposition. Therefore, we also analyzed safety data, including data on severe bleeding, morbidity, resource use, patient disposition, and functional status of this population of older patients with severe sepsis.

METHODS

In this report, we have focused on the subgroup of patients with severe sepsis aged ⩾75 years, because this is becoming a more common reference age than 65 years to define an elderly population [10] and because this age cutoff was chosen as the most widely agreed upon perspective by a consensus of geriatric experts at the Hartford Foundation (sponsored by the Geriatric Educational Retreat for Pulmonary and Critical Care Medicine) [11]. The PROWESS trial was a randomized, placebo-controlled trial that assessed the efficacy and safety of DAA treatment for severe sepsis. In the PROWESS investigation, details of which have been published elsewhere [8], a total of 850 patients were randomized to receive DAA at a dosage of at 24 μg/kg per hour, and 840 patients were randomized to receive placebo continuously for 96 h.

Patients were eligible for the controlled trial if they had a known or suspected site of infection, ⩾3 signs of systemic inflammation, and ⩾1 sepsis-induced organ dysfunction with a duration of no longer than 48 h. Patients who met any of the following criteria were excluded: age of <18 years, pregnancy, recent (<3 months) cerebrovascular accident, intracranial pathology, significant risk of development of severe bleeding, and need for therapeutic doses of heparin or low–molecular-weight heparin. A single amendment, recently described in detail elsewhere [12], to the inclusion and exclusion criteria was implemented early during the PROWESS trial in a blinded fashion for the main purpose of focusing enrollment on patients likely to die of severe sepsis rather than other causes.

Mortality, morbidity, patient disposition, and serious adverse events. Mortality analyses included 28-day, all-cause mortality; in-hospital mortality; and long-term follow-up, reported to 24 months after receipt of the study drug. These long-term follow-up data were part of a study of all 1220 subjects in the PROWESS trial who had survived for 28 days and included 375 (97.2%) of the 386 patients aged ⩾75 years. Resource use analyses included determination of vasopressor therapy, ventilator support, ICU stay, and "free days," as recommended elsewhere [13, 14]. "Free days" were calculated as the number of days that the patient was alive and free of any given measure (i.e., vasopressor use, ventilator use, ICU stay, and hospital stay) during the 28-day study period. For example, for a patient who had septic shock, for whom vasopressor therapy was stopped on day 10, and who lived through day 28, he/she received 18 vasopressor-free days; however, if the same patient had died on day 20, he/she would have only received 10 vasopressor-free days. Additional analysis of resource use included analysis of mean daily and cumulative Therapeutic Intervention Scoring System (TISS)–28 scores. TISS-28 scores are commonly used in such investigations as a comprehensive and quantitative measure of resource use on the basis of selected therapeutic activities performed in the ICU [15].

Patient disposition was evaluated by examining the patient location from hospital discharge information, according to treatment group. Functional dependency status at baseline (obtained by surrogate estimate of the patient's dependency status before the acute septic episode) and at the end of the 28-day study period (obtained by patient testing during recovery) was assessed using activity of daily living (ADL) scores [16]. We also analyzed prospectively defined and reported serious adverse events in the study population. Serious bleeding events were defined as any intracranial hemorrhage, any life-threatening bleeding, a requirement of ⩾3 U of packed RBCs per day for 2 consecutive days, or any bleeding event that met any

of the other criteria defining a serious adverse event [8]. A serious thrombotic event was defined as deep venous thrombosis or pulmonary thromboembolism, cerebral arterial thrombosis, cerebral infarct, cerebrovascular accident, peripheral artery thrombosis, or myocardial infarction.

Statistical analysis. Unless stated otherwise, only patients who received any study medication and who were aged ⩾75 years were included in the analysis. All statistical tests were performed using a 2-tailed significance level of 5%, with the exception of the entrance selection for the stepwise regression, which used a significance level of 10%. SAS statistical software, version 8.2 (SAS Institute), was used to perform all statistical analyses.

Categorical baseline characteristics listed in table 1 (e.g., sex) were analyzed using Pearson's χ^2 test. Functional dependency was defined as dependent patients with ADL scores of >0 and independent patients with ADL scores of 0. Continuous baseline characteristics listed in table 1 (e.g., APACHE II score [17]) were analyzed using 1-way analysis of variance.

All-cause, 28-day, and in-hospital mortality results were analyzed using Pearson's χ^2 test and logit relative risk with 95% CIs as the descriptive statistics. In-hospital mortality analysis incorporated imputed hospital mortality rates for 3 patients who were still in the hospital on day 28 and who were lost to long-term follow-up; mortality rates for patients in the hospital on day 28 who had long-term follow-up data were used. For long-term mortality, we accounted for patients who were lost to follow-up after day 28 with traditional Kaplan-Meier [19] censoring methods. Treatment group survival curves were analyzed by a log-rank test [20].

A logistic regression for 28-day mortality that included all patients in the PROWESS trial with age, treatment assignment, and age-treatment interaction as the independent factors was conducted to determine whether there was an age-treatment interaction. To test the effect of potential baseline imbalances on 28-day mortality, univariate stratified analyses for each categorical baseline characteristic listed in table 1 were performed using the Cochran-Mantel-Haenszel test. The Breslow-Day test was used to test for interactions of the stratified ORs for each baseline characteristic analyzed. Stepwise logistic regression for 28-day mortality incorporating all baseline characteristics listed in table 1 and treatment assignment was performed (retaining in the model any variables with $P < .1$) to test the effect of possible baseline imbalances on mortality. Functional dependency, "admitted from home," and severity of illness (determined with APACHE II scores) were forced into the model, because these variables were believed to be potentially important covariates to the mortality outcome variable. An unadjusted logistic regression for 28-day mortality including only treatment assignment was also performed to compare against the adjusted analysis from the stepwise regression.

Table 1. Baseline characteristics of patients in a study of drotrecogin alfa (activated; DAA) for treatment of severe sepsis.

Characteristic	Placebo group (n = 181)	DAA group (n = 205)
Age, mean years ± SD	80.2 ± 4.18	79.9 ± 4.31
Sex		
Male	105 (58.0)	124 (60.5)
Female	76 (42.0)	81 (39.5)
Ethnicity		
White	168 (92.8)	185 (90.2)
Nonwhite	13 (7.2)	20 (9.8)
Presumed site of infection		
Lung	94 (51.9)	101 (49.3)
Abdomen	45 (24.9)	52 (25.4)
Urinary tract	23 (12.7)	28 (13.7)
Other	19 (10.5)	24 (11.7)
Functional dependency[a]	80 (44.2)	70 (34.2)
Number admitted from home	120 (66.3)	161 (78.5)
Preexisting conditions[b]		
Hypertension	83 (46.1)	94 (47.7)
Myocardial infarction	37 (21.0)	43 (21.9)
Cardiomyopathy	24 (13.5)	18 (9.2)
Diabetes	36 (19.9)	46 (23.2)
Pancreatitis	2 (1.1)	4 (2.0)
Chronic liver disease	2 (1.1)	1 (0.5)
COPD	64 (36.0)	54 (27.1)
Malignancy	56 (32.2)	50 (25.6)
Recent trauma	8 (4.4)	4 (2.0)
Recent surgery	66 (37.5)	72 (35.5)
Severity of illness		
Mean APACHE II score ± SD[c]	27.98 ± 7.32	26.27 ± 6.89
Mean no. of organ failures ± SD[d]	2.56 ± 1.10	2.43 ± 1.12
Receipt of vasopressor therapy	122 (67.40)	130 (63.41)
Receipt of ventilator therapy	145 (80.11)	151 (73.66)

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease.

[a] Functional dependency was measured on the basis of activity of daily living scores [16].

[b] The group size varies for each preexisting condition because of the number of unknown values.

[c] Severity of disease classification system [17].

[d] Measured by Sequential Organ Failure Assessment (SOFA) scores [18].

Morbidity analyses for ventilator-free days, vasopressor-free days, ICU-free days, hospital-free days, and average daily TISS-28 scores were analyzed using 1-way analysis of variance. Cumulative TISS-28 scores were analyzed using a ranked analysis of variance, because the data were not normally distributed. Functional dependency for 28-day survivors, patient disposition for hospital survivors, and all safety analyses in table 2 were analyzed using Pearson's χ^2 test. The Breslow-Day test

Table 2. Serious adverse events in a study of drotrecogin alfa (activated; DAA) for treatment of severe sepsis.

	Patients aged <75 years			Patients aged ⩾75 years		
	No. (%) of patients, by treatment arm			No. (%) of patients, by treatment arm		
Adverse event	Placebo (n = 659)	DAA (n = 645)	P	Placebo (n = 181)	DAA (n = 205)	P
Serious bleeding events	13 (1.97)	22 (3.41)	.11	4 (2.21)	8 (3.90)	.34
Cardiac dysrhythmias	18 (2.73)	13 (2.02)	.40	10 (5.52)	4 (1.95)	.061
Thrombotic events	16 (2.43)	15 (2.33)	.90	9 (4.97)	2 (0.98)	.019
Infection	9 (1.37)	10 (1.55)	.78	2 (1.10)	4 (1.95)	.50
CNS-related event[a]	4 (0.61)	9 (1.40)	.15	5 (2.76)	0	.017
Respiratory complication	6 (0.91)	5 (0.78)	.79	2 (1.10)	1 (0.49)	.49
Gastrointestinal complication	4 (0.61)	3 (0.47)	.73	3 (1.66)	1 (0.49)	.26

[a] Included abnormal vision, cerebral edema, cerebral ischemia, cerebral vascular disorder, coma, convulsion, deafness, encephalopathy, hydrocephalus, mydriasis, paralysis, ptosis, and stupor.

was used to test for interaction of 28-day serious bleeding incidence between patients aged <75 years and patients aged ⩾75 years.

RESULTS

Baseline characteristics, according to treatment group, are shown in table 1 for patients ⩾75 years of age. Compared with younger patients (age, <75 years) not shown in the table, those aged ⩾75 years more frequently had a history of hypertension (34.7% vs. 47.0%; $P < .0001$), myocardial infarction (11.3% vs. 21.5%; $P < .0001$), cardiomyopathy (6.9% vs. 11.2%; $P = .0063$), chronic obstructive pulmonary disease (COPD; 22.8% vs. 31.3%; $P = .0008$), malignancy (15.4% vs. 28.7%; $P < .0001$), and recent surgery (28.1% vs. 35.9%; $P = .0032$). Patients aged ⩾75 years also had higher mean baseline APACHE II scores than did younger patients (27.1 vs. 24.1, respectively; $P < .0001$). This difference in APACHE II scores was the result of an increase in age points (3 points for age of <75 years and 6 points for age of ⩾75 years), as shown by the fact that the mean acute physiology scores for the 2 age groups were not significantly different (20.4 for patients aged <75 years and 20.08 for those aged ⩾75 years; $P = .3$). Younger patients had more infections due to only gram-positive organisms than did older patients (28.5% vs. 17.6%), but they had fewer infections of unknown origin (33.1% vs. 38.6%).

Univariate mortality analysis. The 28-day and in-hospital mortality rates for patients aged ⩾75 years are shown in figure 1. Patients aged ⩾75 years treated with DAA had large absolute risk reductions in 28-day and in-hospital mortality, compared with placebo recipients: 15.5% (33.7% for DAA recipients vs. 49.2% for placebo recipients) and 15.6% (36.9% vs. 52.5%), respectively ($P = .002$ for both). This absolute risk reduction translates to an estimated number needed to treat of 6 (95% CI, 4–17) to save an additional life for patients aged ⩾75 years. The relative risk for 28-day mortality for DAA-treated patients aged ⩾75 years was 0.68 (95% CI, 0.54–0.87); for those aged <75 years, it was 0.85 (95% CI, 0.70–1.03). The in-hospital relative risk for patients aged ⩾75 years was 0.70 (95% CI, 0.56–0.88); for patients aged <75 years, it was 0.91 (95% CI, 0.77–1.09). No statistically significant treatment-age interaction was observed when age was treated as a continuous covariate ($P = .23$). Long-term survival data are presented in figure 2. Older patients treated with DAA had higher survival rates throughout the 2-year follow-up period, with an increase in the median survival duration of ~3 months (88 days), or a 284% increase (31 days for the placebo group vs. 119 days for the DAA group; $P = .02$).

After adjustment for each baseline characteristic shown in table 1, the relative risks were 0.66–0.72. None of the aforementioned tests for interactions had statistically significant results, except for COPD, which had a significant interaction ($P = .035$). The within-subgroup relative risks for patients with and without COPD were 0.49 (95% CI, 0.31–0.77) and 0.82 (95% CI, 0.60–1.12), respectively.

Multivariate mortality analysis. The final stepwise logistic regression model included the following covariates: treatment assignment, functional dependency, "admitted from home," and severity of illness. The stepwise adjusted logistic regression and unadjusted logistic regression for 28-day mortality yielded ORs of 0.57 (95% CI, 0.36–0.91) and 0.52 (95% CI, 0.35–0.79), respectively.

Morbidity analysis and resource use. Morbidity analyses for patients aged ⩾75 years showed that those treated with DAA had significant increases in the mean number of vasopressor-free days (3.1 days; $P = .006$), ventilator-free days (3.7 days; $P = .001$), ICU-free days (3.0 days; $P = .004$), and hospital-free days (1.9 days; $P = .008$), compared with placebo

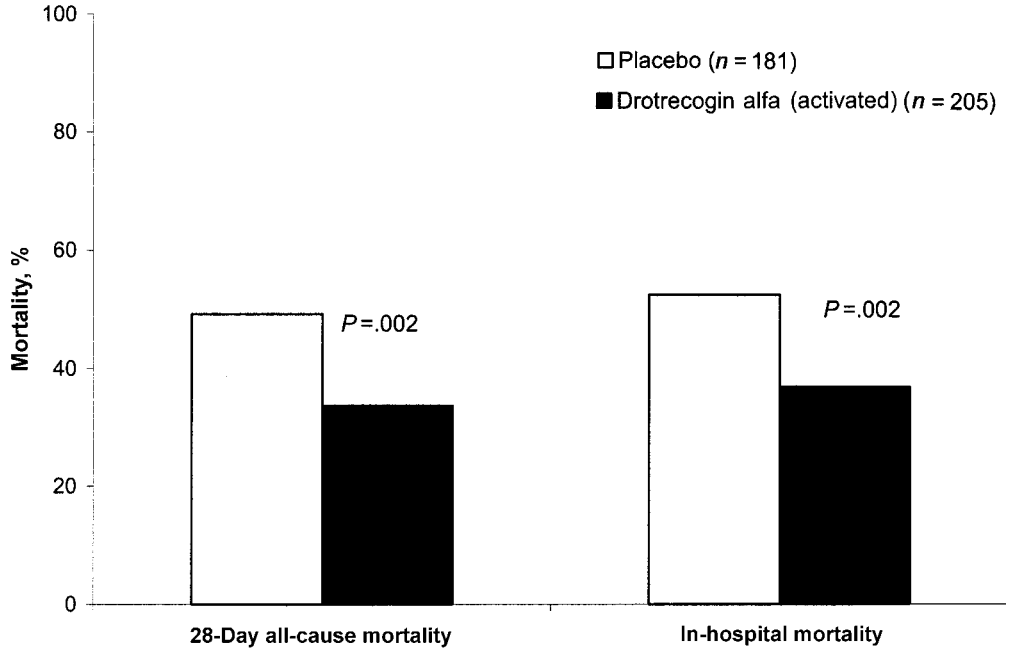

Figure 1 Histogram showing 28-day and in-hospital mortality rates, according to treatment group, for patients ⩾75 years of age. Patients aged ⩾75 years treated with drotrecogin alfa (activated), compared with placebo recipients, had absolute risk reductions in 28-day and in-hospital mortality rates of 15.5% (33.7% vs. 49.2%; $P = .002$) and 15.6% (36.9% vs. 52.5%; $P = .002$), respectively.

recipients (figure 3). Resource use, as analyzed using mean day and cumulative TISS-28 scores (see Methods) showed no difference between the DAA and placebo groups (mean average TISS score per day, 31.5 vs. 33.0, respectively; median cumulative TISS score, 275 vs. 276, respectively).

Patient disposition. Approximately 50% of the 28-day survivors aged ⩾75 years were still hospitalized on study day 28. Discharge disposition for hospital survivors in the DAA group was as follows: 45% were discharged home, 9% were transferred to another hospital, and 44% were transferred to a nursing home; for placebo recipients, 38% were discharged home, 14% were transferred to another hospital, and 47% were transferred to nursing home ($P = .51$). Functional dependency of 28-day survivors also showed no difference between the treatment and placebo groups (75% vs. 73%, respectively; $P = .70$).

Serious adverse events. The rates of serious adverse events collected for DAA and placebo recipients are shown in table 2. Among patients ⩾75 years of age, the incidences of serious bleeding over the 28-day study period in the DAA and placebo groups were 3.9% and 2.2%, respectively ($P = .34$); in patients <75 years of age, the incidences of serious bleeding were 3.4% and 2.0%, respectively ($P = .11$). The increase in the incidence of serious bleeding in the DAA group versus the placebo group was similar for older and younger patients ($P = .97$ for interaction). Of note, among the patients aged ⩾75 years, there was an observed reduction in thrombotic events in the DAA group, compared with the placebo group (2 vs. 9; $P = .019$). Higher rates of cardiac dysrhythmias (5.5% vs. 2%; $P = .06$) and CNS-related events (2.8% vs. 0; $P = .02$) were found in the placebo group than in the DAA group, respectively.

DISCUSSION

In this investigation, we demonstrated that in-hospital mortality among patients aged ⩾75 years with severe sepsis who received placebo was significantly higher than that among similar DAA-treated patients (52.5% vs. 36.9%, respectively). The absolute risk reduction associated with DAA translates to an estimated number needed to treat of 6 to save an additional life for these patients. In addition, the rate of serious bleeding associated with DAA therapy in this older subgroup with severe sepsis was 1.7% higher than among placebo-treated patients, which is similar to the 1.4% increase seen in the younger population.

Although the benchmark for the primary end point of sepsis trials has traditionally been the 28-day mortality rate, longer-term survival and morbidity analyses are increasingly recognized as important outcomes. In addition to reporting improved 28-day and in-hospital mortality rates, as mentioned above, we found that older patients with severe sepsis from the PROWESS trial who were treated with DAA had long-term survival benefits and actually spent significantly more time alive and without vasopressor therapy, without mechanical ventilation, and out of the ICU and hospital. Another concern re-

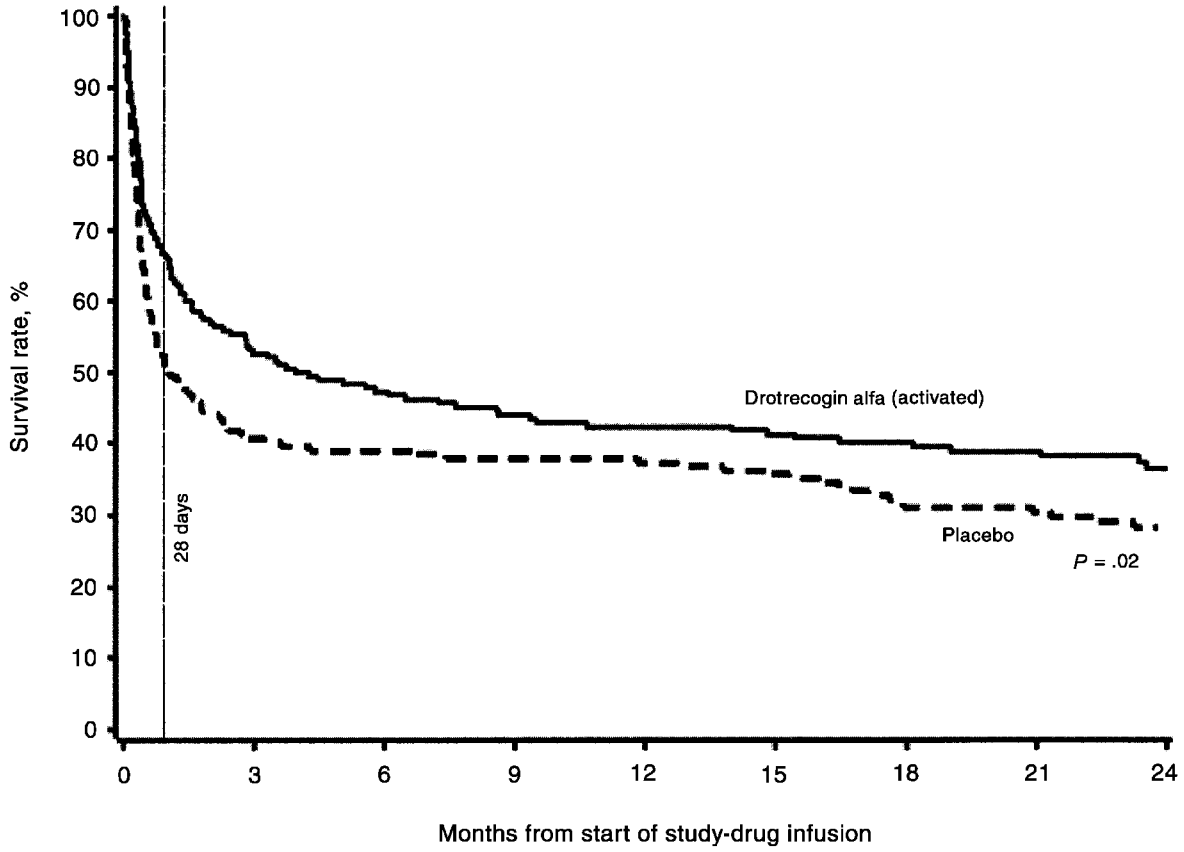

Figure 2. Twenty-four–month Kaplan-Meier survival curves for patients ⩾75 years of age, according to treatment group. Patients aged ⩾75 years treated with drotrecogin alfa (activated; DAA) had significantly higher survival rates sustained throughout the 2-year follow-up period ($P = .02$). Older patients treated with DAA had an increase in the median duration of survival of ~3 months (88 days) (31 days for the placebo group vs. 119 days for the DAA group).

garding the outcomes for older patients in sepsis trials is disposition (e.g., discharge to a nursing home). Of importance, this report has shown that older patients treated with DAA appeared to have the same hospital discharge disposition as the placebo recipients. In addition, survivors treated with DAA appeared to have functional status similar to that of placebo recipients. Taken together, these outcome data support the conclusion that DAA significantly improved survival in older patients without evidence of a "morbidity penalty," such as increased resource use or a decline in functional status.

Older patients are usually perceived to have an increased risk for bleeding complications, such as intracranial hemorrhage [21, 22]. As stated above, we did not observe an increase in DAA-associated serious bleeding in older patients, compared with younger patients. However, because this was a highly selected group of elderly patients enrolled in a clinical trial, these bleeding rates may not be applicable to the elderly population as a whole. We did observe a statistically significant decrease in the incidence of serious thrombotic events among older patients in the DAA group, compared with the placebo group, which may reflect the anticoagulant properties of this new agent.

Given the rapidly growing costs of medical care, some have suggested that health care rationing is inevitable and that age be used as a criterion for such rationing [23, 24]. Such a perspective could diminish the potential life-saving impact of new therapies (such as DAA) in this rapidly expanding segment of our population. Others have argued that, when underlying comorbidities and severity of illness are considered, the mortality rates for critically ill younger and older patients are similar [11, 25]. Although older ICU patients could potentially require more interventions and consume more health care resources, recent studies have shown that older patients actually receive less-aggressive care than do younger patients [4, 26–29]. Age-related bias against use of life-saving therapy, such as thrombolytics for treatment of acute myocardial infarction [30], appears to be an ongoing component of medical decision-making that is often not supported by data. Investigators from the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) [27] demonstrated that me-

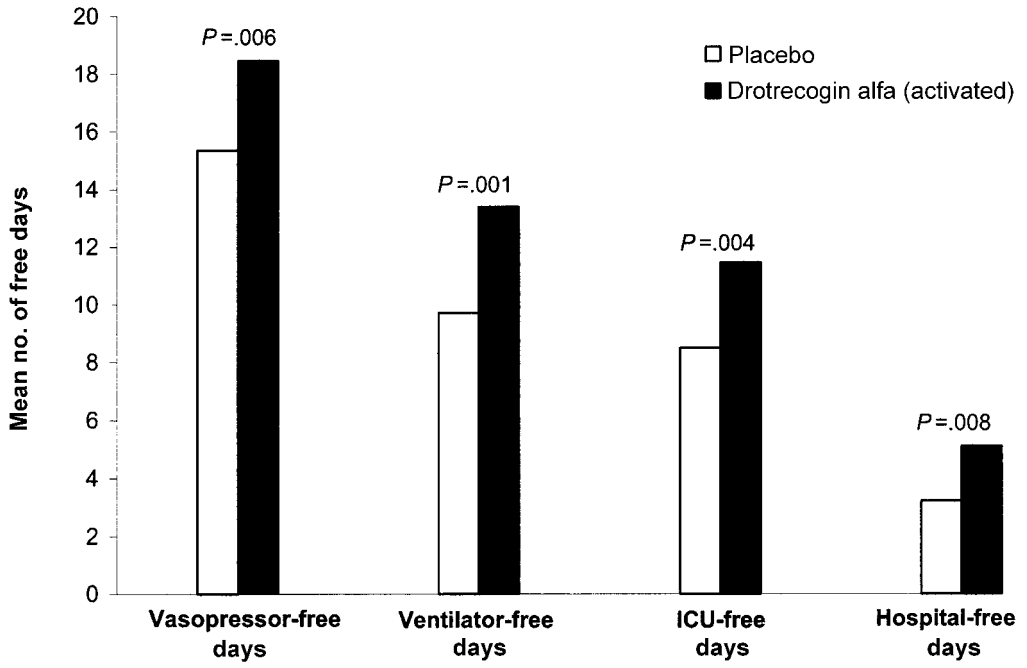

Figure 3. Histogram showing resource use expressed as a "free-day analysis" (i.e., days alive and free of the given measure) for patients aged ⩾75 years, according to treatment group. Patients treated with drotrecogin alfa (activated) had significantly more vasopressor-, ventilator-, ICU-, and hospital-free days, compared with the placebo group.

chanical ventilation is withheld at much higher rates for patients aged >70 years, despite the fact that this was often not in keeping with best estimates of patients' wishes. Levinsky et al. [31] recently showed that the aggressiveness of ICU therapies, such as mechanical ventilation, use of pulmonary artery catheters, and hemodialysis, decreases progressively as age increases. However, multiple studies have suggested that age should not be the deciding factor for treatment decisions in the ICU [11, 26, 32], and this conclusion is certainly supported by our analysis of the efficacy and safety of DAA for treatment of severe sepsis. Indeed, recent studies have found that there are age-related systemic inflammatory and coagulopathic changes that may increase vulnerability among older patients who develop severe sepsis [33–36]. These findings may help explain the large absolute reduction in the mortality rate seen in this population.

Two of the main strengths of this study were the relatively large cohort of older patients with severe sepsis available for analysis and the extensive morbidity and long-term follow-up data. These long-term follow-up data from the PROWESS trial allowed important analyses, with regard to resource use and mortality outcomes far beyond the typical 28-day outcomes. Importantly, this is the first investigation to examine long-term outcomes for older survivors of severe sepsis from a randomized, controlled trial. Comparisons at 3 different time points yielded consistent survival benefits associated with treatment with DAA. Recently, these data influenced the Center for Medicaid and Medicare Services to conclude that, under the Benefits Improvement and Protection Act, DAA meets the substantial improvement criteria for additional payments for new medical services and technologies [37], thereby providing financial assistance for all Medicare patients who receive this therapy.

This study has several important limitations that warrant comment. We conducted this subgroup analysis on the basis of the most recently agreed on age threshold (⩾75 years) [11], which is supported by important epidemiological data indicating that this age group consumes an enormous amount of hospital and financial resources [4, 6], but this was not a prospectively defined subgroup. The unavoidable limitations of subgroup analyses—including decreased statistical power, increased variance, and multiplicity—preclude the clinician from drawing firm conclusions based on their results [38, 39]. Both over- and underinterpretation of subgroup results may lead to harm; inappropriate treatment may be administered or potentially life-saving therapy may be withheld. Of importance, there were some significant baseline imbalances between the 2 study groups. This is common in subgroup analyses, and we used standard methodology to adjust for these covariates. Even after adjustment for these imbalances, the impact of DAA therapy on mortality persisted (i.e., the adjusted OR for dying was 0.57, or 43% lower, in the DAA group). Also, the subset population of elderly individuals in the PROWESS trial may not be generalizable to the elderly population, because certain exclusion

criteria may be more prevalent in the elderly population. Another limitation of this study is the lack of data on long-term functional status or quality of life in these older patients with severe sepsis, because these data were not collected in the PROWESS long-term follow-up observational study. Future research involving new technology for older patients receiving critical care should explore the cost-effectiveness of such interventions. Two studies showing favorable cost-effectiveness of DAA have recently been published [40, 41], and further analysis of cost-effectiveness in older patients will be forthcoming from ongoing investigations.

In conclusion, the significant survival advantages found at 28 days, during hospitalization, and at 2-years after receipt of treatment with DAA were accompanied by reduced morbidity, as assessed by vasopressor-, ventilator-, ICU-, and hospital-free days. In addition, there is no evidence that the main risk of this therapy (i.e., serious bleeding) is affected by patient age. Considering these data, it is appropriate to consider treatment with DAA for older patients (1) who are judged to be at high risk of death due to severe sepsis, such as those on vasopressor therapy or a ventilator due to sepsis, (2) for whom the patient, family, and health care team have chosen aggressive care, and (3) who have a favorable benefit-risk profile

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