Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial

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Summary

Background **Drotrecogin alfa (activated) (DrotAA) is used for the treatment of adults with severe sepsis who have a high risk of dying. A phase 1b open-label study has indicated that the pharmacokinetics and pharmacodynamics of DrotAA are similar in children and adults. We initiated the RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE) trial to investigate the efficacy and safety of the drug in children.**

Methods **Children aged between 38 weeks' corrected gestational age and 17 years with sepsis-induced cardiovascular and respiratory failure were randomly assigned to receive placebo or DrotAA (24 μg/kg/h) for 96 h. We used a prospectively defined, novel primary endpoint of Composite Time to Complete Organ Failure Resolution (CTCOFR) score. Secondary endpoints were 28-day mortality, major amputations, and safety. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov, number NCT00049764.**

Findings **477 patients were enrolled; 237 received placebo, and 240 DrotAA. Our results showed no significant difference between groups in CTCOFR score (p=0·72) or in 28-day mortality (placebo 17·5%; DrotAA, 17·2%; p=0·93). Although there was no difference in overall serious bleeding events during the 28-day study period (placebo 6·8%; DrotAA 6·7%; p=0·97), there were numerically more instances of CNS bleeding in the DrotAA group (11 [4·6%], *vs* 5 [2·1%] in placebo, p=0·13), particularly in children younger than 60 days. For CTCOFR score days 1–14, correlation coefficient was –0·016 (95% CI –0·106 to 0·74); relative risk for 28-day mortality was 1·06 (95% CI 0·66 to 1·46) for DrotAA compared with placebo.**

Interpretation **Although we did not record any efficacy of DrotAA in children with severe sepsis, serious bleeding events were similar between groups and the overall safety profile acceptable, except in children younger than 60 days. However, we gained important insights into clinical and laboratory characteristics of childhood severe sepsis, and have identified issues that need to be addressed in future trials in critically ill children.**

Introduction

Up to one-fifth of the estimated 42 000 children with severe sepsis in the developed world die each year, and the illness is the second leading cause of death in children ages 1–14 years.[1–5] The financial burden of severe sepsis in children is estimated to be $1·97 billion per year in the USA.[5] Apart from antibiotics and supportive care, there are no approved adjunctive therapies for children.

Drotrecogin alfa (activated) (DrotAA), a recombinant form of human activated protein C, has been approved in over 50 countries for treatment of severe sepsis in adults at high risk of death. Approval was based on a highly significant reduction in 28-day mortality shown in the PROWESS trial,[6] which excluded patients younger than 18 years.

An open-label study (called EVAO) in children with severe sepsis indicated that pharmacokinetics and pharmacodynamics of DrotAA are similar to that in adults.[7] Children in the EVAO study had higher rates of cardiovascular dysfunction and two or more organ dysfunctions (93% and 85%, respectively) than did adults in the PROWESS study (72% and 75%, respectively). The most common infection in the EVAO study was that from *Neisseria meningitidis* (26·5%), which was documented in only 1% of PROWESS patients.

Before approval of DrotAA and completion of EVAO, a global open-label trial in adults and children with severe sepsis (ENHANCE) was initiated to gather additional data for mortality and safety.[8] In ENHANCE (n=188), 25 (13·4%) children had died by day 28, and 11 (5·9%) had serious bleeding events during DrotAA infusion.[9] Five (2·7%) children had a CNS bleed.

This randomised placebo-controlled trial, RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE), was implemented to determine the efficacy and safety of DrotAA in children.

Methods

Participants

Between November, 2002, and April, 2005, we enrolled participants from 104 study sites in 18 countries. Participants were eligible if they were aged between 38 weeks' corrected gestational age and 17 years, and fulfilled all the following criteria: a suspected or proven infection, and systemic inflammation, sepsis-induced cardiovascular, and respiratory organ dysfunction within 12 h before entering the study. Exclusion criteria

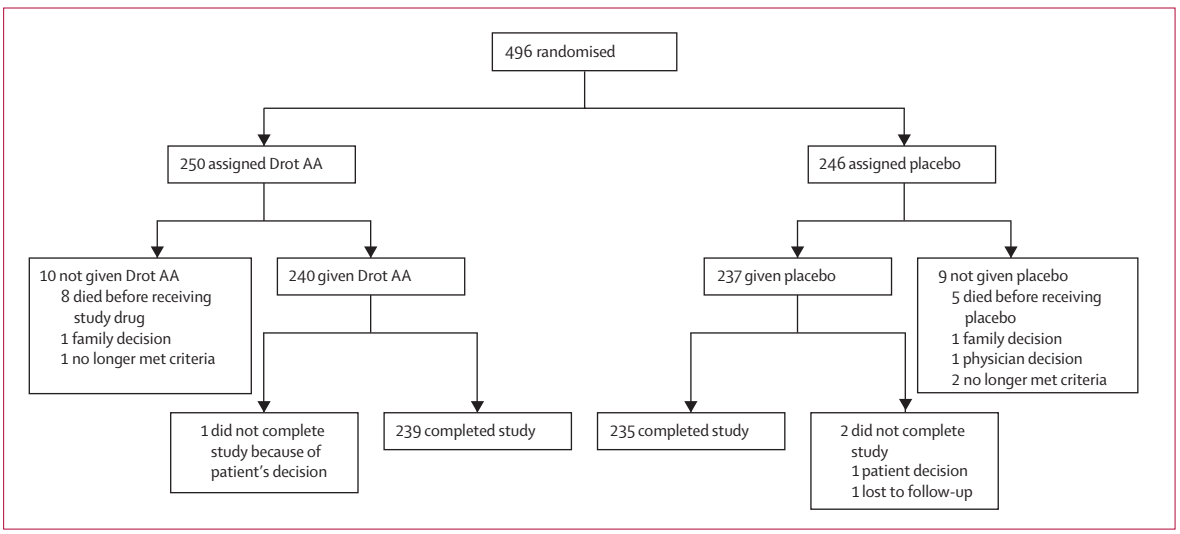

Figure 1: **Trial profile**

included high risk of intracranial bleeding, expected to die before the end of the 28 days of the study from pre-existing conditions, or end-stage renal or liver disease (see webpanel 1 for full inclusion criteria and webpanel 2 for full exclusion criteria).

We randomly allocated individuals to an intravenous infusion of either placebo (0·9% saline) or DrotAA for 96 h (±1 h) (see webfigure for study design). The study drug was to be started within 42 h of the first documented organ dysfunction and within 24 h of dual cardiovascular and respiratory organ dysfunction by block randomisation (block size of 4). Standard of care was at the discretion of the primary physician and not dictated by trial protocol. For initial volume resuscitation, an intravenous fluid load of ≥40 mL/kg within a 2-h period was required for study entry. The type of fluid used (eg, colloids or crystalloids) was not recorded for the study. All study personnel, except the pharmacist responsible for dispensing study drug, remained unaware of treatment assignment for the duration of the study.

All institutional and ethics review boards provided written approval of the study protocol and the patient information and informed consent documents. Each patient's authorised legal representative gave informed consent. This trial is registered with clinicaltrials.gov, number NCT00049764.

Procedures

An international panel of 20 experts from five countries was convened in 2002, and recommended that researchers undertaking trials of severe sepsis in children use composite outcomes that incorporate time to resolution of sepsis-induced organ failures (eg, resolution of need for mechanical ventilation, inotropes/vasopressors, renal replacement therapy) as a primary endpoint.[10]

We assessed baseline clinical and laboratory characteristics, including demographics, organ dysfunctions, and site and type of infection. The Pediatric Risk of Mortality III (PRISM III) score was based on variables assessed for the first 12 h of ICU (intensive care unit) stay and the 12 h immediately preceding infusion of

See Online for webpanels 1 and 2 and webfigure

	Placebo (n=237)	DrotAA (n=240)	p
Demographics			
Male sex	115 (48·5%)	143 (59·6%)	0·02
Age (years), median (IQR)	2·8 (0·7–9·4)	2·3 (0·7–7·8)	0·36
Age group			0·55
0 to <1 month	16 (6·8%)	14 (5·8%)	
1 month to <12 months	59 (24·9%)	62 (25·8%)	
1 year to <5 years	68 (28·7%)	81 (33·8%)	
5 years to <10 years	57 (24·1%)	44 (18·3%)	
10 years to <18 years	37 (15·6%)	39 (16·3%)	
Ethnic origin			0·97
White	152 (64·1%)	162 (67·5%)	
Hispanic	48 (20·3%)	47 (19·6%)	
African descent	15 (6·3%)	13 (5·45)	
Other (mixed racial)	15 (6·3%)	12 (5·0%)	
Western Asian	6 (2·5%)	5 (2·1%)	
East/southeast Asian	1 (0·4%)	1 (0·4%)	
Disease severity			
Chronic disease	88 (37·1%)	80 (33·3%)	0·87
Number of organ failures, median (IQR)	4·0 (3·0–4·0)	4·0 (3·0–5·0)	0·25
Haematological dysfunction	138 (58·2%)	150 (62·55)	0·34
Cutaneous dysfunction†	66 (28·0%)	80 (33·3%)	0·20
Hepatic dysfunction	42 (20·1%)	58 (25·9%)	0·15
Renal dysfunction	36 (15·6%)	47 (19·9%)	0·22
PRISM III at ICU entry, median (IQR)	15 (10·0–21·0)	16 (11·0–22·5)	0·07
DIC	101 (53·2%)	104 (52·3%)	0·86
ARDS	19 (8·4%)	23 (10·3%)	0·49
Baseline steroids	93 (39·2%)	97 (40·4%)	0·79

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Immune status			
Purpura	69 (29·1%)	79 (32·9%)	0·37
Site of infection			0·45
Lung	88 (37·1%)	89 (37·15%)	
Blood	77 (32·5%)	74 (30·8%)	
Intra-abdominal	27 (11·4%)	18 (7·5%)	
CNS	17 (7·2%)	21 (8·8%)	
Skin/skin structures	6 (2·5%)	15 (6·3%)	
Head/EENT	7 (3·0%)	8 (3·3%)	
Urinary tract	3 (1·3%)	4 (1·7%)	
Bone/joint	2 (0·8%)	4 (1·7%)	
Gynaecological	4 (1·7%)	2 (0·8%)	
Vascular catheter	3 (1·3%)	2 (0·8%)	
Cardiac	..	2 (0·8%)	
Pleural	3 (1·3%)	1 (0·4%)	
Infection type			0·33
No culture done or culture negative	85 (35·9%)	74 (30·8%)	
Pure gram-positive	62 (26·2%)	66 (27·5%)	
Pure gram-negative	46 (19·4%)	48 (20·0%)	
Mixed gram	27 (11·4%)	21 (8·8%)	
Fungal	12 (5·1%)	18 (7·5%)	
Viral	4 (1·7%)	12 (5·0%)	
Culture positive but not identified	1 (0·4%)	1 (0·4%)	
Laboratory values			
Platelets (x10^3/mL), median (IQR)	118·0 (69·0–212·0)	130·0 (75·0–200·0)	0·48
PT (INR), median (IQR)	2·0 (1·6–2·6)	2·0 (1·5–2·7)	0·82
aPTT (s), median (IQR)	46·8 (38·9–56·0)	46·5 (38·3–58·1)	0·77
D-dimer (µg/mL), median (IQR)	5·6 (2·5–17·3)	5·9 (2·8–20·8)	0·34
TATc (µg/mL), median (IQR)	9·0 (2·3–19·8)	24·2 (9·8–73·9)	0·24
Procalcitonin (ng/mL), median (IQR)	72·5 (15·7–198·9)	58·8 (16·1–210·8)	0·86
IL-6 (pg/mL), median (IQR)	1369·8 (225·9–13 918)	1998·4 (239·8–18 939)	0·52
IL-8 (pg/mL), median (IQR)	335·9 (96·8–1556·8)	339·1 (102·7–1490·0)	0·75
IL-10 (pg/mL), median (IQR)	34·6 (11·0–218·0)	54·1 (13·6–292·9)	0·48
TNFα (pg/mL), median (IQR)	2·5 (2·5–2·5)	2·5 (2·5–2·5)	0·88
Protein C activity (% normal), median (IQR)	32 (21–45)	29 (18–43)	0·17

Data are n (%) unless otherwise specified. EENT=eyes, ears, nose, throat. PT=prothrombin time. aPTT=activated partial thromboplastin time. INR=international normalised ratio. *Unknowns were not included in this analysis. †Refers to purpura or necrosis, or both.

Table 1: **Baseline characteristics**

	Placebo [n (%)]	DrotAA [n (%)]
Lung		
Staphylococcus aureus	22 (33·3)	19 (25·7)
Pseudomonas aeruginosa	14 (21·2)	13 (17·6)
Candida albicans	8 (12·1)	13 (17·6)
Streptococcus pneumoniae	5 (7·58)	5 (6·76)
Haemophilus influenzae	5 (7·58)	4 (5·41)
Blood		
Neisseria meningitidis	25 (26·3)	26 (25·5)
Coagulase-negative Staphylococcus	23 (24·2)	20 (19·6)
Staphylococcus aureus	12 (12·6)	8 (7·84)
Streptococcus pneumoniae	6 (6·32)	9 (8·82)
Pseudomonas aeruginosa	6 (6·32)	6 (5·88)
CNS		
Neisseria meningitidis	9 (47·4)	9 (45·0)
Streptococcus group B	2 (10·5)	4 (20·0)
Streptococcus pneumoniae	2 (10·5)	3 (15·0)
Streptococcus agalactiae	2 (10·5)	1 (5·00)
Intra-abdominal		
Coagulase-negative Staphylococcus	1 (12·5)	4 (44·4)
Escherichia coli	2 (25·0)	2 (22·2)
Candida albicans	2 (25·0)	2 (22·2)
Streptococcus (strain not determined)	2 (25·0)	1 (11·1)
Urinary tract/urine		
Escherichia coli	6 (27·3)	3 (18·8)
Candida albicans	4 (18·2)	4 (25·0)
Pseudomonas aeruginosa	4 (18·2)	3 (18·8)
Staphylococcus aureus	2 (9·09)	1 (6·25)
Candida (strain not determined)	2 (9·09)	1 (6·25)
Other*		
Staphylococcus aureus	30 (34·5)	23 (26·1)
Coagulase-negative Staphylococcus	23 (26·4)	22 (25·0)
Candida albicans	16 (18·4)	17 (19·3)
Pseudomonas aeruginosa	8 (9·20)	14 (15·9)
Escherichia coli	9 (10·3)	9 (10·2)

*Bone or joint; cardiac; gynaecological; head, ears, eyes, nose, or throat; in-dwelling catheter; skin or skin structure, stool, synovial fluid. Total numbers for each column not included because 62 placebo patients and 69 DrotAA patients had multiple infection sites.

Table 2: **Summary of most common micro-organisms by site of infection**

study drug, if study drug infusion began more than 24 h after ICU admission. All patients, including those who did not receive or discontinued study drug, were followed-up to 28 days.

The primary endpoint for efficacy was a reduction in Composite Time to Complete Organ Failure Resolution (CTCOFR) score of three organ systems: cardiovascular, respiratory, and renal. Resolution was defined as the last day the patient needed vasoactive agents, invasive mechanical ventilation, or renal replacement therapy. Resolution of cardiovascular organ dysfunction was defined as requiring less than 5 µg/kg/min dopamine or dobutamine, or cessation of epinephrine, norepinephrine, phenylephrine, or any other vasoactive agent used for haemodynamic support. Resolution of respiratory organ dysfunction was defined as cessation of invasive mechanical ventilation (ie, not requiring intermittent positive pressure) including continuous positive airway pressure or bimodal positive airway pressure. Resolution of renal organ dysfunction was defined as cessation of renal replacement therapy (peritoneal dialysis, haemodialysis, ultrafiltration, or haemofiltration).

The primary safety measure was assessment of all bleeding events reported as serious adverse events and included any intracranial haemorrhage, fatal, or life-threatening bleeding. To determine the safety

	Placebo (n=235)	DrotAA (n=239)	p
CTCOFR score			
Days 1–14,* median (IQR)	6·0 (4·0–8·0)	6·0 (4·0–8·0)	0·72
Day 15, number not resolved (%)	47 (19·8%)	46 (19·2%)	
Day 16, number who died during study(%)	41 (17·3%)	41 (17·1%)	
Mortality			
28-day mortality†, n (%)	41 (17·5%)	41 (17·2%)	0·93
14-day mortality, n (%)	32 (13·6%)	35 (14·6%)	0·78
In-hospital mortality, n (%)	41 (17·3%)	41 (17·1%)	0·95
Clinically relevant subgroups (28-day mortality only)			
Gender			0·10
Male	19 (16·7%)	30 (21·1%)	
Female	22 (18·2%)	11 (11·3%)	
Age			0·65
0 to <1 month	1 (6·3%)	2 (14·3%)	
1 month to <12 months	14 (24·1%)	13 (21·0%)	
1 year to <5 years	9 (13·2%)	13 (16·0%)	
5 years to <10 years	6 (16·2%)	3 (7·7%)	
10 years to <18 years	11 (19·6%)	10 (23·3%)	
Baseline overt DIC‡			0·05
Yes	22 (22·2%)	15 (14·4%)	
No	10 (11·2%)	17 (18·1%)	
Purpura			0·52
Yes	11 (15·9%)	10 (12·7%)	
No	30 (18·8%)	31 (19·4%)	
Baseline platelets			
<100 000	25 (26·6%)	16 (18·2%)	0·08
≥100 000	16 (11·3%)	24 (16·0%)	
<50 000	10 (37·0%)	6 (26·1%)	0·39
≥50 000	31 (14·9%)	34 (15·8%)	
IL-6			0·08
≤2000	23 (20·0%)	14 (12·7%)	
>2000	17 (17·3%)	25 (22·9%)	
Protein C			0·56
≤40%	26 (20·8%)	27 (19·3%)	
40–80%	4 (7·0%)	5 (9·4%)	
>80%	1 (25·0%)		
Infection site:			0·36
Lung	21 (24·4%)	18 (20·2%)	
Blood	10 (13·0%)	7 (9·5%)	
CNS	2 (11·8%)	5 (23·8%)	
Intra-abdominal	4 (14·8%)	6 (35·3%)	
Other	4 (14·3%)	5 (13·2%)	

Data are number of deaths (%) unless otherwise specified. Two patients lost to follow-up in the placebo group, and one in the DrotAA group. *Correlation coefficient was 0·016 (95% CI –0·106 to 0·74). †Relative risk was 1·06 (95% CI 0·66 to 1·46) for DrotAA *vs* placebo. ‡As previously described.[14]

Table 3: **Efficacy analyses**

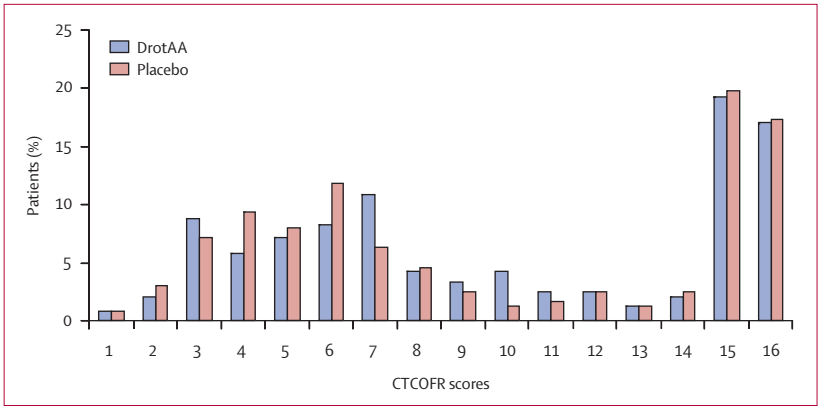

Figure 2: **Distribution of CTCOFR scores**

profile, the following measures were assessed: (1) serious adverse events, including serious bleeding events during both the infusion (days 0–6) and 28-day study period; and (2) serious adverse events thought to be study drug-related. An independent data-monitoring committee was established to monitor safety during the trial and analyse interim results.

Statistical analysis

In view of the low mortality of severe sepsis in children compared with that in adults, using 28-day mortality as the primary endpoint was not feasible. Assuming a 28-day mortality rate of 12% and an absolute risk reduction of 2%, we would have needed to enrol more than 3000 individuals to achieve 80% power at a 0·05 significance level.

Data from the EVAO study[7] suggested that the mean CTCOFR was 7·74 days (SD 5·04). The International Pediatric Sepsis Conference indicated that a reduction in organ failure of 1 day would be clinically relevant.[10] We judged a 15% improvement (1·2 days) in the estimate of 7·74 days as significant. We calculated that a sample size of 600 patients would provide 80% power for a clinically relevant 1·2-day reduction in the duration of organ failure between treatment groups.[10]

CTCOFR was analysed as an ordinal categorical response with categories for each of the first 14 days (score 1–14). Patients whose organ dysfunction was not resolved within 14 days received a CTCOFR score of 15. Patients who died at any time during the study received a CTCOFR score of 16. Analysis was by intention-to-treat.

For CTCOFR, treatment groups were compared by a ranked analysis, using PROC FREQ in SAS with the integer scores option. We did Kaplan-Meier analysis on CTCOFR (patients with CTCOFR score >15 were considered as having censored organ failure at day 14) and 28-day mortality. Treatment groups were compared with χ^2, or Cochran-Mantel-Haenszel tests, or both. Fisher's exact test was used in instances where events were few (<five). Data for continuous variables were summarised using measures of central tendency and dispersion. Continuous variable data were ranked and tested in an analysis of variance (ANOVA) statistical test.

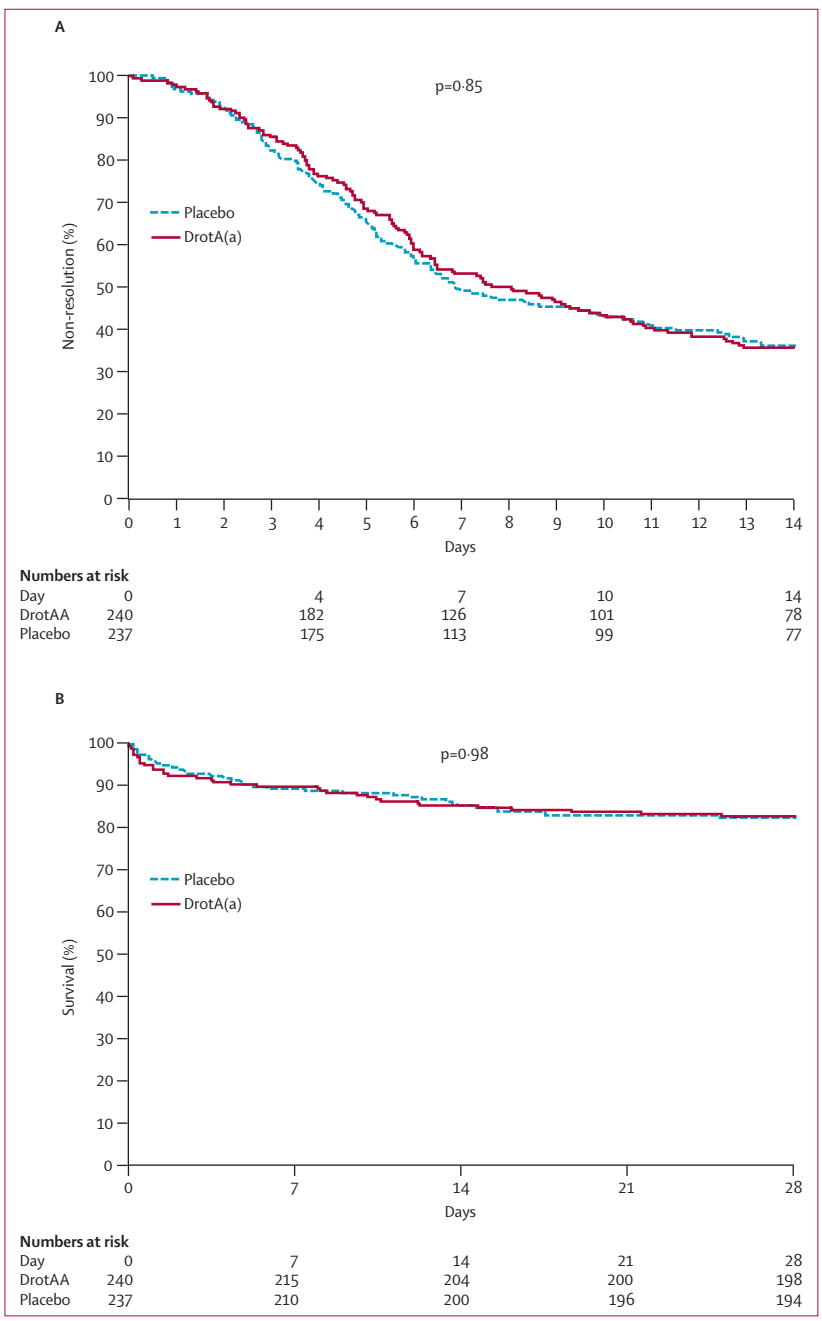

Figure 3: **Kaplan-Meier estimates of CTCOFR (A) and 28-day mortality (B)**

We used a post-hoc multivariable Cox proportional-hazards regression analysis to assess significant baseline risk factors for mortality and organ dysfunction resolution in the placebo group. Data were categorised as dichotomous variables (high or low) for the model. Since there were baseline imbalances between treatment groups, we calculated hazard ratios for the treatment effect using data from both groups, after adjusting for significant risk factors. All statistical calculations were done with the SAS software version 8.2.

Role of the funding source

This study was funded by Eli Lilly, and the authors from the funding company were involved in all aspects of the study. However, all final decisions were made jointly by S Nadel, B Goldstein, and B Giroir, except for the decision to stop the study, which was made by the sponsors at the recommendation of the Data Safety Monitoring Board. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Agreement to submit for publication was obtained from all authors.

Results

We enrolled 477 patients between November, 2002, and March, 2005 (figure 1). In March 2005, enrollment was suspended after the second planned interim analysis suggested there was little chance of reaching the efficacy endpoint by completion of the trial. Follow-up of enrolled patients continued until April 3, 2005.

Baseline characteristics are shown in table 1. There were significantly more male patients in the DrotAA group. Also, the number of organ failures, patients with renal, hepatic, cutaneous, or haematological dysfunction, PRISM III scores,[11] and patients with disseminated intravascular coagulation and acute respiratory distress syndrome, were all numerically higher, suggesting higher disease severity in the DrotAA group. The most common sites of infection were blood and lung, with pure gram-positive organisms being the most common infection (table 2).

There were no significant differences between treatment groups in the primary endpoint, CTCOFR (p=0·72) (table 3). Since there were significant imbalances in sex (p=0·02) and close to significant (PRISM III scores at ICU entry, p=0·07) imbalances in baseline characteristics (table 1) between groups, these were adjusted for and analysed using a multivariable Cox regression model. Even after this adjustment, there was no difference in CTCOFR between treatment arms (p=0·93). The distribution of CTCOFR scores is shown in figure 2. About 20% of patients in both groups (placebo [n=47], DrotAA [n=46]) did not have a resolution of their organ dysfunction by day 14 and therefore received a score of 15. 41 patients in each group (~17%) died during the 28-day period and received a score of 16. In subgroup analyses of CTCOFR score, defined by selected baseline demographic characteristics, pre-infusion organ dysfunction status, and PRISM III score, there were no significant differences in subgroups of more than 50 patients in total (25 per group), except for baseline renal dysfunction (p=0·02).

Analysis of 14-day, 28-day, and in-hospital mortality also showed no significant differences between treatment groups (CTCOFR and 28-day mortality; Kaplan-Meier analyses in figure 3; log-rank p=0·85 and p=0·98, respectively. There were no clinically relevant subgroups where treatment effects reached statistical significance.

More males than females died in the DrotAA group, which was the opposite of what happened in the placebo group. Patients with baseline disseminated intravascular coagulation (DIC), as defined by a modified version of the International Society on Thrombosis and Haemostasis criteria,[12] had numerically lower mortality in the DrotAA group than placebo, while DrotAA patients without baseline DIC had numerically greater mortality than placebo.

There were no significant differences between treatment groups in rate of amputations, hearing loss, and skin grafts in patients diagnosed with meningitis, or purpura fulminans (data not shown). Analysis showed numerically fewer patients discharged to home (n=111 *vs* n=127) and more remaining in the hospital (n=83 *vs* n=72) at 28 days in placebo compared to the DrotAA group (p=0·28).

Given the differences in baseline severity of illness, a post-hoc analysis of placebo baseline measures (age, number of organ failures, DIC, PRISM III score, comorbidity, purpura fulminans, meningitis, immunocompromised, type of infection, D-dimer class, IL-6 class, procalcitonin class, thrombin-antithrombin complex [TATc] class, acute respiratory distress syndrome [ARDS], and geography) was undertaken for inclusion in a multivariate risk of mortality model. Three independent predictors of mortality emerged: TATc, PRISM III, and lung infection. The increased risk of death associated with these factors was 1·30-fold (per unit increase; p<0·001), 1·04-fold (per point increase; p<0·001), and 2·11-fold (compared to non-lung; p=0·001), respectively. There was also a drop in the resolution rate of organ failure associated with baseline TATc (0·79, p<0·001), PRISM III (0·95, p<0·001), and lung infection (0·51, p<0·001), based on the same units as the mortality hazard ratios. After adjusting for these predictors, there was a non-significant 12% decrease in risk of death and a 7% increase in resolution rate of organ failure associated with DrotAA treatment (p=0·57 for both).

Safety analyses for the infusion (0–6 days) and 28-day periods are shown in table 4. Overall, there were no significant differences between groups in serious adverse events, serious bleeding, or CNS bleeding. The predominant DrotAA-related complication associated with the drug was bleeding. Numerically more CNS bleeding events occurred in the DrotAA group during infusion (5 *vs* 1, p=0·10) and the 28-day period (11 *vs* 5, p=0·13). Of the five DrotAA patients with CNS bleeding during infusion, four were younger than 60 days and weighed less than 4 kg, and three had overt DIC at baseline. Two CNS bleeds in the DrotAA group were petechial haemorrhages within a pre-existing area of infarct; one was asymptomatic and detected on a screening cranial ultrasound. During the infusion period, two DrotAA patients had CNS bleeding events (one fatal and one non-fatal but clinically severe), which were associated with major protocol violations (one patient with a platelet count of 22 000/mm^3 during infusion and the other had increased intracranial pressure with ventricular tap). During the 28-day period, two patients in each group had fatal CNS events. Fatal bleeding events over the 28-day study period occurred in five placebo and two DrotAA patients. There were significantly more study-drug-related serious adverse events and serious bleeding events during the infusion and 28-day periods in the DrotAA group. However, at the time the serious bleeding events actually occurred, eight DrotAA patients were still receiving study drug, compared with only one placebo patient.

	Placebo* (n=237)	DrotAA* (n=240)	Total* (n=477)	p
Serious adverse events				
Days 0–6	26 (11·0)	25 (10·4)	51 (10·7)	0·85
Days 0–28	45 (19·0)	44 (18·3)	89 (18·7)	0·86
Serious bleeding events				
Days 0–6	8 (3·4)	9 (3·8)	17 (3·6)	0·83
Days 0–28	16 (6·8)	16 (6·7)	32 (6·7)	0·97
CNS bleeding events				
Days 0–6	1 (0·4)†	5 (2·1)†	6 (1·3)	0·22
Days 0–28	5 (2·1)	11 (4·6)	16 (3·4)	0·13
Study-drug related serious adverse events				
Days 0–6	1 (0·4)	10 (4·2)	11 (2·3)	0·01
Days 0–28	2 (0·8)	12 (5·0)	14 (2·9)	0·01
Study-drug related serious bleeding events				
Days 0–6	1 (0·4)	8 (3·3)	9 (1·9)	0·04
Days 0–28	2 (0·8)	10 (4·2)	12 (2·5)	0·04

*Data are number (%). †One patient at increased risk of CNS bleeding at baseline in the placebo group (cerebral oedema) and two in the DrotAA group (cerebral oedema, platelets=30K).

Table 4: **Safety analyses**

Subgroup analyses of serious adverse events and serious bleeding events during the infusion period suggested treatment-by-subgroup interactions in the subgroup defined by age. DrotAA patients younger than 60 days of age were at increased risk for a serious adverse event (p=0·03) and tended to have more serious bleeding events (p=0·14).

Discussion

RESOLVE was the largest randomised placebo-controlled trial so far in critically ill children, and the only placebo-controlled study of DrotAA in children. There was no significant difference in either CTCOFR or mortality between patients on DrotAA compared with those on placebo. Nor were there any significant differences between groups in serious adverse events, serious bleeding, or CNS bleeding.

The background serious bleeding rate in paediatric severe sepsis had not been defined until this study. Our results showed that children with severe sepsis have a background serious bleeding rate of about 7% over 28 days,

including a 2% risk of CNS bleeding. As noted previously[6,8,13] DrotAA's anticoagulant activity increased bleeding risk during treatment. However, there was no difference between groups in the incidence of serious bleeding during the infusion or 28-day study periods. Although not significant, more DrotAA patients had CNS bleeding than did placebo patients, during the infusion and 28-day study periods. Further safety analyses showed that four of the five patients in the DrotAA group with a CNS bleeding event during infusion were younger than 60 days and weighed less than 4 kg, and two had serious protocol violations. Overall, DrotAA seemed to have an acceptable safety profile in children older than 60 days weighing more than 4 kg.

Given the lower mortality[1–5,14] and relative paucity of children available for inclusion in any trial targeting life-threatening illness, there are some key caveats and limitations in this study. To maximise the opportunity for a valid outcome, several strategies were undertaken: 104 major paediatric centres in 18 countries were enlisted and extensively trained in screening and assessment procedures; only patients at the highest risk of mortality or significant morbidity were included; and a primary outcome variable was selected that was meaningful to the clinician, patient, and patient's family.

Heterogeneity in patient populations and therapeutic approaches could have influenced the trial's outcome. The large number of centres, each enrolling few patients, might have resulted in a "first patient effect", which could significantly impact a clinical trial result.[15] Although each site underwent extensive education in patient identification, recruitment, and study procedures, most had very limited previous experience with administration and use of DrotAA in children.

The choice of primary outcome variable could also have been inappropriate, although a similar endpoint has been useful in other paediatric studies.[16] Endpoints such as cessation of mechanical ventilation (the definition of respiratory organ resolution) or resolution of cardiovascular failure could have been influenced by local weaning practices, which were not dictated by the study protocol. Differing medical practice in intensive care units, within and between countries, might also affect the reliability of an endpoint such as CTCOFR in multi-centre studies. Nonetheless, the standard deviations of CTCOFR in each treatment arm were within our statistical assumptions and appropriately powered to detect a 1·2-day difference between groups.

Because mortality is a dominant component of the CTCOFR endpoint, there would have to be a large difference in mortality, or much faster organ resolution in the interventional group, or both, to create a difference. If there were a reduction in mortality but an associated increase in resource use, the CTCOFR score could have remained similar between groups. However, if mortality was significantly reduced because of a short-term increase in hospital stay, the study's results (albeit formally negative) could have supported use of DrotAA in children. In future trials, the nuances of CTCOFR use should be carefully considered.

Our results are different to those from the PROWESS trial in adults, in which DrotAA significantly reduced mortality compared with placebo.[6] In the PROWESS trial, mortality in the placebo group was about 31%, whereas mortality in RESOLVE was considerably lower at 17%. We now know there was only 31% power in this trial to show a 20% relative risk reduction in mortality for a sample size of 600 patients, assuming a mortality in controls of 17%. Therefore, this study does not exclude a mortality advantage in children, equivalent to that seen in the PROWESS study. These disparities also emphasise the folly of trying to extrapolate results directly from children to adults, or vice versa. Differences between trials in the natural history of sepsis (eg, mortality), the comparatively low numbers of patients in RESOLVE, and completely different endpoints, preclude direct extrapolation or comparison of the two trials.

The comparatively small size of RESOLVE led to numerical imbalances in some baseline characteristics. Most notable was the greater disease severity in the DrotAA group (more organ failures and dysfunction, higher PRISM III, more DIC and ARDS). Multivariate analysis showed that lung infection, TATc, and PRISM III scores were independent predictors of death. Moreover, after adjusting for severity of illness, there was a non-significant advantage for the DrotAA group, for both CTCOFR and 28-day mortality. Given the inherent limitations of small sample size and the likely imbalances that will occur, a primary outcome variable with severity adjustment should be considered for future trial designs.

Arguably, the results of this trial casts doubt on the efficacy of DrotAA. However, this study was testing the drug in children and was not designed to re-test the efficacy of DrotAA in critically ill adults with severe sepsis. Although important data concerning the natural history of sepsis and safety issues in children were obtained, a clearer understanding of the appropriate use of DrotAA in adults was not.

There may be several reasons for the apparent conflicting results between children and adults with sepsis. First, there were clear differences between RESOLVE and PROWESS in baseline characteristics, trial design, and statistical power. Second, it is likely there are differences in the pathophysiology of paediatric and adult sepsis. Patients in RESOLVE had lower protein C levels, higher D-dimer levels, and higher IL-6 levels than the adult patients in PROWESS. Lastly, it is possible that dosing of DrotAA was insufficient in the children in this study; it might have been more effective if dosed according to protein C levels rather than on a weight basis.

RESOLVE also provided important insights into childhood severe sepsis. It better defined clinical and laboratory characteristics, quantified the baseline severe bleeding rate, and revealed three independent predictors

of mortality: baseline TATc, PRISM III score, and lung infection. Finally, in this study we identified important methodological issues that need to be addressed in future randomised trials in critically ill children.

Despite not demonstrating a positive effect, RESOLVE has documented the natural history of severe sepsis and paved the way for future randomised placebo-controlled trials in the field of pediatric critical care medicine.

Contributors

B Giroir, S Nadel, B Goldstein, M D Williams, H Levy, and W L Macias contributed to the conception and design of the study. B Giroir, S Nadel, B Goldstein, M D Williams, H Dalton, M Peters, S A Abd-Allah, and R Angle contributed to data collection. B Giroir, S Nadel, M D Williams, W L Macias, D Wang, D P Sundin, and R Angle contributed to the analyses. B Giroir, S Nadel, M D Williams, and D P Sundin drafted the manuscript. All authors reviewed and helped revise the manuscript, and approved the final version of the manuscript.

Conflict of interest statement

This study was supported by Eli Lilly. S Nadel, B Goldstein, and B Giroir have been paid consultants for Eli Lilly. S Nadel, B Goldstein, H Dalton, M Peters, and B Giroir have participated in previous trials sponsored by Eli Lilly. M D Williams, W L Macias, H Levy, D Wang, D P Sundin, and R Angle are all employees and stockholders of Eli Lilly. S A Abd-Allah has no conflict of interest to declare.

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See **Online** for webappendix