

**NHS NORTHERN AND YORKSHIRE**

**REGIONAL DRUG AND THERAPEUTICS CENTRE**

**THE USE OF DROTRECOGIN ALFA  
(ACTIVATED) IN THE MANAGEMENT OF  
SEVERE SEPSIS**

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## SUMMARY

- Severe sepsis has a high morbidity and mortality and results from a complex series of host events in response to infection. These may lead to the development of disseminated intravascular coagulation and microvascular thrombosis, acute multi-organ failure and death. Despite advances in supportive care the mortality rate is 30 - 50% and has not altered significantly in recent years.
- Drotrecogin alfa (activated) is recombinant human activated protein C which is an important modulator of the systemic response to infection and affects the processes of inflammation, thrombosis, and fibrinolysis. In severe sepsis protein C is converted to activated protein C, however protein C levels are rapidly depleted and patients with severe sepsis typically have low levels at diagnosis.
- Drotrecogin alfa (activated) has recently been licensed for the treatment of adult patients with severe sepsis and multiple organ failure. It is given as an infusion over 96 hours.
- In the PROWESS study, drotrecogin alfa (activated) reduced the risk of death within 28 days from 30.8% (placebo) to 24.7% (drotrecogin alfa (activated), absolute risk reduction 6.1%) in patients with severe sepsis. The number needed to treat to prevent 1 death at 28 days was 16. Post hoc analysis by the FDA indicated that patients with an APACHE II score  $\geq 25$  were most likely to benefit from therapy and licensed the drug on this basis. In Europe, following similar analysis the EMEA licensed the drug for the treatment of severe sepsis and *multiple* organ failure.
- The incidence of severe bleeding was higher in the active treatment group (3.5% vs 2.0%,  $p=0.06$ ). This difference was only observed during the infusion period.
- The cost of a course of drotrecogin alfa (activated) for a 70 kg patient is £5020 (excluding VAT). This gives a cost of £80,300 to prevent one death at 28 days using PROWESS study data. The cost per life year saved has been calculated to be £15,729 in patients with an APACHE II score of  $\geq 25$ .
- Specialists in the region estimate that between 2-5% of ICU admissions might be treated with drotrecogin alfa (activated).
- Drotrecogin alfa (activated) should only be considered for those patients meeting current licensed criteria. Any patients prescribed this treatment should be subject to a formal audit of severity-adjusted patient outcome.
- Drotrecogin alfa (activated) has recently completed trials in paediatric patients and a license extension to children would be anticipated. Other agents to treat sepsis are currently undergoing trials and an anti-TNF agent, afelimomab is expected to be licensed in 2003.

## BACKGROUND

Severe sepsis is a disorder with a high morbidity and mortality. Despite advances in supportive care, including intense antibiotic therapy and organ-system support techniques, the mortality rate of between 30 - 50% has not altered significantly in recent years.<sup>1,2</sup>

Severe sepsis results from a complex host response to insult after infection and involves the integration of three components, inflammation, coagulation, and impaired fibrinolysis.<sup>2</sup> In severe sepsis, although the underlying infection may be treated, the cascade events may lead to the development of disseminated intravascular coagulation (DIC) and microvascular thrombosis. These, in turn, may lead to acute multi-organ failure and death.

In the past the various treatment approaches attempted have included: blocking microbial products (i.e., endotoxin), blocking inflammatory mediators (i.e., tissue necrosis factor [TNF] and interleukin [IL]-1). However, to date, none of these have significantly altered clinical outcome.<sup>2</sup>

Endogenous protein C is converted to activated protein C to restore homeostasis by modulating the processes of inflammation, thrombosis and fibrinolysis. However protein C is rapidly depleted and patients with severe sepsis typically have low levels on diagnosis. Protein C levels have been inversely correlated with morbidity and mortality.<sup>2</sup> There is also some evidence that conversion of protein C to activated protein C may be impaired in sepsis.<sup>3</sup>

Drotrecogin alfa is a recombinant form of human activated protein C investigated for the treatment of severe sepsis. Like endogenous activated protein C, recombinant drotrecogin alfa (activated) is an important modulator of the coagulation and inflammatory processes seen during severe sepsis.<sup>3</sup>

The purpose of this report is to review the efficacy and place in treatment of drotrecogin alfa (activated) (Xigris<sup>®</sup>, Lilly) which has recently been licensed by the EMEA for the treatment of patients with severe sepsis with multiple organ failure when added to best standard care.

## EFFICACY

In a double-blind, Phase II study, published in abstracts only, 131 patients with severe sepsis were randomised to receive either low dose drotrecogin alfa (activated) (12 or 18 micrograms/kg/hour), high dose drotrecogin alfa (activated) (24 or 30 micrograms/kg/hour) or placebo for either 48 or 96 hours.<sup>4,5</sup> Endpoints included D-dimer reduction (a measure of microvascular coagulopathy), IL-6 reduction (a marker for inflammation), and 28 day mortality. The reduction in D-dimer levels were significantly greater in the high-dose group after 48 hours compared with placebo ( $p < 0.01$ ) and continued for the rest of the infusion period ( $p < 0.01$  at 72 and 96 hours). High-dose drotrecogin alfa (activated) was also associated with a significantly higher reduction in IL-6 levels compared with placebo ( $p = 0.05$ ). There was a trend towards improved mortality in the high dose group, but this was not significant and the trial was not powered to detect this difference (21% 28 day mortality in the high-dose group compared with 35% and 34% in the low-dose and placebo group, respectively, relative risk reduction = 40%,  $p = 0.21$ ).

In a multicentre, double blind study, 1,690 patients with severe sepsis were randomised to receive either drotrecogin alfa (activated) (24 micrograms/kg/hour for 96 hours) or placebo (PROWESS study).<sup>6</sup> Patients had to meet a stringent set of criteria prior to randomisation (Appendix 1) including three or more signs of systemic inflammation and sepsis induced dysfunction of at least one organ or system that lasted no longer than 24 hours. The primary endpoint was death from any cause 28 days after the initiation of the infusion. The study protocol did not standardise the approach each centre took to other aspects of critical care (e.g., use of antibiotics, ventilatory support, or fluids). There was no significant differences in patient demographics at the start of therapy and appropriate antibiotics were started in the majority of patients in both groups within 48 hours of diagnosis of severe sepsis (91.3% and 91.2% for drotrecogin alfa (activated) and placebo, respectively). The trial was halted early after a second interim analysis showed a significant difference in mortality between the drotrecogin alfa (activated) and placebo groups.

At the end of the study period there was an absolute reduction in risk of death of 6.1% (24.7% vs 30.8% of drotrecogin and placebo patients died, respectively,  $p=0.005$ ). Stratifying the patients according to APACHE II score<sup>a</sup>, age, and protein C activity produced similar results ( $p=0.005$ ). The difference in efficacy was seen within days of infusion initiation and continued to increase for the remainder of the 28 day period.

In a recently published abstract, long term survival data was presented from patients who had enrolled in the PROWESS study.<sup>7</sup> In patients with APACHE II scores  $\geq 25$  median survival was significantly increased compared to patients receiving placebo (450 days vs 71 days,  $p=0.0005$ ). There was no significant benefit in median survival in patients with an APACHE II score of  $<25$ . The mortality rate was highest in both arms during the first 90 days but was significantly better in patients receiving drotrecogin alfa (activated) ( $p=0.048$ ). After 3 months the most important risk factors for mortality were age and pre-existing health status.

Two recent reviews of the PROWESS study and the subsequent analyses of the data presented to the Food and Drug Administration (FDA) raise a number of issues in relation to the conduction of the trial.<sup>8,9</sup> After the enrolment of approximately a third of patients into the trial the protocol was amended to exclude those patients who were expected to die of complications other than sepsis during the 28 day study period (e.g., bone marrow transplants). Thus for the remaining period of the trial patients with less severe underlying disease or more acute infectious illness were enrolled. At the same time a new placebo and cell line to produce drotrecogin alfa (activated) was introduced. Extensive studies failed to find any differences between the old and new preparations of drotrecogin alfa (activated). After these changes were made there was an improvement in 28 day mortality (prior to the amendments 30% vs 28% of placebo vs drotrecogin patients died; relative risk of death 0.94,  $p=0.57$ ; after the amendments 31% vs 22% of patients died; RR of death = 0.71,  $p=0.001$ ). Following post hoc analyses of the data the FDA decided to licence drotrecogin alfa (activated) in high risk patients (APACHE II score  $>25$ ) as this was the group of patients where most benefit was seen. In addition when the results of patients at high risk were analysed it was found that these patients benefited from

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<sup>a</sup> APACHE II score - Acute Physiology and Chronic Health Evaluation II score stratifies patients according to severity of disease

treatment both before and after the protocol changes. The FDA concluded that the changes to study protocol probably had no effect on study outcome.

A multicentre, uncontrolled, open label, tolerability and safety study of drotrecogin alfa (activated), ENHANCE, is currently in progress. This trial has similar entry criteria to the PROWESS trial and in addition to 28-day mortality will also assess outcome at 90 days in terms of patient location (e.g., home, hospital etc).<sup>10</sup> The results are expected to be published in Q2/Q3 2003.<sup>11</sup>

## ADVERSE EFFECTS

In the PROWESS study the only adverse event which was higher in the drotrecogin alfa (activated) group was the incidence of severe bleeding (3.5% vs 2.0% for drotrecogin alfa (activated) vs placebo,  $p=0.06$ ). This difference was only observed during the infusion period. Patients with an increased risk of bleeding had been excluded from the trial (Appendix 2). However, serious bleeding mainly occurred in patients with other risk factors such as gastrointestinal ulceration, prolonged prothrombin time, activated partial-thromboplastin time of more than 120 seconds, low platelet count etc.

Warren et al report that open label use of drotrecogin (alfa) caused a higher incidence of intracranial bleeding than that seen in the PROWESS study (13/520 patients, 2.5%, eight of which occurred during the infusion period; only 0.2% of patients in the PROWESS study had this complication).<sup>8</sup> In a letter the PROWESS authors refute this increase in intracranial haemorrhage and report that the current rate is 0.5% (haemorrhages in 13/2786 patients receiving open label drotrecogin alfa (activated)).<sup>12</sup> Nine of the 13 cases occurred in patients with a platelet count  $< 30,000/\text{mm}^3$ .

## DOSAGE, ADMINISTRATION AND COST

The cost of a 96 hour course of drotrecogin alfa (activated) for a 70 kg patient is £5020 (excluding VAT). The number needed to treat to prevent 1 death within 28 days of treatment is 16 at a cost of £80,300.

Using data from the Intensive Care National Audit and Research Centre (ICNARC) between 1996 and 2000, 28% of all intensive care admissions met the entry criteria used in the PROWESS study.<sup>13</sup> Hospital mortality of these patients was found to be 44.7%, higher than the 28 day mortality rate in the placebo group in the PROWESS study (30.8%). Recent communication with ICNARC reveals that if the exclusion criteria used in the PROWESS study are applied then the figure is reduced to 15% (comparative figures using data from Northern & Yorkshire ICUs were 29% and 14%, respectively).<sup>14</sup> These patients numbers are much higher than specialists within the region have estimated (2 – 5%) as they are based on the PROWESS study criteria rather than licensed criteria.<sup>15,16</sup> However other colleagues within the North East and Cumbria Critical Care Network have estimated that of the 7,300 annual admissions to ICUs within the Network, 630 (8.7%) would meet FDA licensed criteria to be treated with drotrecogin alfa (activated) (i.e., an APACHE II score  $\geq 25$ ).<sup>17</sup> Data from a London hospital showed that in an ICU admitting 1200 patients/year 26% had a diagnosis of severe sepsis, 3.6% of whom were entered into the ENHANCE study.<sup>16</sup> This figure is confirmed by the estimates of uptake that both Leeds Teaching Hospitals NHS Trust and Newcastle upon Tyne NHS Trust

have made. Newcastle upon Tyne Hospitals NHS Trust has two intensive care units and treat approximately 1800 patients/year. They estimate that approximately 3% of these admissions might receive drotrecogin alfa (activated). Leeds Teaching Hospitals also have two intensive care units and admit approximately 1500 patients/year. It is estimated that between 3-4% of patients would meet licensed criteria for treatment with drotrecogin alfa (activated) based on experience of enrolling patients into the ENHANCE study.

Manns et al estimated the cost effectiveness of drotrecogin alfa (activated) compared with conventional care in patients with severe sepsis using data from the PROWESS study and the post hoc analyses performed by the FDA.<sup>18</sup> The analyses were made from a Canadian health care perspective with sensitivity analyses that included indirect costs due to premature death. The authors were unable to assess health-related quality of life as no valid utility scores have been defined for survivors of sepsis, however they expected that this would be reduced and this was considered in the sensitivity analysis. They estimated that the cost per life-year gained was \$27,936 (£18,000); this figure was reduced if only patients with an APACHE II score of 25 or more received treatment (\$24,484, £15,729) and increased to \$575,054 (£369,459) for patients with an APACHE II score <24 if the FDA estimates of effectiveness were used. The cost per life-year gained also increased with age.

## PLACE IN TREATMENT

Drotrecogin alfa (activated) should only be considered in those patients with multiple organ failure who have severe sepsis. Post hoc analyses by the FDA suggest that patients who benefit most are those with an APACHE II score  $\geq 25$ .

## ARRANGEMENTS FOR PRESCRIBING

Drotrecogin alfa (activated) should only be used in patients who are under the care of a specialist in intensive care. Due to the concerns around the PROWESS study design and the subsequent licensed indications (both FDA and EMEA) determined by post hoc analysis of the trial data, all patients should be enrolled in a formal audit of severity-adjusted patient outcome.

## FUTURE DEVELOPMENTS

Lilly has recently announced that a study investigating the efficacy of drotrecogin alfa (activated) in patients with severe sepsis at lower risk of death than its current license. The ADDRESS study will recruit 11,000 adult patients and is expected to end in March 2005.<sup>19</sup>

Drotrecogin alfa (activated) is currently unlicensed in children. However a trial has recently been completed in nine paediatric centres in the US involving babies from 38 weeks gestation.<sup>20</sup>

An anti-tumour necrosis factor antibody, afelimonab (Segard<sup>®</sup>, Knoll Ltd) is currently in Phase III trials for the treatment of sepsis/septic shock in patients with high levels of interleukin-6. It is expected to be licensed in the UK in 2003.<sup>21</sup>

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## REFERENCES

- 1 Friedman G, Silva E, Voncent J-L. Has the mortality of septic shock changed with time? *Critical Care Medicine* 1998;26:2078-86
- 2 Lyseng-Williamson KA, Perry CM. Drotrecogin alfa (activated). *Drugs* 2002;62:617-30
- 3 The European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products European Public Assessment Report (EPAR). Xigris. May 2002
- 4 Fisher CJ, Helterbrand JD, Bernard GR. Recombinant human activated Protein C (rhAPC) improves coagulation abnormalities, morbidity and 28 day mortality in patients with severe sepsis. *Journal of Antimicrobial Chemotherapy* 1999; 44 (Suppl A): 10 Abstract 11-51
- 5 Hartman DL, Bernard GR, Helterbrand JD et al. Recombinant human activated protein C (RHAPC) improves coagulation abnormalities associated with severe sepsis. *Intensive Care Medicine* 1998;24 (Suppl 1):S77. Abstract 229
- 6 Bernard GR, Vincent J-L, Laterre P-F et al. Efficacy and safety of recombinant human activated Protein C for severe sepsis. *New England Journal of Medicine* 2001;344:699-709
- 7 Angus DC, Laterre P-F, Helterbrand J et al. The effects of drotrecogin alfa (activated) on long-term survival after severe sepsis. *Chest* 2002;144:51S
- 8 Warren HS, Suffredini AF, Eichacker PQ et al. Risks and benefits of activated protein C treatment for severe sepsis. *New England Journal of Medicine* 2002;347:1027-30
- 9 Siegel JP. Assessing the use of activated protein C in the treatment of severe sepsis. *New England Journal of Medicine* 2002;347:1030-4
- 10 London New Drugs Group. Drotrecogin alfa (activated). Guidance document. May 2002
- 11 Personal communication Eli Lilly
- 12 Ely EW, Bernard GR, Vincent J-L. Activated protein C for severe sepsis. *New England Journal of Medicine* 2002/347:1035-6
- 13 Padkin A, Rowan K, Black N. Using high quality clinical databases to complement the results of randomised controlled trials: the case of recombinant human activated protein C. *BMJ* 2001;323:923-6
- 14 Personal communication Dr K Rowan, Intensive Care National Audit and Research Centre
- 15 Personal communication Dr AT Cohen, Leeds Teaching Hospitals NHS Trust
- 16 Personal communication Dr A Kilner, Freeman Hospital, Newcastle upon Tyne
- 17 Personal communication Dr SV Baudouin, University of Newcastle upon Tyne
- 18 Manns BJ, Lee H, Doig CJ et al. An economic evaluation of activated protein C treatment for severe sepsis. *New England Journal of Medicine* 2002;347:993-1000
- 19 Anon. *Scrip* 2002;2783:27
- 20 Personal communication Leeds Teaching Hospitals NHS Trust Medicines Information Centre
- 21 Regional Drug and Therapeutics Centre. New drug treatments and their implications for the NHS. 7<sup>th</sup> edition. July 2002

## APPENDIX 1. SUMMARY OF INCLUSION CRITERIA FOR THE PROWESS STUDY<sup>6</sup>

Infection criteria	Modified Systemic Inflammatory Response Syndrome (SIRS) criteria	Criteria for dysfunctional organs or systems
<p>Patients had to have a known infection, as evidenced by <math>\geq 1</math> of the following:</p> <ul style="list-style-type: none"> <li>• white cells in normally sterile body fluid</li> <li>• perforated viscus</li> <li>• X-ray evidence of pneumonia + purulent sputum</li> <li>• A syndrome associated with high risk of infection (e.g., ascending cholangitis)</li> </ul>	<p>Patients had to meet <math>\geq 3</math> of the following:</p> <ul style="list-style-type: none"> <li>• Core temperature <math>\geq 38^{\circ}\text{C}</math> or <math>\leq 36^{\circ}\text{C}</math></li> <li>• Heart rate <math>\geq 90</math> beats/min or receiving treatment that would prevent tachycardia</li> <li>• Respiratory rate <math>\geq 20</math> breaths/min or a <math>\text{PaCO}_2 \leq 32</math> mmHg or on mechanical ventilation for an acute respiratory process</li> <li>• White cell count <math>\geq 12,000/\text{mm}^3</math> or <math>\leq 4,000/\text{mm}^3</math> or a differential count showing <math>&gt; 10\%</math> immature neutrophils</li> </ul>	<p>The first sepsis-induced organ or system failure had to develop within 24 hours before enrolment.</p> <p>Patients had to meet <math>\geq 1</math> of the following:</p> <p><b>For CVS dysfunction:</b></p> <ul style="list-style-type: none"> <li>• Arterial SBP <math>\leq 90</math> mmHg or mean arterial pressure <math>\leq 70</math> mmHg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in an attempt to maintain a SBP of <math>\geq 90</math> mmHg or a mean arterial pressure <math>\geq 70</math> mmHg</li> </ul> <p><b>For kidney dysfunction:</b></p> <ul style="list-style-type: none"> <li>• Urine output <math>&lt; 0.5</math> ml/kg/h for 1 hour, despite adequate fluid resuscitation</li> </ul> <p><b>For respiratory system dysfunction:</b></p> <ul style="list-style-type: none"> <li>• Ration of <math>\text{PaO}_2</math> to <math>\text{FiO}_2 \leq 250</math> in the presence of other dysfunctional organs or systems or <math>\leq 200</math> if the lung was the only dysfunctional organ</li> </ul> <p><b>For haematologic dysfunction:</b></p> <ul style="list-style-type: none"> <li>• Platelet count <math>&lt; 80,000/\text{mm}^3</math> or decreased by 50% in 3 days before enrolment</li> </ul> <p><b>For unexplained metabolic acidosis:</b></p> <ul style="list-style-type: none"> <li>• <math>\text{PH} \leq 7.3</math> or the base deficit had to be <math>\geq 5.0</math> mmol/l + plasma lactate level that was <math>&gt; 1.5</math> times upper limit of normal value</li> </ul>

## APPENDIX 2. SUMMARY OF EXCLUSION CRITERIA FOR THE PROWESS STUDY<sup>6</sup>

Pregnancy or breastfeeding

Age <18 years or weight > 135 kg

Conditions increasing the risk of bleeding:

- Surgery requiring general or spinal anaesthesia within 12 hours of infusion
- Potential need for surgery during infusion
- Evidence of cranial surgery, or stroke within 3 months of study, or history of intracerebral arteriovenous malformation
- Cerebral aneurysm, or mass lesions of the CNS
- History of bleeding diatheses
- Gastrointestinal bleeding within 6 weeks prior to study unless corrective surgery had been performed
- Trauma considered to increase risk of bleeding

Known hypercoagulable condition:

- Resistance to protein C
- Hereditary deficiency of protein C, protein S, or antithrombin III
- Presence of anticardiolipin antibody
- Antiphospholipid antibody
- Lupus anticoagulant, or homocysteinaemia
- Recently documented (within 3 months) or highly suspected DVT or PE

Aggressive treatment not indicated:

- Patients family, doctor, or both not in favour or an advance directive to withhold life-sustaining treatment
- Not expected to survive 28 days due to uncorrectable medical condition
- Death perceived imminent

HIV infection + last known CD4 count  $\leq 50/\text{mm}^3$

History of bone marrow, lung, liver, pancreas, or small bowel transplantation

Chronic renal failure requiring dialysis (acute renal failure not an exclusion)

Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis, or chronic ascites

Acute pancreatitis with no established source of infection

Participation in another investigational study within 30 days of current study

Use of the following drugs or treatment regimes:

- Unfractionated heparin to treat an active thrombotic event within 8 hours before infusion
- Low molecular weight heparin at a higher dose than recommended for prophylactic use within 12 hours of infusion
- Warfarin if used within 7 days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution
- Aspirin, > 650 mg/day within 3 days of infusion
- Thrombolytic therapy within 3 days before study (except for use for the treatment of thromboses within a catheter)
- Glycoprotein IIa/IIIb antagonists within 7 days before study
- Antithrombin III at a dose more than 10,000 U within 12 hours before the study
- Protein C within 24 hours before the study