



Drotrecogin alfa (recombinant human activated protein C) in severe sepsis – a New Zealand viewpoint

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Abstract

Aim Sepsis is a serious and increasing worldwide intensive care problem. In response to intensivists' concerns over the benefits, risks and financial implications of the use of drotrecogin alfa (recombinant human activated protein C), the first adjunctive therapy for sepsis licensed in New Zealand, the New Zealand Region of the Australian and New Zealand Intensive Care Society (ANZICS) requested an advisory statement from a working party of New Zealand intensivists.

Methods We reviewed (a) the PROWESS study of drotrecogin alfa recombinant; (b) the submission made by the sponsoring company to the FDA; (c) recent discussions and an economic evaluation of the use of the agent; (d) Australian pharmaceutical benefits scheme positive recommendations; (e) guidelines produced by the Eli Lilly Australian Advisory Board; (f) Australian hospital decisions on availability; and (g) New Zealand pricing and payment arrangements. We then formulated suggested New Zealand guidelines.

Results We recommend that hospital pharmacy and therapeutics committees review the agent now. If the agent is made available for use, we recommend that: (a) specialists prescribing the agent be required to contribute clinical data to a national register of patients, (b) patients considered for treatment should first be treated with all appropriate surgical and medical therapy for severe sepsis with high illness severity in an intensive care unit by an intensivist; (c) patients considered for treatment should not have severe comorbidity or predetermined treatment limitations or contraindications to the agent in the original phase III study; and (d) patients should be considered only if seen to be not clearly improving after a six-hour period of intensive treatment. Once a decision has been made to treat with drotrecogin alfa, treatment should commence as soon as possible and within 24 hours of meeting criteria. Although the agent is recommended for use in adults, it may be reasonable to treat some older children.

Conclusions Despite high cost and moderate benefit, it may be reasonable to treat highly selected New Zealand patients with drotrecogin alfa.

Sepsis is a serious intensive care problem worldwide.¹ The incidence of sepsis in intensive care units is reported to be increasing² and New Zealand experience is in keeping with this.³ Most recent intensive care unit (ICU) sepsis studies report mortality of around 25–50% but many factors, including the extent of comorbidity, the nature and site of infection, adequacy of surgical and antimicrobial therapy, and the severity of the acute illness, influence the outcome.¹ Sepsis was the reason for ICU admission in 349 of all 1404 ICU deaths (25%) in New Zealand ICUs in one year.⁴

The accepted general principles of the treatment of severe sepsis are to support oxygen transport,⁵ to identify and if possible remove the septic source,^{6,7} and to provide appropriate antimicrobial therapy.^{3,8-11} A firm consensus on the place of adjunctive therapies is not yet established despite considerable research and recent promising reports, including the PROWESS study of drotrecogin alfa (recombinant human activated protein C).¹² This agent (Xigris™, Eli Lilly) is the first adjunctive therapy for sepsis to be licensed in many countries including the US, UK, Europe, Australia and, most recently, New Zealand. The agent is expensive and intensivists have expressed concerns about the benefits, risks, and financial implications of its use. These concerns led the New Zealand Region of the Australian and New Zealand Intensive Care Society to request an advisory statement on the agent from a working party of New Zealand intensivists – the authors of this paper.

Methods

We reviewed the original (PROWESS) study of drotrecogin alfa recombinant in sepsis,¹² the submission made by the sponsoring company to the (US) FDA,¹³ more recent discussions in the *New England Journal of Medicine*,¹⁴⁻¹⁶ a Canadian economic evaluation of the use of the agent,¹⁷ Australian pharmaceutical benefits scheme positive recommendations,¹⁸ guidelines for the use of drotrecogin alfa in sepsis produced by the Eli Lilly Australian Advisory Board (personal communication, M Fisher, 2002), positive (personal communications, M O'Leary, J Reeves, Y Shehabi, G Dobb, G Skowronski, R Herkes, J Lipman, D Stephens, JW Mulder, D Cook, 2002), negative (personal communications, M Fisher, JF Cade, P Harrigan, J Santamaria, 200) and still pending (personal communications, B Richards, M Parr, D Milliss, 2002) Australian hospital-pharmacy-committee decisions on availability and New Zealand pricing and payment arrangements. We then formulated consensus guidelines for the use of this agent in New Zealand.

Results

Review of relevant information The PROWESS study (a multicentre controlled trial in 1690 randomised adult patients with severe sepsis, published in March 2001) showed a 6.1% absolute reduction (30.8% to 24.7%, $p = 0.005$) in all-cause 28-day mortality from a 96-hour infusion of drotrecogin alfa at 24 ug/kg body weight/hour, despite a possibly increased risk of serious bleeding (3.5% versus 2.0%, $p = 0.06$) in the drotrecogin alfa group.¹² The company that sponsored the study (Eli Lilly) sought product registration in the United States in September 2001 and provided the FDA with extensive documentation¹³ but only one phase III randomised controlled trial. Despite approving the agent for use for 'insert indication', the FDA Anti-infective Drug Advisory Committee was split 10 to 10 as to whether the agent is safe and efficacious.¹⁶ The 'key matters of concern' for the FDA were changes made during the trial, the use of APACHE II scores,¹⁹ and the risk of serious bleeding. The decision to approve the agent despite these concerns has recently been discussed and defended by a senior FDA member.¹⁵ Concern over inconsistency of the efficacy of the agent throughout the trial (with possible implications that the mid-trial protocol amendment or changes in the formulation of the agent were responsible) has led to a recently expressed view¹⁶ that the data at present do not provide sufficient evidence for the use of the agent to become 'the standard of care'. In subsequent correspondence¹⁴ the PROWESS authors discuss these concerns (but do not refute them directly) and suggest that 'clinicians can already incorporate level I evidence from PROWESS into their practice to obtain life-saving benefit for their patients'. A recent Canadian economic analysis suggested that the cost per life-year gained by treatment with the agent was US\$27 936 if all eligible ICU patients are treated, and

US\$24 484 if only patients with APACHE II scores of 25 or more are treated.¹⁷ Furthermore, if patients with such high APACHE II scores are treated, the cost per life-year gained was related to the age of the patient (US\$16 309 aged over 40, US\$28 100 aged 80 or more). The Australian PBAC recommendations¹⁸ were that the agent be 'Recommended for listing for 'Adult patients with severe sepsis who have a high risk of death as determined by acute organ dysfunction in at least two organs or modified APACHE II score of at least 25' on the basis of acceptable cost-effectiveness', and be 'restricted to patients with two or more failed organs to prevent use in less severely ill patients where the risks may outweigh the benefits'. The Eli Lilly Australian Clinical Advisory Board recommendations were in keeping with the PBAC recommendations but included a recommendation that assessment of progress be made after four hours' full resuscitation in an intensive care unit, including surgical therapy and antibiotics and that 'if objective improvement in organ function occurs' that administration 'be delayed'. This Board also recommended that, for the purposes of defining respiratory 'organ dysfunction', this should be due to 'lung injury/ARDS secondary to sepsis' and that any patient given the agent would be expected to be receiving ventilatory support. Several tertiary Australian hospitals have not approved the use of the agent because of the 'extreme financial implications'. The New Zealand price of the agent (to a hospital pharmacy) is currently \$1909 plus GST per 20 mg vial (personal communication, Eli Lilly, 2002), which would result in a cost of \$17 181 (including GST) for the treatment (total 160 mg) of a 70 kg patient. Hospitals wishing to use the agent will have to find this cost from within existing budgets.

Suggested guidelines for the use of drotrecogin alfa in New Zealand If the agent is made available for use, we recommend that specialists prescribing it be required to contribute clinical data to a national register of patients, and we recommend the following guidelines for its use:

1. Patients should be in an intensive care unit and being treated by an intensivist (or other specialist with experience in intensive care medicine capable of providing comprehensive support of patients with severe sepsis at a high risk of death).
2. Patients should have severe sepsis, as defined in the PROWESS study,¹² and not have the exclusion criteria indicated in the study (eg, trauma patients with increased risk of life-threatening bleeding, pregnant patients, those with recent haemorrhagic stroke or with an epidural catheter in situ).
3. Patients in whom PROWESS exclusion criteria¹² are not present but who are otherwise at increased risk of serious bleeding should be carefully considered as to the balance of risk and possible benefit.
4. Patients should have two or more organ failures as defined in the PROWESS study.¹²
5. Patients with severe comorbidity likely to strongly adversely affect their outcome from severe sepsis (eg, severe congestive heart failure), those suffering from terminal disease or those in whom a decision has already been made to limit other intensive therapies (eg, dialysis) should not receive the agent.

6. Prior to administration of the agent, a trial of all other appropriate therapy (including surgery or other drainage of infection, appropriate antibiotics, fluid therapy, ventilatory and inotropic support) should have been given.
7. Patients seen to be clearly improving after a period (perhaps six hours) of such intensive treatments are at reduced risk of death and should not receive the agent.
8. Patients with high illness severity (eg, APACHE II score of 25 or more)¹⁹ not clearly improving at this time should be considered for treatment.
9. Although the PROWESS study¹² enrolled patients aged 18 years and over, it may be reasonable to treat 'older' children.
10. Once a decision has been made to treat with drotrecogin alfa, treatment should commence as soon as possible, and within 24 hours of meeting treatment criteria, bearing in mind the need for secure haemostasis to be ensured if surgery has just been performed. (A period of 12 hours of post-operative haemostasis was required before commencing treatment with the agent in the PROWESS study.¹²)

Discussion

It is likely that there is an overall beneficial therapeutic effect (net reduction in 28-day mortality) from the use of drotrecogin alfa recombinant in selected intensive care patients with severe sepsis but this is debated.¹⁶ The size of this effect (and thereby the number of patients needed to treat) is debatable in the New Zealand clinical context. The PROWESS data suggested an NNT of 16.4 (95% confidence limits 9.6–52.6)¹² to result in one additional 28-day survivor. The increased risk of bleeding in the study was small in patients selected not to have high risk of bleeding.

Of particular concern in the New Zealand (and Australian) context is the problem of young patients with severe meningococcal disease, many of whom have at least moderate coagulopathy and would thereby have been excluded from the PROWESS study.¹² Although these patients may benefit from the agent, they are almost certainly at higher than usual risk of bleeding and a cautious approach to treatment is advised. To date, there have been only five reported cases (age 18–41, median 22) where drotrecogin alfa was used in meningococcal purpura fulminans.^{20,21} Profound thrombocytopenia before treatment with drotrecogin alfa was present in two patients and these were given platelet transfusions 'to maintain platelet count above 30×10^9 per litre'. No adverse bleeding events were reported. Children under 18 were excluded from the PROWESS study and there are no published randomised controlled trials in children with severe sepsis, although one is underway.²² The median time till death in a small series of children dying of meningococcal disease in Auckland was four hours and thrombocytopenic cerebral haemorrhage was a significant cause of late deaths (personal communication, J Beca, 2003). In view of the strong association of profound thrombocytopenia with mortality in young children with meningococcal disease,²³ we recommend a cautious approach to the use of drotrecogin alfa in such patients.

The issue of very high cost, moderately effective treatment is not just one for intensive care. The price of drotrecogin alfa is large and the resultant cost per life-year gained is of similar order to that of a small number of other treatments (eg, imatinib

(Glivec®) for liver transplantation, iloprost for pulmonary hypertension) that in New Zealand are subject to rationing. Drotrecogin alfa was given provisional consent in New Zealand on 19 September 2002.²⁴

Although New Zealand ICU practice^{25,26} probably differs from Canadian practice^{17,27} in casemix and approach, the relative cost-benefit implications of age and illness severity will remain relevant. Possible suggested strategies that might increase the cost effectiveness of this agent include restricting it to patients who are not 'clearly improving' after six hours of 'full intensive care therapies' in an ICU and restricting its use to younger patients with high severity of illness¹⁷ (eg, APACHE II over 25) who do not have limiting non-septic comorbidity. We support these strategies in our recommendations for use.

The responsibility for providing access to this agent is that of individual hospitals and this decision is expected to fall on hospital pharmacy committees. We recommend that individual area health-board pharmacy and therapeutics committees review the agent now and decide whether or not they will support its purchase and use.

Finally, we note that timing and appropriateness of surgical⁶ and antibiotic⁸⁻¹¹ therapy and resuscitation of oxygen delivery⁵ are powerful determinants of outcome in severe sepsis and suggest that all hospitals would be well advised to formally establish systems that ensure these factors of treatment are provided.

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References:

1. Angus DC, Wax RS. Epidemiology of sepsis: an update. *Crit Care Med* 2001;29(7 Suppl):S109-16.
2. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
3. Thomas MG, Streat SJ. Infections in intensive care patients. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ, editors. *Antibiotic and chemotherapy*. London: Harcourt; 2002.
4. Streat S, Judson J, Newby L, et al. Prospective audit of death, brain death and organ donation in New Zealand intensive care units. Submitted for publication.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
6. Clark MA, Plank LD, Connolly AB, et al. Effect of a chimeric antibody to tumor necrosis factor-alpha on cytokine and physiologic responses in patients with severe sepsis - a randomised, clinical trial. *Crit Care Med* 1998;26:1650-9.
7. Streat SJ, Plank LD, Hill GL. Overview of modern management of patients with critical injury and severe sepsis. *World J Surg* 2000;24:655-63.

8. Jensen AG, Wachmann CH, Espersen F, et al. Treatment and outcome of *Staphylococcus aureus* bacteremia: a prospective study of 278 cases. *Arch Intern Med* 2002;162:25–32.
9. Booy R, Habibi P, Nadel S, et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001;85:386–90.
10. Dupont H, Mentec H, Sollet JP, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med* 2001;27:355–62.
11. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000;118:146–55.
12. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
13. Eli Lilly. FDA briefing document: Anti-infective Advisory Committee. Drotrecogin alfa (activated), [recombinant human activated protein C (RhAPC)], Xigris™, BLA#125029/0. 12th September 2001. Available online: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3797b1_02_FDA briefing.pdf Accessed September 2003.
14. Ely EW, Bernard GR, Vincent JL. Activated protein C for severe sepsis. *N Engl J Med* 2002;347:1035–6.
15. Siegel JP. Assessing the use of activated protein C in the treatment of severe sepsis. *N Engl J Med* 2002;347:1030–4.
16. Warren HS, Suffredini AF, Eichacker PQ, Munford RS. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;347:1027–30.
17. Manns BJ, Lee H, Doig CJ, et al. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002;347:993–1000.
18. Australian Pharmaceutical Benefits Scheme. Positive recommendations of the Pharmaceutical Benefits Advisory Committee. June 2002. Drotrecogin Alfa (activated). Available online: <http://www.health.gov.au/pbs/general/listing/pbacrec/pbacrecjun.htm> Accessed September 2003.
19. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
20. Bachli EB, Vavricka SR, Walter RB, et al. Drotrecogin alfa (activated) for the treatment of meningococcal purpura fulminans. *Intensive Care Med* 2003;29:337.
21. Weisel G, Joyce D, Gudmundsdottir A, Shasby DM. Human recombinant activated protein C in meningococcal sepsis. *Chest* 2002;121:292–5.
22. Nimah M, Brill R. Coagulation dysfunction in sepsis and multiple organ system failure. *Crit Care Clin* 2003;19:441–58.
23. Peters MJ, Ross-Russell RI, White D, Kerr SJ, Eaton FE, Keengwe IN, Tasker RC, Wade AM, Kline NJ. Early severe neutropenia and thrombocytopenia identifies the highest risk cases of severe meningococcal disease. *Pediatr Crit Care Med* 2001;2:225–31.
24. NZ Gazette. New medicine – provisional consent. Drotrecogin alfa, activated (Xigris™). 19 September 2002, Available online: <http://www.medsafe.govt.nz/reg.htm> Accessed September 2003.
25. Streat S, Judson JA. Cost containment: the Pacific. *New Zealand. New Horiz* 1994;2:392–403.
26. Zimmerman JE, Knaus WA, Judson JA, et al. Patient selection for intensive care: a comparison of New Zealand and United States hospitals. *Crit Care Med* 1988;16:318–26.
27. Barnett R, Shustack A. Cost containment: the Americas. *Canada. New Horiz* 1994;2:332–5.

Comment:

Drotrecogin alpha (activated): a magic bullet or budget blowout?

For the first time since antibiotics were introduced for the treatment of infection, an adjunctive therapy has been shown to improve survival. In the presence of sepsis, drotrecogin alpha (recombinant human activated protein C) modulates the systemic inflammatory, procoagulant, and fibrinolytic host responses to infection.¹ The PROWESS multicentre study in which drotrecogin alpha (activated) was randomised to 1690 patients showed an absolute all-cause 28-day mortality reduction of 6.1% overall.¹ However, the benefits were most marked in more severe sepsis (Acute Physiology and Chronic Health Evaluation (APACHE) II score >25).²

This treatment is not cheap. The cost of a 96-hour treatment is NZ\$17 181.³ If one uses the PROWESS entry data, for each life saved 16 patients need to be treated. Drotrecogin alpha (activated) costs US\$160 000 (NZ\$278 000) per life saved, but as little as US\$27 400 (NZ\$48 000) per quality-adjusted life-year when limited to patients with an APACHE II score =25.²

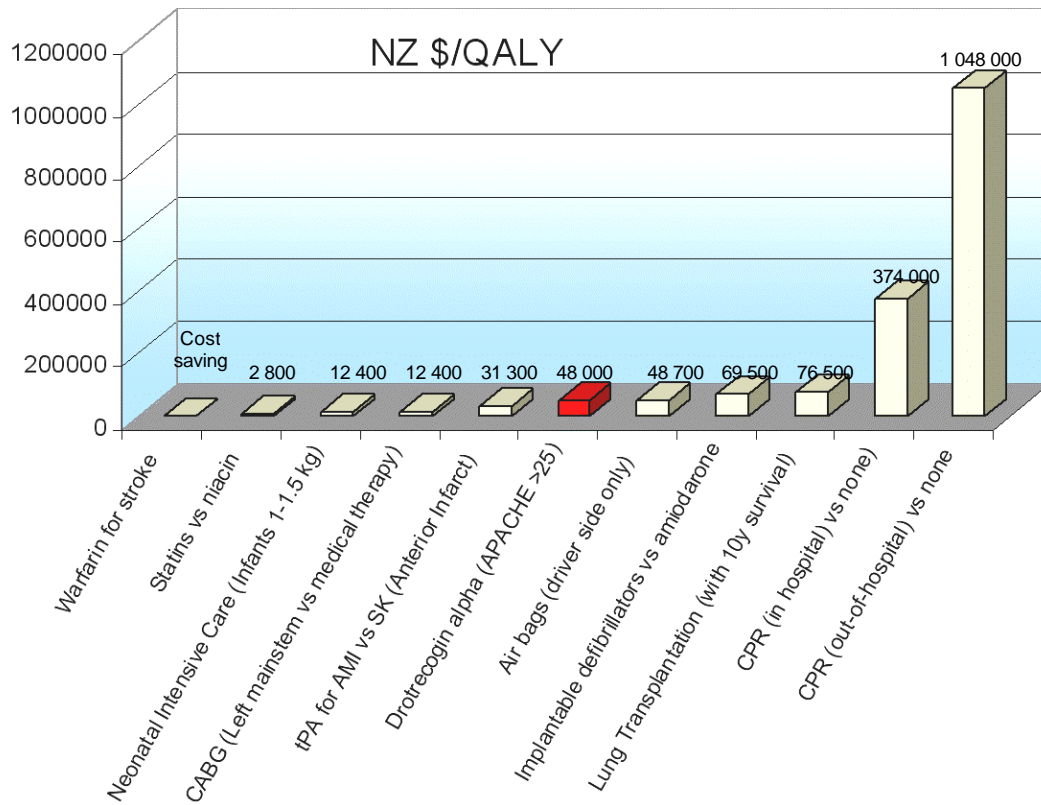
How does this stack up against other high-cost therapies? The cost effectiveness of drotrecogin alpha (activated) is comparable to most of the interventions in Figure 1 and better than that of airbags, implantable defibrillators, lung transplantation, and cardiopulmonary resuscitation.

In selected patients this therapy is clearly cost effective and beneficial. The problem is that New Zealand's public hospital system is fragmented into 21 district health boards and (unlike our Australian, UK, and US counterparts) concentrates on cost cutting as opposed to efficiency gains. In an environment where the funding for drotrecogin alpha (activated) is dependent on hospital pharmaceutical budgets it seems doubtful that all New Zealanders who may benefit from this treatment will get it. Inequity of access is at odds with Right 4 (3, 4) of the Health and Disability Code of Rights:⁴

- Every consumer has the right to have services provided in a manner consistent with his or her needs.
- Every consumer has the right to have services provided in a manner that minimises the potential harm to, and optimises the quality of life of, that consumer.

In the US, drotrecogin alpha (activated) has been granted new-technology status from the Centers for Medicare and Medicaid Services (CMS). This allows hospitals to receive additional reimbursement for treatment of Medicare patients.⁵ Similarly, New Zealand should fund drotrecogin alpha (activated) nationally, with the conditions of that funding based upon agreed guidelines, and at the same time develop a central database. This would improve equity of access and allow audit of the impact of the use of drotrecogin alpha (activated) on both patients and budgets.

Figure 1. Comparison of drotrecogin alpha with other widely used interventions, NZ\$ per quality-adjusted life-years (adapted from Figure 6, reference 2)



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References:

1. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
2. Angus DC, Linde-Zwirble WT, Clermont G, et al; PROWESS Investigators. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med* 2003;31:1–11.
3. Liang J, Streat S, Torrance J, et al. Drotrecogin alfa (recombinant human activated protein C) in severe sepsis – a New Zealand viewpoint. *NZ Med J* 2003;116(1181). URL: <http://www.nzma.org.nz/journal/116-1181/586/>
4. The Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulation 1996. Available online. URL: http://www.hdc.org.nz/aboutus/the_code/TheCode.html Accessed September 2003.
5. Maggon K. Risk benefit assessment of APC. *Healthcare Management* 2003, 1–15 April. Available online. URL: <http://www.expresshealthcaregmt.com/20030415/edit2.shtml> Accessed September 2003.