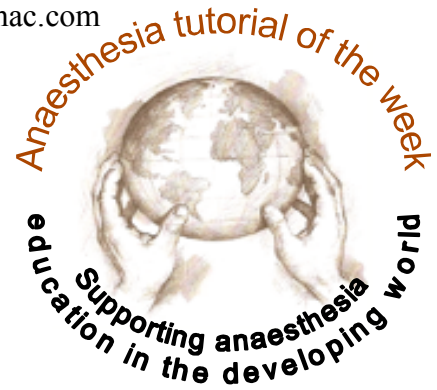


RECOMBINANT HUMAN ACTIVATED PROTEIN C IN THE TREATMENT OF SEVERE SEPSIS

ANAESTHESIA TUTORIAL OF THE WEEK 133

11TH MAY 2009

Dr Richard Eve, Royal Cornwall Hospital, Cornwall, UK
Correspondence to richardlloydeve@gmail.com
Dr Mike Duffy, Derriford Hospital, Plymouth, UK



QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation.

1. Severe Sepsis
 - a. Is associated with disordered response of innate immunity.
 - b. Has a mortality of between 20-30%.
 - c. Is linked to reduced levels of IL-1, 6 and 8.
 - d. Requires organisms or endotoxin to bind to CD8 receptors on macrophages.
2. Protein C
 - a. Is activated by endothelial exposure.
 - b. Is produced in the bone marrow and thymus.
 - c. Is an endogenous procoagulant.
 - d. Causes decreased leukocyte adhesion and tissue infiltration.
3. Recombinant Human Activated Protein C
 - a. Has shown a 28 day mortality benefit in a large randomized controlled trial.
 - b. Causes a significant increase in the rates of intracerebral haemorrhage in children.
 - c. Confers a mortality benefit in children with severe sepsis.
 - d. Is given at a dose of 24mg/kg for 96 hours.

INTRODUCTION

This tutorial focuses on the role of recombinant human activated protein C (rhAPC) in the treatment of severe sepsis. By the end of the tutorial the reader should be able to:

- Define severe sepsis and understand it's pathogenesis.
- Understand the mechanism of action of rhAPC.
- Critically appraise the PROWESS study.
- Discuss the main results of other large studies into rhAPC
- Make an informed choice as to whether they would use rhAPC.

SEVERE SEPSIS

Severe sepsis is a life threatening illness with a mortality of 30-50%. It is defined as a systemic inflammatory response secondary to infection resulting in organ failure. There are 750,000 cases in the US each year of whom at least 225,000 will not survive. The incidence of severe sepsis is increasing as our population ages. The host response determines the severity of the disease rather than the infecting organism and severe cases are characterized by over-zealous activation of the host's innate immune system (everything except the T and B cells) resulting in activation of the coagulation cascade, inflammation, systemic vasodilatation increased capillary permeability, end organ dysfunction and ultimately multi-organ failure and death. The initial stage following infection requires CD14 receptors on macrophages to present elements of the infecting organism to Toll-like receptors (TLR4) resulting in macrophage activation and abundant release of pro-inflammatory mediators such as tumour necrosis factor (TNF), interleukin (IL) 1,6 and 8 together with uncontrolled activation of the coagulation cascade.

Current treatment of severe sepsis involves early appropriate antibiotic therapy, surgical drainage of infected collections and supportive therapy. In spite of this mortality remains high, therefore the search continues for novel therapies to treat this aggressive disorder.

A ROLE FOR PROTEIN C?

How Does Protein C Work?

Protein C is synthesised in the liver and activated following endothelial exposure, it modulates coagulation and inflammatory response. It is an anticoagulant by virtue of its inactivation of factor Va and VIIIa. In addition it inhibits synthesis of plasminogen activator inhibitor, inhibits thrombin activatable fibrinolysis inhibitor and blocks further thrombin generation. It dampens the inflammatory response through a number of mechanisms including reduced production of tumour necrosis factor α (TNF α) by monocytes and reduced leukocyte adhesion and tissue infiltration. Activated protein C (APC) also confers endothelial protection. Levels of APC are reduced in sepsis and this reduction has been linked with poor outcome. If APC were replaced, could severe sepsis be controlled?

Recombinant Human Activated Protein C

Promising results from animal models prompted the pharmaceutical company Eli Lilly to develop a recombinant form of human activated protein C (rhAPC) called Drotrecogin Alfa [activated] (DAA) marketed worldwide as Xigris[®]. This drug has been the subject of 4 large randomized controlled trials (RCT) in severe sepsis and continues to generate much interest and debate.

What is the Dose?

A phase II dose finding study (n=131) demonstrated that an infusion of 24 μ g/kg for 96 hours resulted in maximally reduced D dimer and IL-6 levels without significant bleeding risk.

The PROWESS and ENHANCE Studies

The initial phase III study (PROWESS n = 1690) was a multicentre RCT investigating the role of rhAPC in adult patients with severe sepsis. Patients were randomised to an infusion of rhAPC over 96 hours or placebo. This demonstrated a 19.4% relative reduction and a 6.1% absolute reduction in 28 day mortality with rhAPC (number needed to treat = 16). To obtain additional efficacy and safety data a single-arm open-label study known as ENHANCE (n= 2378) was performed. Entry criteria were similar to PROWESS and the trial showed a similar mortality rate at 28 days (25.3% vs 24.7%) thereby providing supportive evidence for the use of rhAPC.

Following the results of PROWESS and the support provided by ENHANCE the National Institute for Clinical Excellence (NICE) in the UK and the recent Surviving Sepsis Campaign guidelines suggest that adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have an APACHE II \geq 25 or multiple organ failure should receive rhAPC.

ADDRESS and XPRESS

However, the mortality benefit reported in PROWESS has not been replicated in all patient groups. The ADDRESS trial (n = 2613) was a RCT investigating the role of rhAPC in patients with severe sepsis and a low risk of death (APACHE II score <25 or single organ failure). This failed to show a mortality benefit but serious bleeding occurred in more patients in the rhAPC group than with placebo during both the infusion (2.4% vs 1.2%) and the 28-day study period (3.9% vs 2.2%). In addition, surveys of clinical use of rhAPC have demonstrated higher rates of serious bleeding and mortality than those published in trial data.

XPRESS (n=1994) was a third RCT exploring whether concomitant heparin prophylaxis increased serious bleeding risk (suggested by subgroup analyses from PROWESS). Concomitant heparin prophylaxis was not shown to increase 28 day mortality.

RESOLVE– A Paediatric Trial

This study (n=477) used a composite time to complete organ failure resolution score as its primary end point. There was no significant difference between the 2 groups but there were numerically more episodes of intracranial haemorrhage in the rhAPC group but this was not significant.

APPRAISAL OF PROWESS

Over the last few years there have been questions raised about the efficacy of rhAPC, partly because of various aspects of the conduct of the PROWESS trial. Following the first interim analysis (which did not demonstrate a difference between groups) there were a number of important changes to the trial. An amendment was accepted enabling trial coordinators to exclude patients not expected to benefit from rhAPC. Also, following this amendment the master cell bank for drug production was changed. By the second interim analysis at 1690 patients a significant difference existed. Blinding also proved problematic as rhAPC foamed when shaken whilst the placebo (0.9% saline) did not. The placebo was changed to 0.1% albumin but this solution was not permitted in all centres. At this stage there was a change in ‘do not resuscitate’ (DNR) rates; these fell from 16% to 9% in the rhAPC group but with placebo remained at 18%. Additionally, 20 trial sites were removed and 45 sites added; dropped sites tended towards poor drug effect whereas added sites were more supportive of useful drug effect. Although in PROWESS there was a significant difference in 28-day mortality almost all of the survivors remained in hospital. When 90-day survival rates from this study were published there was no significant difference in survival between the groups.

Supporters of the PROWESS study argue that the second cell bank had equivalent *in vitro* activity as the first batch and therefore is unlikely to have influenced the results. Unblinding because of problems with albumin was only required in 1 out of 11 countries and again it is argued this is unlikely to have influenced the result. The amendment change reminded investigators to exclude patients with advanced cancer or liver failure. Patients with significant underlying baseline disease fared proportionately better than other groups and so their exclusion is unlikely to have made the treatment effect more pronounced.

CONCLUSION

A recent Cochrane Review has concluded that there is insufficient evidence to support the use of rhAPC and that there is an increased risk of bleeding. Three more RCT's are ongoing, PROWESS Shock, APROCCHS (adding steroid therapy to rhAPC) and RESPOND (using APC as a biomarker). Severe sepsis is a complex condition and heterogeneous but given the current trials it is difficult to justify using rhAPC until more evidence is available that it confers a genuine, long lasting mortality benefit.

- Severe sepsis carries a high mortality; antibiotics and supportive therapy are the mainstay of treatment.
- rhAPC has demonstrated a mortality benefit in one large RCT but the validity of this study has been questioned.
- rhAPC significantly increased the risk of serious bleeding events in 2 large RCT's.
- rhAPC should not be used in children.
- More precisely defined roles are required if rhAPC is to become a widely accepted treatment for severe sepsis.

ANSWERS TO QUESTIONS

1. Severe Sepsis
 - a. TRUE
 - b. FALSE The mortality is between 30-50%
 - c. FALSE Levels of IL1, 6 and 8 are increased
 - d. FALSE Organisms or endotoxin are bound to CD14 receptors on macrophages
2. Protein C
 - a. TRUE
 - b. FALSE Its produced in the liver
 - c. FALSE It is an anticoagulant
 - d. TRUE
3. Recombinant Human Activated Protein C
 - a. TRUE
 - b. FALSE It causes a non-significant increase in the rates of intracerebral haemorrhage in children
 - c. FALSE It does not confer a mortality benefit in children with severe sepsis
 - d. FALSE The correct dose is 24µg/kg for 96 hours.

WEBLINKS

<http://ccforum.com/content/11/S5/S4>

REFERENCES and FURTHER READING

1. Bernard, G.R., et al., Efficacy and safety of recombinant human activated protein C for severe sepsis; *N Engl J Med*, 2001; **344**(10); p. 699-709.
2. Abraham, E., et al., Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death; *N Engl J Med*, 2005; **353**(13); p. 1332-41.
3. Nadel, S., et al., Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial; *Lancet*, 2007; **369**(9564); p. 836-43.
4. Levi, M., et al., Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated); *Am J Respir Crit Care Med*, 2007; **176**(5); p. 483-90.
5. Dellinger, R.P., et al., Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008; *Crit Care Med*, 2008; **36**(1); p. 296-327.
6. Marti-Carvajal, A., G. Salanti, and A.F. Cardona, Human recombinant activated protein C for severe sepsis; *Cochrane Database Syst Rev*, 2008;(1); p. CD004388.