Activated Protein C

A shocking failure or cautionary tale
The meaning of a voluntary market withdrawal

✔ Did our regulatory system function properly or fail?
✔ Have we done more good than harm from societal perspective?
Reassessing recombinant human activated protein C for sepsis: Time for a new randomized controlled trial*

In this issue of Critical Care Medicine, Dr. Vincent and colleagues (1) present an uncontrolled evaluation of recombinant human activated protein C (rhAPC) (Extended Evaluation of rhAPC trial, ENHANCE) in sepsis. This trial suggests that the risk of hemorrhage with rhAPC may be greater than originally estimated in the phase III rhAPC Worldwide Evaluation in Severe Sepsis Trial (PROWESS) (2). In addition to ENHANCE and PROWESS, however, two as yet unpublished randomized controlled trials have been completed in adults and children that prospectively tested the efficacy of rhAPC in sepsis (3, 4). Neither of these controlled trials reproduced the beneficial effect of rhAPC reported in PROWESS, raising the question whether there is a population of septic patients who can be identified a priori who will benefit from this agent. We believe this question can only be answered with an additional prospective placebo-controlled trial.

Analysis of the mortality data from the PROWESS trial by the Food and Drug Administration (FDA) was based on prospectively defined subsets of patients (5, 6). This analysis found that the mortality difference between rhAPC and placebo was limited to those patients with a higher risk of death, as defined by an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25 (i.e., the third and fourth quartile APACHE II scores). In the FDA analysis, the APACHE II appeared most effective in classifying patients by risk of death and by likelihood of benefit from rhAPC. After approval, based on this analysis and risk-benefit assessment, the package insert indicated that rhAPC was for use in patients with severe sepsis and a high risk of death as determined by, for example, APACHE II score (6, 7). In approving rhAPC, the FDA also anticipated receiving the results of additional testing planned by the manufacturer in lower risk adult patients (APACHE <25) and in children (5). These two randomized placebo-controlled trials were conducted in patients with low APACHE II scores (Administration of Drotrecogin Alfa (Activated) During Early Severe Sepsis [ADDRESS] trial) and pediatric patients. Both trials were stopped by their respective data monitoring committees for futility (Table 1). In the ADDRESS trial, the control mortality rate was low (17%) and similar to the low-risk groups (APACHE II 3–24, 19%) in the PROWESS trial (Table 1, Fig. 1).

When the results from the ADDRESS trial are analyzed in combination with the APACHE II subgroups from PROWESS, the lack of benefit from rhAPC for adult pa-

*See also p. 2266.

Key Words: recombinant human activated protein C; ENHANCE; PROWESS

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Analysis of the mortality data from PROWESS trial by the Food and Administration (FDA) was based on selectively defined subsets of patient (6). This analysis found that the mortality difference between rhAPC and placebo was limited to those patients with higher risk of death, as defined by the Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥ 25. In the third and fourth quartile APACHE II scores, the FDA in the analysis, the APACHE II appeared most effective in classifying patients by risk of death and by likelihood of benefit from rhAPC. After approval based on this analysis and risk-benefit

Recombinant human activated protein C in sepsis: Inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials

Peter Q. Eichacker, MD; Charles Natanson, MD

In March 2001, investigators reported the results of a phase III trial enrolling 1,600 patients with severe sepsis showing that drotrecogin alfa (activated) (i.e., recombinant human activated protein C, rhAPC) significantly reduced the relative and absolute risks of death (19.4% and 6.1%, respectively). The prevalence of bleeding as a serious adverse event during the 28-day follow-up period was greater with rhAPC (2.5%) than placebo (0.2%), but this did not reach statistical significance (p = 0.06). In light of the high mortality with sepsis and lack of alternative therapies, these encouraging results were welcomed by many healthcare professionals who expected APC to be quickly available for clinical use (2, 3).

In general, when there are no alternative therapies for a lethal disease like sepsis, a new drug should receive rapid approval and clinical acceptance if the original trial results are very consistent and the agent's mechanism of action is well understood and its safety profile is strong. Further review of rhAPC after the initial report of the phase III trial raised concerns on each of these points. These concerns were sufficient for half of the 29 members of the Anti-infective Drugs Advisory Committee working with the Food and Drug Administration to request a Food and Drug Administration review of rhAPC to evaluate the drug's benefit in sepsis. In the first agent undergo additional phase III testing before a final decision about its use clinically (4). The FDA did approve rhAPC for treatment of severely septic patients, but because of concerns, it restricted its use to those with a high risk of death (5). In addition, the FDA requested that the manufacturer conduct additional phase IV studies to address its effects in several specific subgroups. Understanding the basis for the questions and concerns raised during the FDA evaluation of rhAPC may assist clinicians now responsible for determining when and in what patients rhAPC should be applied.

LACK OF CONSISTENCY OF TRIAL RESULTS

Further analysis of the phase III trial results showed that rhAPC was substantially more beneficial in the second than first half of the trial. This change in effect was associated with an amendment modifying trial enrollment criteria (4). The amendment was instituted after the trial was nearly half done to more effectively exclude patients from study related to die of conditions not related to sepsis. The trial organizers appropriately believed such patients would unlikely be benefited by the effects of rhAPC. In the first change was also introduced into the manufacturing of rhAPC. Although an analysis did not show detectable differences between the two products, as noted the FDA, the complexity of rhAPC might still have permitted undetected differences to exist between the two (4). It is therefore possible that variation in the efficacy of rhAPC between the first and second halves of the study were either a function of inconsistent effects related to the change in drug manufacturing process or very dependent on the population of septic patients chosen for study.

HYPOTHESIZED MECHANISM OF ACTION

Based on the pathogenic role microvascular coagulation may have in sepsis, the mechanism of action that was originally proposed for rhAPC related to its antithrombotic effects. However, two other agents, antithrombin III and tissue factor pathway inhibitor, which also both reduce intravascular thrombin production, failed to show significant benefit in phase III trials of sepsis (6, 7). Because all three agents were associated with increased bleeding in patients with severe sepsis as a result of their antithrombotic effects, the mechanism of action under...
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Analysis of the mortality data from the Food and Drug Administration phase III trials revealed the first published results of a randomized controlled trial of rhAPC for sepsis. This trial was designed to evaluate the efficacy and safety of rhAPC in patients with severe sepsis. The trial was stopped early due to an increased risk of death in the rhAPC group. However, the results of this trial were not confirmed in a subsequent, larger randomized controlled trial (2).

Recombinant human activated protein C in sepsis: Inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials

Peter O. Eichacker, MD; Charles Natanson, MD

Commentary
Drotrecogin alfa (activated): does current evidence support treatment for any patients with severe sepsis?

Jan O Friedrich,1,2 Neel K Acharya,1,3 and Maureen O Meade4

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Abstract
Two international multicentre randomised controlled trials of Drotrecogin alfa (activated) (DrotAA), the Recombinant Human PROWESS and Administration of Drotrecogin Alfa (Activated) in Severe Sepsis (PROWESS) and Administration of Drotrecogin Alfa (Activated) in Severe Sepsis (ADDRESS), failed to show a benefit in reducing the risk of death in severe sepsis. The results of these trials have been questioned due to the methodological issues surrounding the design and analysis of the trials. The results of these trials have been interpreted as showing no benefit of DrotAA in the treatment of severe sepsis, but the interpretation of these trials is controversial. The results of these studies have been reanalysed using different statistical methods, and the results have been reinterpreted. The reanalysis of these trials has shown that the results of these trials are consistent with a benefit of DrotAA in the treatment of severe sepsis.

HYPOTHESIZED MECHANISM OF ACTION

Based on the pathogenic role of systemic inflammation in sepsis, the mechanism of action of DrotAA, a recombinant activated protein C (APC), likely involves the inhibition of pro-inflammatory cytokines and other molecules that contribute to the development of sepsis. DrotAA is a recombinant form of human APC that is produced in the laboratory and is administered to patients with severe sepsis. DrotAA acts by inhibiting the activation of coagulation factors, reducing the production of pro-inflammatory cytokines, and promoting the resolution of inflammation. The mechanism of action of DrotAA is based on the concept that activated protein C (APC) is a naturally occurring anti-inflammatory molecule that is produced in response to inflammation. APC is a serine protease that cleaves and inactivates specific intracellular factors, including interleukin-1 beta-converting enzyme (ICE) and nuclear factor kappa B (NF-kappa B), which are involved in the regulation of pro-inflammatory cytokine production. DrotAA is a recombinant form of human APC that is produced in the laboratory and is administered to patients with severe sepsis. DrotAA acts by inhibiting the activation of coagulation factors, reducing the production of pro-inflammatory cytokines, and promoting the resolution of inflammation. The mechanism of action of DrotAA is based on the concept that activated protein C (APC) is a naturally occurring anti-inflammatory molecule that is produced in response to inflammation. APC is a serine protease that cleaves and inactivates specific intracellular factors, including interleukin-1 beta-converting enzyme (ICE) and nuclear factor kappa B (NF-kappa B), which are involved in the regulation of pro-inflammatory cytokine production.

Effect of DrotAA on 28-day survival
Figure 1 shows the effect of DrotAA on 28-day survival as observed in all three published trials (a phase II additional unpublished trial in children with severe sepsis [8] and a recent systematic review and meta-analysis of DrotAA [9] found no additional trials). PROWESS suggested a survival benefit for all septic patients who received DrotAA. However, the results of the ADDRESS trial were not consistent with the results of PROWESS, and the results of the phase III trial were inconsistent with the results of the phase II trial. The results of these trials suggest that the effect of DrotAA on 28-day survival is uncertain and that further randomized controlled trials are needed to clarify the role of DrotAA in the management of severe sepsis.

Introduction
Severe sepsis is a condition with important public health ramifications because it is common and has a high mortality rate [1]. Drotrecogin alfa (activated) (DrotAA), more commonly known as recombinant human activated protein C (rhAPC), is the first marketed product of this technology. The results of this study demonstrate no significant benefit of DrotAA in patients with severe sepsis. However, the results of the ADDRESS trial suggest that DrotAA may be effective in reducing the risk of death in patients with severe sepsis. The results of these trials have been interpreted as showing no benefit of DrotAA in the treatment of severe sepsis, but the interpretation of these trials is controversial. The results of these studies have been reanalysed using different statistical methods, and the results have been reinterpreted. The reanalysis of these trials has shown that the results of these trials are consistent with a benefit of DrotAA in the treatment of severe sepsis.
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Commentary

Drotrecogin alfa (activated): does current evidence support treatment for any patients with severe sepsis?

Jan O Friedrich1,2, Neil K K Adhikari1,3 and Maureen O Meade4

Abstract

Two international multicentre randomised control trials (ACT II and ADDRESS) of recombinant human activated protein C (rhAPC) have recently been reported. Neither of these controlled trials produced the beneficial effect of recombinant human activated protein C (rhAPC) as reported in PROWESS, raising the question whether there is a population of patients who can be identified who will benefit from this agent. I believe this question can only be answered with an additional prospective placebo-controlled trial. Analysis of the mortality data from PROWESS trial by the Food and

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Recombinant human activated protein C in sepsis: Inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials

Peter Q. Eichacker, MD; Charles Natanson, MD

Activated protein C (Xigris®) treatment in sepsis: a drug in trouble

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Drotrecogin alfa (activated) or recombinant human activated protein C (rhAPC) has been registered for use as adjuvant treatment in severe sepsis since 2001 under the trade name Xigris® essentially based on the results from one large clinical trial (the PROWESS trial). In a recently published second randomized clinical trial (the ADDRESS trial), enrolling patients with severe sepsis but with less risk of death, no effect of the treatment was shown, not even a trend to a positive effect in the subgroup of patients with a high risk of death that would match the present prescription label for Xigris®. In addition, a large randomized, placebo-controlled trial with rhAPC in paediatric sepsis has recently been terminated prematurely because of lack of efficacy.

Altogether, the robustness of the data supporting rhAPC in treating patients with severe sepsis may be questioned. A confirmatory clinical trial is required before it can be used with confidence. The side-effects of rhAPC are well documented but its efficacy is not.

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Key words: sepsis; severe sepsis; septic shock

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Activated protein C (Xigris®) treatment in sepsis: a drug in trouble

Stockholm, Sweden

Activated protein C: do more survive?

Alasdair F. MacKenzie

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Commentary

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Activated protein C (Xigris®) treatment in sepsis: a drug in trouble

Alasdair F. Mackenzie

Activated protein C: do more survive?

Research article

A meta-analysis of controlled trials of recombinant human activated protein C therapy in patients with sepsis
Christian J Wiedermann*1,2 and Nicole C Kaneider2

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Other examples of regulatory concerns
Recombinant factor VIIa in the treatment of massive bleeding
Aprotinin in cardiac surgery

Aprotinin (BPTI)

Lysine Residues

Plasmin Catalytic Domain
Current “Model”

Can we meet the needs of all stakeholders?

Does the drug do what it is supposed to? – proof of concept and is it safe?

Does therapy do more good than harm?

Is the drug good value for money?

Does the drug do what it is supposed to? – proof of concept
The benefit-harm profile

Number of patients getting drug

Efficacy – Effectiveness Gap

Regulatory studies  Labeled Use  Inappropriate Use

Benefit-to-Harm

(Modified from T Lönngren 2010)
Challenges in current system

Challenges with pre-approval evidence

• Approvals based on RCTs
  – Regulatory trials only provide limited evidence of efficacy
  – RCTs designed to win in fewest patients possible
  – Little to no safety data

• No studies in children or pregnancy
Differences in explanatory and pragmatic trials

<table>
<thead>
<tr>
<th>Feature</th>
<th>Explanatory attitude</th>
<th>Pragmatic attitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Efficacy: Can the intervention work?</td>
<td>Effectiveness: Does the intervention work when used in normal practice?</td>
</tr>
<tr>
<td>Setting</td>
<td>Tightly controlled, well resourced, “ideal” setting</td>
<td>Normal practice</td>
</tr>
<tr>
<td>Participants</td>
<td>Highly selected; poorly adherent participants and those with conditions that might</td>
<td>Little or no selection beyond the clinical indication of interest</td>
</tr>
<tr>
<td></td>
<td>dilute the effect are often excluded</td>
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<tr>
<td>Intervention</td>
<td>Strictly enforced; adherence is monitored closely</td>
<td>Applied flexibly as it would be in normal practice</td>
</tr>
<tr>
<td>Comparator</td>
<td>Strictly enforced; adherence is monitored closely</td>
<td>Often usual care, with usual variation; applied flexibly as it would be in normal</td>
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<tr>
<td></td>
<td></td>
<td>practice</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Often short-term surrogates or process measures</td>
<td>Directly relevant to participants, funders, communities and health care practitioners</td>
</tr>
<tr>
<td>Relevance to practice</td>
<td>Indirect: little effort is made to match the design of the trial to the decision-</td>
<td>Direct: the trial is designed to meet the needs of those making decisions about</td>
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<td>making needs of those in the usual setting in which the intervention will be</td>
<td>treatment options in the setting in which the intervention will be implemented</td>
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*Adapted, with permission, from Zwarenstein M, Treweek S, Gagnier J, et al.; CONSORT and Pragmatic Trials in Healthcare (Practihs) groups. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390. The table in BMJ was adapted from a table presented by Marion Campbell, University of Aberdeen, at the 2008 Society for Clinical Trials meeting.

Zwarenstein, M. et al. CMAJ 2009;180:998-1000
Next time

• Avoid early termination at all costs
• Early confirmatory trial
• A regulatory framework that will protect us from ourselves
  – Improved monitoring (passive and active as well as greater use of systematic review)
  – Patient-oriented research and comparative effectiveness
  – System of rapid removal from market
Being an early adopter or a sceptic

The Chasm

- Innovators: 2.5%
- Early adopters: 13.5%
- Early majority: 34%
- Late majority: 34%
- Laggards: 16%
Being an early adopter or a sceptic

- Early goal directed therapy
- Activated Protein C
- Intensive Insulin treatment
Being an early adopter or a sceptic

Intensive Insulin treatment
Early goal directed therapy
Activated Protein C

The Chasm

Innovators: 2.5%
Early adopters: 13.5%
Early majority: 34%
Late majority: 34%
Laggards: 16%
Next time

• Clearly important to separate approval from paying and monitoring actual usage
• For Canada, implementing a national pharmaceutical strategy including
  – Paying for all drugs
  – a system to evaluate effectiveness and costs
  – (NICE Canada)