tients with severe sepsis. In particular, activated protein C is the first antisepsis drug that has met predefined efficacy criteria for premature termination of a trial, and the level of statistical significance reached was impressive (P = 0.005). In addition, the drug was efficacious in many different subgroups. There are, however, some points of concern. Many of these derive from the fact that populations of patients with sepsis are highly heterogeneous, so that trials enrolling patients with sepsis are difficult to perform, interpret, and reproduce. Careful analysis failed to reveal a reason why the efficacy of activated protein C was not more consistent throughout the trial. It is impossible to exclude the possibility that, in some way, the amendments to the protocol or the changes in the drug may have been responsible. Of particular concern is the possibility that the significant results in the second phase of the trial may reflect the use of a functionally different lot of the protein and that there is no laboratory test that can predict the efficacy of future lots. The difficulty in balancing these conflicting ideas was reflected by the vote of the FDA Anti-Infective Drugs Advisory Committee, which was split 10 to 10 as to whether activated protein C is safe and efficacious.

Although the data regarding activated protein C are very encouraging, we believe that there is not sufficient evidence at present for it to become the standard of care. Although the data from the trial suggest that activated protein C was efficacious in a subgroup of patients with high APACHE II scores before infusion, this hypothesis needs to be tested in a confirmatory trial that prospectively incorporates a prognostic scoring system such as APACHE II. A successful outcome of such a trial would constitute a major advance, would settle the current controversy, and would justify the use of the drug in this subgroup of patients with severe sepsis.

H. Shaw Warren, M.D.
Massachusetts General Hospital
Boston, MA 02114

Anthony F. Suffredini, M.D.
P. Peter Q. Eichacker, M.D.
National Institutes of Health
Bethesda, MD 20892

Robert S. Munford, M.D.
University of Texas Southwestern Medical Center
Dallas, TX 75390

Supported by grants (R01-GMS0694-02, to Dr. Warren, and AI18188, to Dr. Munford) from the National Institutes of Health.

Dr. Warren is a cofounder of Critical Therapeutics. All the authors served as consultants to the Food and Drug Administration Anti-Infective Drugs Advisory Committee for Activated Protein C.

The views expressed in this article do not necessarily represent those of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

REFERENCES


Copyright © 2002 Massachusetts Medical Society.

ASSessing the Use of Activated Protein C in the Treatment of Severe Sepsis

In 2001, the Food and Drug Administration (FDA) evaluated an application for the use of drotrecogin alfa (activated), or recombinant human activated protein C (Xigris, Eli Lilly), in patients with severe sepsis. The use of activated protein C, as compared with placebo, was associated with a significant reduction in mortality in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial (24.7 percent vs. 30.8 percent, P = 0.005). Extensive review by physicians and scientists at the FDA confirmed the principal findings of the PROWESS trial but raised issues regarding the interpretation of data and appropriate use of the drug.
These issues were discussed with experts on sepsis from outside the FDA at a public meeting of the agency’s Anti-Infective Drugs Advisory Committee on October 16, 2001. The committee members provided valuable input, highlighted specific issues of concern, some of which are summarized in the accompanying Sounding Board by Warren et al.; and were evenly divided in a vote on a recommendation regarding approval. The FDA then performed substantial additional evaluations addressing the issues that had been raised and concluded that activated protein C had been demonstrated to be safe and effective in reducing mortality among patients with severe sepsis and a high risk of death, as determined, for example, by the Acute Physiology and Chronic Health Evaluation (APACHE II) score. In this article, I summarize the findings of the FDA regarding several key matters of concern—in particular, changes made during the trial, the use of APACHE II scores, and the risk of serious bleeding.

CHANGES DURING THE TRIAL

Near the midpoint of the activated protein C trial, the study protocol was amended, and activated protein C produced with the use of a new master cell bank was introduced. The reduction in mortality associated with treatment with activated protein C was greater after these changes were made than it had been up to that point (Table 1), raising questions about whether changes in the protocol, the drug, or both accounted for the improved results and therefore about the applicability of the results of the trial to the use of activated protein C. The apparent inconsistencies over the course of the study were limited to the patients with lower risk; the high-risk population (patients with an APACHE II score of 25 or more), covered by the indication approved by the FDA, showed consistent benefit (Table 1).

FDA analyses indicate that differences over time as large as or larger than those seen in the PROWESS study would be expected to occur by chance alone in 8 percent of trials. As summarized below, FDA analyses do not support the belief that changes in either the protocol or the drug accounted for such differences.

Patients with Serious Preexisting Diseases

In order to increase the capacity of the trial to detect effects on mortality due to sepsis, the eligibility criteria for the activated protein C study attempted to exclude patients who were likely to die from underlying disease within 28 days. The amendments to the eligibility criteria were intended to make this exclusion more effective. Two analyses indicate that these amendments did not account for the improved study outcomes.

First, among the patients enrolled before the protocol was amended, those who would not have met the amended eligibility criteria actually had a substantially larger absolute reduction in mortality (8 percent) (Table 1) than those whose eligibility would not have been affected by the changes (1 percent). Second, in analyzing the effect of underlying disease on treatment effect, the FDA used the chronic health points that had been prospectively assigned to subjects. Chronic health points, a component of the APACHE II score that assesses the risk of death, are assigned only to those patients with preexisting severe organ failure or immunosuppression. It was just

### Table 1. Outcome Data from the PROWESS Trial Before and After Amendment of the Protocol.

<table>
<thead>
<tr>
<th>Group of Patients</th>
<th>Mortality Before Amendment</th>
<th>Mortality after Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Group</td>
<td>Activated Protein C Group</td>
</tr>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>%</td>
</tr>
<tr>
<td>All patients</td>
<td>109/360 (30)</td>
<td>102/360 (28)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>34/185 (18)</td>
<td>48/195 (25)</td>
</tr>
<tr>
<td>≥25</td>
<td>75/175 (43)</td>
<td>54/165 (33)</td>
</tr>
<tr>
<td>Amended eligibility criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would not be met</td>
<td>17/40 (42)</td>
<td>14/41 (34)</td>
</tr>
<tr>
<td>Would be met</td>
<td>92/320 (29)</td>
<td>88/319 (28)</td>
</tr>
</tbody>
</table>

*The difference is shown as the mortality in the activated protein C group minus the mortality in the placebo group.
such patients in whom most of the beneficial effect of activated protein C therapy was seen (Table 2). Treatment with activated protein C was associated with a 3 percent absolute reduction in mortality among patients without chronic health points on APACHE II but with a 19 percent absolute reduction in mortality among patients who had chronic health points. The P value for the interaction of treatment effect and APACHE II chronic health points was 0.01.

Both of these analyses indicate that the amendments to the protocol, rather than accounting for improved results, actually excluded patients who appeared more likely to benefit from therapy. In addition, these two analyses address the generalizability of the results of the PROWESS trial to patients with sepsis who have serious preexisting disease. They suggest strongly that serious preexisting disease should not, in general, be a reason for withholding activated protein C therapy.

End Points

Notwithstanding some confusion at the meeting of the Anti-Infective Drugs Advisory Committee, resulting from differences between the study objectives and the primary end point, the PROWESS trial had a single, primary, prospectively identified end point — 28-day mortality among all treated patients. This end point did not change during the trial, except that the amended protocol added the protein C activity level as a covariate for adjustment of the primary analysis and eliminated shock as a covariate. This change had a negligible effect on the size of the resulting treatment effect and the associated P value (P=0.008 according to the analysis described in the unamended protocol). The assessment of mortality in subgroups defined according to base-line protein C activity was, from the start, intended to be a secondary analysis. In addition and appropriately, the amendments to the protocol modified the stated study objectives to align them better with the primary end point.

Changes in the Product

Around the time the amendments were made to the protocol, Eli Lilly began using activated protein C that had been produced with the use of a new master cell bank. Changes in a master cell bank can result in changes in the product. The FDA and Eli Lilly conducted exhaustive comparisons of the primary, secondary, tertiary, and quaternary structure, pharmacokinetics, enzyme kinetics, and binding affinity of activated protein C produced from the two master cell banks. No significant differences were found.

Although differences in complex proteins may escape detection, the results of the extensive comparability testing performed indicate that it is unlikely that undetected differences account for the apparent change in clinical outcomes. If the change in the master cell bank did account for the improved clinical results, then the newer, marketed product is superior to the earlier product and highly effective, and one should be wary about future changes in the master

Table 2. Outcome Data from the PROWESS Trial for Selected Subgroups.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MORTALITY IN THE PLACEBO GROUP</th>
<th>MORTALITY IN THE ACTIVATED PROTEIN C GROUP</th>
<th>ABSOLUTE DIFFERENCE*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
<td>%</td>
</tr>
<tr>
<td>All patients</td>
<td>259/840 (31)</td>
<td>210/850 (25)</td>
<td>−6</td>
</tr>
<tr>
<td>Chronic health points on APACHE II†</td>
<td>83/176 (47)</td>
<td>47/169 (28)</td>
<td>−19</td>
</tr>
<tr>
<td>Yes</td>
<td>176/664 (27)</td>
<td>163/681 (24)</td>
<td>−3</td>
</tr>
<tr>
<td>No</td>
<td>First</td>
<td>26/215 (12)</td>
<td>3</td>
</tr>
<tr>
<td>Second</td>
<td>57/222 (26)</td>
<td>49/218 (22)</td>
<td>4</td>
</tr>
<tr>
<td>Third</td>
<td>85/437 (19)</td>
<td>82/436 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Fourth</td>
<td>176/403 (44)</td>
<td>128/414 (31)</td>
<td>−13</td>
</tr>
</tbody>
</table>

*The difference is shown as the mortality in the activated protein C group minus the mortality in the placebo group.
†Chronic health points are assigned to patients with preexisting severe organ dysfunction, immunosuppression, or both.
‡The ranges of scores in the quartiles were as follows: first quartile, 3 to 19; second quartile, 20 to 24; third quartile, 25 to 29; fourth quartile, 30 to 53.
USE OF THE APACHE II SCORE

Consideration of measures of risk and severity in general, and the APACHE II score in particular, played an important part in the assessment of the activated protein C trial and in the labeling of activated protein C. The evidence suggesting that the treatment effect of activated protein C varies with the risk of death is strong. Subgroup analyses are most persuasive when they are based on prespecified analyses, have strong biologic plausibility, and are supported by strong and consistent evidence. All these conditions were met in this case.

Analysis of the treatment effect according to the quartile of APACHE II score was prespecified in the PROWESS trial as an important analysis and the principal analysis of outcome according to measures of severity or risk.2 3 The hypothesis that a treatment effect might be observed best in higher-risk patients with sepsis is a highly plausible one that has been incorporated into many trials. If a drug prevents a fixed proportion of deaths due to sepsis, benefits will be greatest in those populations with the highest risk of death, whereas the frequency of adverse effects might be similar in all subgroups.

In the activated protein C trial, treatment-related benefit consistently increased with the risk of death as assessed by a variety of indexes of baseline severity, including the number of failing organ systems and the presence or absence of shock. Indeed, each of the three risk-related components of the APACHE II score — acute physiological changes, older age, and the assignment of chronic health points — correlated with a greater treatment effect.2 6

There are strong reasons for selecting the APACHE II score from among the various measures of risk and severity as a tool for guiding activated protein C therapy. First, the APACHE II score was by far the best discriminator of the risk of death: mortality in the placebo group was 12 percent in the quartile with the lowest APACHE II score and 49 percent in the quartile with the highest score (Table 2). In addition, the APACHE II score was the best predictor of survival benefit from activated protein C. All benefit was observed among the half of subjects who had APACHE II scores of 25 or more (a 13 percent absolute reduction). The subjects with lower risk showed no benefit from activated protein C, and patients in the lowest APACHE II quartile had somewhat higher mortality with activated protein C than with placebo (Table 2).

In contrast, other measures of risk and severity, while supporting the hypothesis that the level of risk determined the amount of benefit, did not discriminate among levels of risk of death or likelihood of benefit as well as the APACHE II score did. For example, low-risk patients defined as those with failure of one organ system (failure of at least one organ system being required for a diagnosis of severe sepsis and for enrollment in the study) had a mortality rate of 21 percent if they were given placebo, as compared with 12 percent for low-risk patients as defined according to the APACHE II score. The patients with failure of one organ system had a mortality rate of 20 percent if they were treated with activated protein C.2 3 6

Another advantage of using the APACHE II score rather than other measures in guiding therapy is that the APACHE II score assesses not just the severity of the acute disease process, but also other risk factors that correlated with greater treatment effect — that is, age and preexisting health status. The practicality of using the APACHE II score to guide therapy was assessed by FDA physicians, who found that the APACHE II score could be determined rapidly with the use of data routinely available for patients with severe sepsis.

APACHE II scores in the activated protein C trial were calculated with the use of the most abnormal laboratory measurements and vital signs obtained during the 24 hours preceding treatment; thus, responses to resuscitation would not affect the score. Although the timing of APACHE II scoring differed somewhat from the timing used in validation studies,2 6 the results of the trial provide strong evidence that the APACHE II score, as assessed in the trial, is a very successful predictor of the risk of death. In clinical practice, the timing of APACHE II scoring to guide the use of activated protein C need not and probably should not deviate substantially from the timing used in the PROWESS trial.

The FDA recognizes that the hypothesis that the benefit of activated protein C in patients with severe sepsis is limited to high-risk patients (those with an APACHE II score ≥25), although strongly supported by the data from the PROWESS trial, has not been proved. To assess better the potential for use of activated protein C in lower-risk patients with severe sepsis, the FDA has requested an additional placebo-controlled study involving such patients, and Eli Lilly has committed itself to conducting such a trial with more than 11,000 patients.

RISK OF BLEEDING AND SURVIVAL BENEFITS

Use of activated protein C in severe sepsis is clearly associated with an increased risk of serious hemorrhage during the infusion period — that is, from the start of the infusion through the day after the discontinuation of the infusion. After this period, the rate of
hemorrhage in the activated protein C group was essentially the same as that in the placebo group. Serious bleeding events (defined in the trial as any intracranial hemorrhage, any life-threatening bleeding episode, any bleeding event requiring the administration of 3 or more units of packed red cells per day for two consecutive days, or any bleeding event otherwise assessed as serious) occurred during the infusion period in 20 of 850 patients treated with activated protein C (2.4 percent) and 8 of 840 patients given placebo (1.0 percent). Although the incidence of intracranial hemorrhage during the infusion period was 0.2 percent (2 of 850) in the activated protein C group in the PROWESS trial, a higher incidence (1.5 percent [8 of 520]) was observed among patients receiving activated protein C in uncontrolled studies. These findings suggest that hemorrhagic complications of activated protein C therapy may be more common outside of highly controlled and monitored settings. They thus emphasize the importance of selection and monitoring of patients in minimizing the risk of hemorrhage. The FDA-approved labeling for activated protein C provides information regarding its safe use.

The absolute survival benefit observed in the PROWESS trial was 6 percent overall and 13 percent in the high-risk population for whom use of activated protein C has been approved (Table 2). Even when one takes into account the possibility that risks may be somewhat higher in clinical practice than they were in the trial, and that some survivors might have prolonged hospitalizations, the survival benefits balance quite favorably against the risk of hemorrhage.

CONCLUSIONS

There is still much to be learned about the optimal use of activated protein C. At the request of the FDA, Eli Lilly has made extensive commitments to conduct controlled trials involving more than 13,000 patients to investigate the use of activated protein C in lower-risk patients with severe sepsis, its use in children with severe sepsis, and the optimal use of low-dose heparin with activated protein C.

It is common and appropriate that biologic therapeutics offering important new benefits are approved at a time when the safety and efficacy of their use as specified in the labeling have been established but when much remains to be learned in order to optimize their use. Enanercept (Enbrel, Immunex), infliximab (Remicade, Centocor), trastuzumab (Herceptin, Genentech), rituximab (Rituxan, IDEC), and abciximab (ReoPro, Lilly) are a few examples of drugs about which much has been learned since they received initial approval. The data currently available for activated protein C strongly support the conclusion that the use of this drug as labeled will save many lives as we gather the information necessary to refine its use further.

JAY P. SIEGEL, M.D.
Center for Biologics Evaluation and Research
Rockville, MD 20852

I am indebted to Drs. Karen Weiss, Linda Forsyth, Jawahar Tiwari, Robert Lindblad, and Gibbes Johnson and to the remainder of the FDA Xigris review team for performing many of the data analyses and developing many of the concepts discussed in this article.

REFERENCES


Copyright © 2002 Massachusetts Medical Society.