Sounding Board

Risks and Benefits of Activated Protein C Treatment for Severe Sepsis

A new hypothesis with implications for the treatment of sepsis has recently been tested — the hypothesis that part of the pathophysiology of sepsis is caused by unrestricted or inappropriate coagulation in the microcirculation. Three agents that block coagulation at different stages have now been evaluated in large, multicenter trials as adjunctive therapy for sepsis. Neither antithrombin III nor tissue-factor-pathway inhibitor was effective in patients with severe sepsis or septic shock. In contrast, treatment with activated protein C (drotrecogin alfa [activated]) was associated with a significant reduction in 28-day mortality. Of the patients who received activated protein C, 24.7 percent had died at 28 days, as compared with 30.8 percent of those who received placebo (P = 0.005). However, the use of activated protein C was also associated with greater risk of serious bleeding (3.5 percent vs. 2.0 percent, P = 0.06).

In November 2001, the Food and Drug Administration (FDA) approved recombinant human activated protein C (Xigris, Eli Lilly) for the treatment of patients with severe sepsis who have a high risk of death (as determined, for example, by the Acute Physiology and Chronic Health Evaluation [APACHE II] severity-of-illness scoring system). The purpose of this article is to provide clinicians with information that is not found in the published account of the clinical trial of activated protein C or in the marketing literature prepared by the sponsor. Most of this information was presented by the FDA at the October 16, 2001, meeting of the Anti-Infective Drugs Advisory Committee. A more detailed account of this meeting is available on the Internet.

Three important issues regarding the clinical use of activated protein C arose during these deliberations. First, there were changes in the study protocol and in the drug preparation that appeared to divide the trial into two discernible phases in which the efficacy of activated protein C was different. Second, there was new information about the efficacy of the drug in various subgroups of patients. Third, there were new data on the toxicity of the drug.

The Two Phases of the Activated Protein C Trial

In June 1999, after 720 patients had been enrolled in the trial of activated protein C, the sponsor amended the study protocol. The entry criteria were modified to exclude patients who had received bone marrow transplants or solid-organ transplants, who had metastatic cancer or pancreatitis, or for whom a commitment for aggressive treatment had not been obtained. Patients who had had organ failure for more than 24 hours at the time they met all other criteria for inclusion were also excluded. These changes, which were made in a blinded manner and before the first interim analysis by the data and safety monitoring committee, shifted the composition of the study population toward patients with less severe underlying disease and more acute infectious illnesses.

In addition, a new placebo (0.1 percent albumin instead of saline) was introduced, and protein C deficiency status was eliminated as a primary variable for the analysis. The manufacture of activated protein C requires expression of the recombinant protein from cells in culture, enzymatic cleavage of the protein, and several other post-translational modifications. In August 1999, a new master lot of cells was introduced to make recombinant activated protein C. Extensive in vitro studies did not reveal differences between the old and new preparations of activated protein C. The new preparation was used for the remainder of the trial.

After these changes were made, there was an improvement in the protective efficacy of activated protein C. The cumulative mortality curves for the trial are shown in Figure 1. Because these curves depict mortality at 28 days and are graphed according to the date of randomization and because of variable phase-in times, the effects of changes are likely to be apparent after a slight delay. For most of the trial, mortality in the placebo group was relatively flat. The mortality in the activated protein C group decreased somewhat beginning in February 1999, then increased, and then decreased progressively beginning in October 1999. The FDA analysis indicated that the efficacy of the drug after the amendment of the protocol differed substantially from its efficacy before the changes were made. Whereas activated protein C did not improve survival in the phase before amendment of the protocol (720 patients; mortality in the placebo group, 30 percent; mortality in the activated protein C group, 28 percent; relative risk of death, 0.94; P = 0.57), it was very effective in the phase after the protocol was amended (970 patients; mortality in the placebo group, 31 percent; mortality in the activated protein C group, 22 percent; relative risk of death, 0.71; P = 0.001). It is not possible to tell from the available data whether the striking improvement in efficacy resulted from the enrollment of a somewhat different population of patients, an undetected change in the drug itself, chance alone, or some combination of the three.
Although the trial had the power to determine whether activated protein C is more effective than placebo in patients with severe sepsis, the efficacy of the drug was also examined in numerous subgroups. Definitive conclusions often cannot be reached on the basis of post hoc analyses of subgroups within a large clinical trial, especially if the trial does not have sufficient power to detect differences in smaller numbers of patients. Nevertheless, activated protein C seems to have been effective in numerous subgroups. Its efficacy was most apparent in patients older than 50 years of age, in patients with more than one dysfunctional organ system, in patients with an APACHE II score of more than 24 before the infusion of the drug, and in patients who had shock at the time of the infusion. Subgroups in which benefit was not apparent included patients who had undergone surgery and patients with failure of a single organ.

The FDA licensed activated protein C for the treatment of adult patients with severe sepsis who have a high risk of death, as indicated by an APACHE II score of 25 or more. APACHE II is a bedside scoring system that combines physiological data with information about age and chronic disease. It was developed to predict a patient’s risk of dying in the intensive care unit and was designed and validated for patients who have been in the intensive care unit for 24 hours. In the activated protein C trial, APACHE II scores before the infusion of activated protein C were calculated as a measure of the severity of illness, in part to ensure comparability of the patients enrolled in the two treatment groups. Data were collected for the calculation of the APACHE II score within the 24-hour period preceding the administration of the study drug. The FDA recommendation was based on the finding in this pivotal trial that activated protein C was most beneficial in patients whose APACHE II score before infusion exceeded 24.

There is, however, no precedent for using the APACHE II system to select patients for novel therapies. When it is applied to the administration of activated protein C in clinical practice, the APACHE II score will most likely be based on data acquired in “real time.” A score calculated in this way may change as the patient’s physiological status improves or deteriorates. It is unclear whether or not patients should receive activated protein C if their APACHE II score falls from, say, 26 to 23 as they are resuscitated before the infusion of the drug has begun. Furthermore, the interobserver and intraobserver variability in the determination of APACHE II scores among experienced intensive care physicians may be as high as 10 to 20 percent. The use of APACHE II scores in this new manner — as a screening test to determine which patients should receive a new therapy and which patients should not — has not been validated. Correct use of APACHE II scoring is of major importance, because activated protein C was not effective in patients who had APACHE II scores of less than 20, and it was associated with an increased risk of bleeding in such patients (Table 1).

An additional consideration for practitioners may be
the fact that, despite the broad entry criteria used for the study, the patients who were actually enrolled in the trial represented a rather narrow subgroup of the total population of patients with sepsis found in most medical centers. More than 80 percent of the patients in the trial were living at home before hospitalization, and more than 50 percent were admitted with respiratory failure. Patients who had had organ failure for more than 24 hours were excluded. The risk–benefit ratio of the drug in the patients studied might well differ from that in patients who have been in the hospital for a much longer time, yet the latter group of patients might still meet the criteria established by the FDA for treatment with the drug.

RISK OF SERIOUS HEMORRHAGE

The use of activated protein C was associated with an increased risk of serious bleeding in the controlled, randomized trial. Four deaths due to hemorrhage occurred during the infusion of activated protein C, whereas none occurred during the infusion of placebo. A total of 3.5 percent of patients who received activated protein C had serious bleeding (defined as intracranial hemorrhage, a life-threatening bleeding episode, or a requirement for 3 or more units of blood per day for two consecutive days, or any bleeding episode otherwise assessed as serious), as compared with 2 percent of the patients who received placebo (P = 0.06). The incidence of serious bleeding may increase when activated protein C is used in less controlled circumstances. During the open-label use of activated protein C after the trial, for which similar criteria were used for the selection of patients in order to minimize the risk of bleeding, 13 of 520 patients, or 2.5 percent, had an intracranial hemorrhage, and eight of these hemorrhages occurred during the infusion period. Only 0.2 percent of the patients who received the drug in the controlled trial had this complication.

CONCLUSIONS

Activated protein C is the first biologic agent approved in the United States for the treatment of severe sepsis. Its success came after almost two decades of intensive research and more than 20 large clinical trials of other candidate therapeutics. As is the case with other anticoagulants, it may cause serious hemorrhage, and the risk of this complication needs to be assessed in the context of the potential benefit of the drug.

The overriding task that now faces clinicians is to decide which patients should receive activated protein C and whether the balance of available data supports its widespread use. For many drugs, extensive testing in animals provides reassurance that the concept, mechanisms of action, and drug formulation are compatible with the clinical results. In this case, the proposed mechanisms of protection by activated protein C are unproven. In the pivotal trial, there was no relation between protein C levels before infusion or measures of clotting after infusion and the efficacy of the drug; moreover, the antiinflammatory properties proposed for activated protein C require confirmation in vivo. Unfortunately, the species specificity of activated protein C has limited its testing as a treatment for sepsis to studies in baboons in which a very large bacterial challenge is used. Interpretation of the single trial involving human subjects thus has special importance.

Several important points support the conclusion that activated protein C is effective in at least some pa-
patients 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.

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Supported by grants (RO1-GM59694-02, to Dr. Warren, and AI18188, to Dr. Munford) from the National Institutes of Health.

Dr. Warren is a co-founder 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


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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.