Activated protein C was cost-effective for prolonging survival in a subgroup of patients with severe sepsis

Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C. **An economic evaluation of activated protein C treatment for severe sepsis.** N Engl J Med. 2002;347:993-1000.

QUESTION

In patients admitted to the intensive care unit (ICU) with severe sepsis, is treatment with recombinant human-activated protein C more cost-effective than conventional care for prolonging survival?

DESIGN

Cost-effectiveness analysis from a patient perspective using a Markov model with benefit data from a {randomized (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trial with 28-day follow-up (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS])}†. A separate 3-year cohort studied conventionally treated patients after discharge.

SETTING

Southern Alberta, Canada.

PATIENTS

A conventional care cohort of 787 patients (mean age 61 y, 56% men) with severe sepsis was assembled and followed for 3 years after hospital discharge to derive probabilities of transition between clinical states (i.e., alive in the ICU, alive on the hospital ward, alive at home, and dead) for use in the Markov model and estimates of resource use. The effectiveness of activated protein C, as determined by PROWESS, was used in the economic analysis. 39 of 40 randomly selected patients from the conventional care cohort met the inclusion criteria for PROWESS. After discharge, the cost of caring for survivors treated with activated protein C was assumed to be equal to that for those receiving conventional care.

INTERVENTION

{In PROWESS, patients were allocated to recombinant human-activated protein C, 24 μg/kg body weight per hour (n = 857), or placebo (n = 871) administered intravenously at a constant rate for a total of 96 hours}†. Patients in the conventional care cohort received conventional care for severe sepsis in the ICU and on the hospital ward.

MAIN COST AND OUTCOME MEASURES

Incremental cost-effectiveness defined as the cost per year of life gained, survival, and health care resource use. Costs were in 2001 U.S. dollars with a 5% annual discount rate.

MAIN RESULTS

The acquisition cost of activated protein was $6800 per therapeutic course. The mean cost of care for patients in the conventional cohort in the ICU and on the ward was $20 528 and $12 422, respectively. At 1, 2, and 3 years after hospital discharge, the mean health care costs for patients in the conventional cohort were $14 181, $4698, and $4579, respectively. The cost per life-year gained by treating patients (overall) with activated protein C was $27 936. It was more cost-effective to treat patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ≥ 25 ($24 484 per life-year gained) than those with scores ≤ 24 ($35 632 per life-year gained). However, this ratio increased to $575 054 per life-year gained when estimates of effectiveness from a post hoc reanalysis of the data by the Food and Drug Administration (FDA) were considered.

CONCLUSION

In patients admitted to the intensive care unit with severe sepsis, treatment with recombinant human-activated protein C was cost-effective for prolonging survival in those with more severe illness.

Source of funding: Institute of Health Economics.

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*See Glossary.

†**Bernard GR, Vincent JL, Laterre PF, et al.** N Engl J Med. 2001;344:699-709.

COMMENTARY

The PROWESS trial, reported in 2001, showed that treatment with recombinant human-activated protein C reduced mortality (from 30.8% in the placebo group to 24.7% in the treatment group) in patients with severe sepsis (≥ 1 associated organ failure) (1). Subsequent reports revealed that the effectiveness of activated protein C in PROWESS was essentially limited to the 50% of patients with an APACHE II score ≥ 25 (2, 3). As discussed by the FDA, analysis of treatment effect by quartile of APACHE II score was a prespecified analysis, and therefore the APACHE II score was incorporated into the labeling of the approved product (3).

The cost of activated protein C may impede its use. Therefore, the analyses by Manns and colleagues are informative. Of note, their findings are corroborated in a recent study by Angus and colleagues (4), who had the advantage of access to actual short-term (d 1 to 28) resource utilization and hospital charges from a subset of PROWESS patients treated in the United States. Angus and colleagues determined that activated protein C costs $27 400 per quality-adjusted life-year when limited to patients with an APACHE II score ≥ 25. By way of comparison, the cost per quality–adjusted life-year for airbags (driver side only) is $28 000, for coronary artery bypass grafting (left main disease) $7100, for tissue-plasminogen activator compared with streptokinase (anterior myocardial infarction) $18 000, and for statins (secondary prevention) $1600 (4). Overall, therefore, the studies by Manns and colleagues and Angus and colleagues (4), using different methodologies, both indicate that use of activated protein C in patients with severe sepsis is associated with an acceptable cost-effectiveness profile when targeted to patients with the greatest severity of illness (e.g., an APACHE II score ≥ 25).

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