An economic evaluation of activated protein C treatment for severe sepsis
Manns B J, Lee H, Doig C J, Johnson D, Donaldson C

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of recombinant human activated protein C (Xigris, Eli Lilly) for patients admitted to the intensive care unit (ICU) for severe sepsis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised adult patients admitted to the ICU with severe sepsis.

Setting
The setting was tertiary care. The clinical trial data were from a multi-national randomised controlled trial. The economic analyses were carried out in Canada.

Dates to which data relate
The PROWESS clinical trial reported results in 2001 (study enrolment July 1998 - June 2000). The patients included in the cohort study were admitted to ICUs with suspected or known infection between 1 April 1996 and 31 March 1999. The cost data were calculated on the basis of 2001 Canadian dollars.

Source of effectiveness data
The effectiveness data were taken from a single trial (the PROWESS study) and a cohort study. The effectiveness data for conventional treatment came from the cohort study. Relative treatment effects for activated protein C were taken from the PROWESS trial, even though the comparator was placebo. The methods and results of the trial were reported elsewhere (Bernard et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The effectiveness data were derived from a single trial and a cohort study. The cost data were obtained from the cohort study (long-term costs from retrospective study) and from published sources (bleed costs and intervention cost).

Modelling
A cost-effectiveness model was constructed to estimate the costs and benefits associated with treatment, compared with conventional care. A Markov model was used to track weekly transitions between four health states. The four health states were being alive in the ICU, alive on the hospital ward, alive at home, and dead. There was a lifetime horizon.
Outcomes assessed in the review
The outcomes assessed were the relative risk of death and the absolute reduction in risk of death following conventional therapy and activated protein C.

Study designs and other criteria for inclusion in the review
There was no review of the literature. The effectiveness data were derived from a cohort study undertaken by the authors and the PROWESS clinical trial.

Sources searched to identify primary studies
Not relevant.

Criteria used to ensure the validity of primary studies
Not relevant.

Methods used to judge relevance and validity, and for extracting data
Not relevant.

Number of primary studies included
Two primary studies were included.

Methods of combining primary studies
Not relevant.

Investigation of differences between primary studies
Not relevant.

Results of the review
Treatment with drotrecogin alfa (activated) was associated with a reduction of 19.4% (6.6 to 30.5%) in the relative risk of death and an absolute reduction of 6.1% in the risk of death, (p=0.005).

The incidence of serious bleeding was higher in the treatment group (3.5%) than in the placebo group (2.0%), (p=0.06).

The PROWESS study did not originally report differences in THE effectiveness across sub-groups.

Methods used to derive estimates of effectiveness
The authors made assumptions to derive some estimates of effectiveness.

Estimates of effectiveness and key assumptions
A key assumption of the analysis was that the relative risk outcomes of activated protein C compared to placebo in the trial represented the relative risk of activated protein C compared with conventional treatment.

Measure of benefits used in the economic analysis
The measure of benefit was the life-years gained (LYG). The difference in mortality at 28 days from the trial results
was used to model the difference in LYG. The baseline analysis reported the LYG as the measure of benefit, thereafter the sensitivity analysis used quality-adjusted life-years (QALYs). The LYG were discounted at an annual rate of 5%.

**Direct costs**
The analysis included the category of hospital costs. These related to inpatient care, day surgery and emergency visits. The authors estimated the costs of conventional care from the cohort study and available costing data for the Calgary Health Region, Canada. The costs of care per week for the ICU and on the hospital ward were calculated. The follow-up costs for years 1 to 3 were also calculated. After year 3 it was assumed that these costs remained constant. Resource use and costs were not reported separately. The costs for treatment with activated protein C comprised acquisition cost per therapeutic course and a small cost attributed to the increased risk of serious bleeding. The cost for treating bleeding was calculated by multiplying the published cost for the treatment of clinically important gastrointestinal bleeding in the ICU by the excess risk of 1.5%. In other respects, the costs for the two groups were assumed to be equal. The costs were discounted at an annual rate of 5%.

**Statistical analysis of costs**
The costs were treated stochastically as part of the sensitivity analyses.

**Indirect Costs**
The indirect costs were calculated for use in sensitivity analyses. The authors used a published employment rate of 16.9% for patients under 61 years who were discharged from the ICU and were subsequently employed, and multiplied it by the average gross annual salary for a full-time Canadian worker (Can$33,384).

**Currency**
US dollars ($). These were converted from Canadian dollars (Can$) at a rate of $1 = Can$1.47.

**Sensitivity analysis**
Sensitivity analyses presenting supplementary cost-utility estimates of the cost per QALY were reported. The authors used 0.6 as the utility value for the cost-utility analysis. This estimate was a published estimate of the overall health-related quality of life, one year after hospital discharge, in a group of patients admitted to the ICU with acute respiratory distress syndrome. This estimate was varied in further sensitivity analyses. Other sensitivity analyses addressed relative risk estimates, in-hospital and subsequent death rates. Sensitivity analyses were also undertaken on the estimate of cost of hospital care and subsequent health care, and on the cost of activated protein C treatment. The discount rates were varied in sensitivity analyses. In addition to these univariate sensitivity analyses, a Monte Carlo simulation was performed to simultaneously consider the sensitivity of all variables for which the estimates were uncertain.

**Estimated benefits used in the economic analysis**
The incremental gain in life-years per patient, for all patients, was 0.38 for the use of activated protein C in comparison with conventional treatment.

The incremental gains in life-years per patient by APACHE II score were r0.01 for scores of less than or equal to 24, and 0.76 for scores greater than or equal to 25.

The incremental gains in life-years per patient by age were 0.30 for under 40-year-olds, 0.40 for 40- to 59-year-olds, 0.40 for 60- to 79-year-olds, and 0.32 for 80 years and older.

When calculating the QALYS, the study used a QALY value of 0.6 in the baseline analysis. This QALY estimate was derived from a study reporting the quality of life (1 year after discharge) in a group of patients admitted to the ICU with acute respiratory distress syndrome. Discounted benefits (5%) were reported.
Cost results
The mean health care costs after hospital discharge for all patients were $14,181 per patient in year 1, $4,698 in year 2 and $4,579 in year 3 (year 3 costs were used for subsequent years). These costs were all presented by age group and APACHE II score groupings (<=24 and >=25).

Synthesis of costs and benefits
The cost and benefits were combined by calculating a cost-effectiveness ratio for the cost per LYG in the baseline analysis, and for the cost per QALY in the sensitivity analyses.

The incremental cost per LYG for all patients was $27,936. The costs and benefits were discounted at 5%.

The cost per QALY was $46,560.

The cost per LYG varied between $25,991 and $32,393 among age groups.

Where the study used data from the Food and Drug Administration (FDA)'s analysis of the PROWESS study, the cost per LYG was $19,723 for those patients with an APACHE II score of at least 25, and $575,054 for those with a score of less than or equal to 24. The cost per QALY results were $32,872 (>=25) and $958,423 (<=24), respectively.

Various sensitivity analyses were performed, including Monte Carlo simulations. The results were sensitive to estimates of the relative risk of death associated with activated protein C. The results shown above indicate the differences in subgroups by APACHE II score. The Monte Carlo simulation indicated there was an 86% probability that the use of activated protein C for all patients with severe sepsis would be cost-effective if one were willing to pay $50,000 per QALY.

Authors' conclusions
Activated protein C is relatively cost-effective when targeted at patients with severe sepsis, greater severity of illness (APACHE II score of 25 or more), and a reasonable life expectancy if they survive the episode of severe sepsis.

CRD COMMENTARY - Selection of comparators
The comparator was conventional care and the rationale for this was clear.

Validity of estimate of effectiveness:
The estimates of effectiveness, used to derive the parameters for a Markov model to calculate the LYG, were derived from a cohort study and the PROWESS clinical trial. A cohort study is an appropriate source from which to derive transition probabilities. A major assumption was made, which was that the relative effect of activated protein C in comparison with placebo (from the trial) reasonably reflected conventional treatment. It is hard to assess if this was appropriate, as conventional treatment was not clearly defined.

Validity of estimate of measure of benefit
The measure of benefit was the LYG and this was influenced by the life expectancy of survivors of severe sepsis and the additional number of survivors in the treatment (activated protein C) group.

The quality of life estimates used in the sensitivity analysis were from published estimates of quality of life in a patient group with acute respiratory distress syndrome. The authors cited a reference, which drew similarities between this patient group and the severe sepsis patient group. There was an absence of data on QALY values for severe sepsis. Therefore, there will remain some uncertainty over the validity of the QALY estimate used in this study. However, the authors did report a sensitivity analysis on the QALY value used.
Validity of estimate of costs
The baseline analysis was limited to the direct costs, with other indirect costs being considered in the sensitivity analyses. The study did not report the disaggregated total costs for each group, and the exact costing methodology used in the analysis was unclear. The study stated the additional costs (activated protein C and bleed costs) in the treatment group, but the model structure indicated that the hospital (ICU and ward) costs also formed part of the model structure.

The cost-effectiveness analysis used the long-term health care costs for the survivors of severe sepsis, but this issue may be open to some methodological debate. The study provided sensitivity analyses with some alterations to these costs, but did not provide cost-effectiveness estimates that excluded the long-term health care costs for survivors.

Other issues
The issue of generalisability to other patient groups should be considered in the context of the baseline risks of the group. This study used Canadian data with 28-day mortality at 30.7% for all patients with severe sepsis. This varied from 12.4 to 43.1% by age group, and from 18.5 to 54.5% according to APACHE II scores (<=24 and <=25, respectively). The economic evaluation used FDA data from a post hoc analysis of the PROWESS study to consider differential benefits according to APACHE II score. The authors of this study stated that the results of the sub-group analyses by APACHE II score were dependent on the validity of the analysis performed by the FDA.

Implications of the study
The findings from this study suggested that it may be reasonable to restrict the use of activated protein C to patients (in Canada and the USA) with APACHE II scores of at least 25, until further evidence is available. The study indicated that treatment may best be targeted at patients with greater severity of illness (APACHE II score of 25 or more), and a reasonable life expectancy if they survive the episode of severe sepsis. This may have equity implications in relation to age and severity of illness.

Source of funding
Supported by a grant from the Institute of Health Economics, Edmonton (AB), Canada.

Bibliographic details

PubMedID
12324556

DOI
10.1056/NEJMsa020969

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
APACHE; Adult; Aged; Aged, 80 and over; Anti-Inflammatory Agents, Non-Steroidal /economics /therapeutic use; Cost-Benefit Analysis; Female; Humans; Male; Middle Aged; Protein C /economics /therapeutic use; Quality-Adjusted Life Years; Recombinant Proteins /economics /therapeutic use; Risk; Sepsis /classification /drug therapy /economics /mortality; Value of Life

**AccessionNumber**
22002008247

**Date bibliographic record published**
31/05/2004

**Date abstract record published**
31/05/2004