Cost-effectiveness of recombinant human activated protein C and the influence of severity of illness in the treatment of patients with severe sepsis

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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 (drotrecogin alfa) for patients with severe sepsis who were being treated in an intensive care unit (ICU). Four strategies were compared:

all patients were treated with usual anti-infective therapy and support care (strategy 1);

all patients were treated with rhAPC in addition to usual therapy (strategy 2);

combined treatment with rhAPC and usual therapy for patients with very severe sepsis (APACHE 11 score of at least 25) (strategy 3); and

combined treatment with rhAPC and usual therapy for only those patients with less severe sepsis (APACHE 11 score of less than 25) (strategy 4).

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of patients suffering from severe sepsis that matched the patients' characteristics in the PROWESS trial (see Other Publications of Related Interest). Patients were excluded if they were under 18 years of age, had a condition with increased risk of bleeding or thrombosis, or had poorly controlled neoplasm or other end-stage disease. They were also excluded if they were expected to die within 28 days.

Setting
The setting was secondary care (the initial phase of treatment, at least, was conducted in an ICU). The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were taken from the PROWESS trial (2001) and other studies published between 1989 and 1995. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived mainly from a single study (PROWESS study), although the authors also made ad-hoc use of other published studies.
Modelling
A Markov model was used to assess the cost-effectiveness of the treatment strategies for severe sepsis. The model described the course of each patient through the acute phase of a septic illness, including all the risks or adverse events associated with the treatment and disease. All patients who survived the initial septic illness entered into the Markov model to capture the benefits and costs of survival, both immediate and long-term. The patients were followed for the duration of their lifetime.

Outcomes assessed in the review
The outcomes assessed in the review were the probabilities of the following:
- early complications with both usual treatment and rhAPC treatment;
- early death with and without rhAPC treatment;
- early death with very severe sepsis, with and without rhAPC treatment;
- early death with less severe sepsis, with and without rhAPC treatment;
- early death with protein C deficiency, with and without rhAPC treatment;
- early death with normal protein C activity, with and without rhAPC treatment; and
- late age-related death.

Study designs and other criteria for inclusion in the review
The effectiveness data were obtained mainly from a large worldwide study (PROWESS trial). No other inclusion criteria were reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported. However, the majority of the data were retrieved from the PROWESS study.

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

Number of primary studies included
The effectiveness data were derived from 6 primary studies. The utility data were derived from a further 3 studies.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Point estimates and ranges for all the outcomes assessed in the review were reported in full. Point estimates and ranges were also reported for the utility data.

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

**Estimates of effectiveness and key assumptions**
The authors assumed that rhAPC administration itself had no direct effect on utilities. They also assumed that, independent of whether the patient received usual care or rhAPC, sepsis would increase the patient's mortality risk by the same amount.

**Measure of benefits used in the economic analysis**
The measures of benefit were the quality-adjusted life-years (QALYs) and the life-years gained. These were obtained through the model. All the benefits were discounted at a rate of 3%, with 0% and 5% used in the sensitivity analysis.

**Direct costs**
The study included the costs of initial treatment with rhAPC, acute complications (serious bleeds), hospitalisation and future health care for survivors of severe sepsis. The model also included a cost for death ($5,310), which was from a published estimate. The cost data for serious gastrointestinal bleeds were from US Medicare (estimate of $1,237 per event). The cost of rhAPC was estimated for a person weighing 70 kg ($6,700). The cost data for hospitalisation were from an observational cohort study of hospital discharge records (1995) for several large US states. The hospitalisation cost (acute sepsis care) was estimated to be $24,332 (in 2001 US dollars). Future health care costs were from age-specific medical expenditure data for the US (1998) for people aged 55 - 64 years, 65 - 74 years and 75 years. The resource use and costs were not reported separately. The costs were discounted at an annual rate of 3%, with 0% and 5% in used in the sensitivity analysis. The price year was 2001.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The study did not refer to the indirect costs.

**Currency**
US dollars ($). These were converted to 2001 values using a gross domestic product deflator.

**Sensitivity analysis**
One-way sensitivity analyses were undertaken. Where pairs of variables were found to be influential, a multi-way sensitivity analysis was undertaken. The authors stated that Monte Carlo methods were used for model variables, assuming log normal distributions for cost inputs, and norm or logistic distributions for probabilities and health state utilities.

Sensitivity analyses were run on all the cost, probability and utility inputs where assumptions were made in the model. One-way sensitivity analyses were also conducted on variables with most clinical relevance.

Analyses were also conducted for various patient groups, according to the severity of illness (APACHE II score) and protein C deficiency (or normal protein C levels).
Estimated benefits used in the economic analysis
For all patients, treatment with rhAPC resulted in 6.63 QALYs (8.31 life-years), while treatment with usual care resulted in 6.09 QALYs (7.63 life-years). The net difference was 0.54 QALYs (0.68 life-years). The short-term 28-day survival was 0.061 lives saved per treated patient.

For patients with less severe sepsis (APACHE II score less than 25), treatment with rhAPC resulted in 7.15 QALYs (8.94 life-years), while treatment with usual care resulted in 7.13 QALYs (8.92 life-years). The net difference was 0.017 QALYs (0.02 life-years). The short-term 28-day survival was 0.002 lives saved per treated patient.

For patients with very severe sepsis (APACHE II score at least 25), treatment with rhAPC resulted in 6.08 QALYs (7.60 life-years), while treatment with normal care resulted in 4.96 QALYs (6.20 life-years). The net difference was 1.12 QALYs (1.4 life-years). The short-term 28-day survival was 0.128 lives saved per treated patient.

Cost results
For analysis including all patients, the total costs were $61,751 for treatment with rhAPC and $51,006 for usual care. The net difference was $10,745.

For patients with less severe sepsis (APACHE II score less than 25), the total costs were $65,645 for treatment with rhAPC and $57,794 for usual care. The net difference was $6,851.

For patients with very severe sepsis (APACHE II score at least 25), the total costs were $57,659 for treatment with rhAPC and $42,493 for usual care. The net difference was $15,166.

Synthesis of costs and benefits
The incremental cost-effectiveness ratio (ICER) for the all patients analysis was $20,047 per QALY and $15,801 per life-year saved.

The ICER for patients with less severe sepsis (APACHE II score less than 25) was $403,000 per QALY and $342,550 per life-year saved.

The ICER for patients with very severe sepsis (APACHE II score at least 25) was $13,493 per QALY and $10,833 per life-year saved.

The study reported a cost per QALY of $7,503 for treating patients with protein C deficiency with rhAPC.

No significant differences were reported when sensitivity analyses were undertaken. The authors reported the results of the probabilistic sensitivity analysis, which suggested that 95% of the 10,000 simulated ICERs for using rhAPC to treat very severe sepsis would be between $9,400 and $25,400 per QALY.

Authors’ conclusions
Recombinant human activated protein C (rhAPC) is a cost-effective treatment for the population of patients with very severe sepsis, as described by an APACHE II score of at least 25 in the PROWESS trial. When treating patients with less severe sepsis (APACHE II score less than 25), rhAPC does not appear to be cost-effective by generally accepted standards. Treatment in a pooled population of patients with severe sepsis may appear cost-effective. Patients with less severe sepsis should generally not be treated with rhAPC, as it has negligible effectiveness and is not cost-effective.

CRD COMMENTARY - Selection of comparators
The comparator was usual care and the rationale for this choice was clear. It was standard practice in the authors’ setting. You should decide if it represents a valid comparator in your own setting.

Validity of estimate of effectiveness.
The authors did not undertake a systematic review of the literature to inform the model parameters. However, the majority of the data were derived from a single source, which, given its size and design, is likely to have had high internal validity. Despite this, it was not apparent whether there may have been alternative sources of evidence that the authors neglected to include. As such, a systematic review would have ensured that any potential biases were minimised. Where data other than those obtained from the PROWESS study were used, the authors did not report whether there were any differences in the studies used or how any synthesis of the estimates was undertaken. The uncertainty surrounding all assumptions and input values was investigated in the sensitivity analysis. In addition, the authors stated that survival rates had been adjusted to reflect the rates of acute complications, although it was unclear from the description of the model how this was done.

Validity of estimate of measure of benefit
The QALYs and life-years gained were selected as the summary benefit measures in the economic evaluation. Both appear to have been appropriate. The use of QALYs (life-years gained) allows comparisons to be made with the benefits of other treatments. Both measures were obtained through the model. Discounting was conducted, although its applicability to benefits is still a controversial issue. The total benefits gained with each strategy and incremental gains were both reported.

Validity of estimate of costs
The perspective of the study was stated to have been societal, but it was unclear whether the indirect costs were included in the analysis. The omission of the indirect costs would mean that the perspective was not societal and, in fact, the study appears to have been undertaken from the perspective of the hospital. The methods used to estimate the cost data appear reasonable. The costs and the quantities were not reported separately, which may hinder the generalisability of the results. The costs were derived using the hospital-specific cost-to-charge ratios. In addition, the authors also used long-term health care costs in their analysis, which may be open to some methodological debate. Discounting was conducted and the rate was varied in the sensitivity analysis. The price year was reported, which will aid any future reflation exercise.

Other issues
The authors undertook limited comparisons with other studies in the same area, but did not directly address the issue of generalisability. However, they did undertake substantial sensitivity analyses, including a Monte Carlo simulation, all of which help to show the robustness of the results obtained. The authors do not appear to have reported their results selectively and the conclusions reached are within the scope of the analysis. The authors reported some of the limitations of their study, but provided only limited detail.

Implications of the study
The findings from this study suggested that it may be reasonable to restrict the use of rhAPC (in the USA) to patients with APACHE II scores of 25 or more, until further evidence is available.

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None stated.

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Other publications of related interest


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