Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom

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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
Two treatment strategies for severe sepsis in patients with multiple organ failure were compared, drotrecogin alfa (activated) and placebo (best usual care). Drotrecogin alfa (activated) was supplied in 5-mg vials and was administered as a 96-hour intravenous infusion of 24 microg/kg per hour.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population was a cohort of patients with severe sepsis and multiple organ failure.

Setting
The setting was tertiary care, adult ICUs. The economic study was carried out in the UK.

Dates to which data relate
The studies providing the effectiveness evidence dated from 2001 to 2003, while those supplying the cost data were from 1997 to 2003. The price year was 2002.

Source of effectiveness data
The estimates of effectiveness were derived from a review or synthesis of published studies and authors’ assumptions.

Modelling
An epidemiologic model was used to derive the likely benefits and costs of the treatment strategies. The study combined patient-specific data from a clinical trial, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS study), and the follow-up study (called EVBI), with secondary data sources to model the relevant costs and long-term outcomes in the UK. The analyses were based on absolute risk reductions, with a sensitivity analysis performed on key parameters. Two analyses were performed. One was based on the 28-day all-cause hospital mortality, while the other employed the final observed all-cause hospital mortality.

Outcomes assessed in the review
The outcomes considered in the study were survival after discharge, absolute risk reductions, and ICU and hospital length of stay.
Study designs and other criteria for inclusion in the review
The main sources of effectiveness were a clinical trial and a long-term follow-up study (PROWESS study, Bernard et al. 2001, and EVBI study, Angus et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details). Other study designs, used to extrapolate results to the UK setting, included cohort studies and secondary UK databases.

Sources searched to identify primary studies
Not reported.

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

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

Number of primary studies included
The authors reported that at least 12 primary studies were included in the review for different purposes.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
The authors did not investigate any differences between the primary studies, nor provide an explanation of such differences. They also did not investigate how these differences affected the estimate of effectiveness.

Results of the review
In patients with two or more organ dysfunctions in the PROWESS study, the absolute risk reduction was 7.3% in 28-day all-cause hospital mortality, (p=0.005) and 4.6% at final hospital discharge, (p=0.086).

The patterns of length of stay, when stratified by survivors and non-survivors, showed very similar lengths of stay. This suggested that an adjustment of UK data for differences in length of stay for patients who received drotrecogin alfa (activated) was not required.

Survival curves and Kaplan-Meier curves for each gender were graphically reported from one of the UK databases. For survival after discharge, 99 patients (50 females) survived at least 60 days after discharge and were assumed to be hospital survivors. The relative risks obtained, from Cox proportional hazards models, for increasing age (per year) were 1.058 (95% confidence interval, CI: 1.001 - 1.117) for females and 1.049 (95% CI: 1.009 - 1.091) for males.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
The authors made several key assumptions. They assumed that deaths among the cohort 60 days after admission to the ICU were after discharge from hospital, as the actual day of discharge was not available. They also assumed that the impact of bleeding events was offset by other differences in adverse events or benefits to the patients, thus bleeding
events were not included.

Measure of benefits used in the economic analysis
The authors used life-years (LYs) and quality-adjusted life-years (QALYs) gained as the measures of benefit. The LYs gained for survivors in the placebo and drotrecogin alfa (activated) arms were calculated by averaging the expected survival of all patients according to age and gender. The QALYs were estimated on the basis of a single utility estimate for survivors of severe sepsis (0.69), applied over the remaining lifetime of all patients. The utility data were derived from a published study, but there was no discussion of the methods used in the literature to derive the utility weights.

The LYs were discounted at a rate of 1.5%.

Direct costs
In-hospital medical direct costs were included in the analysis. These were for stay in the ICU, stay in the ward and drotrecogin alfa (activated). The costs related to severe sepsis that were incurred after discharge from the hospital were not included. According to the authors, no future general health care costs were included, as advised by the National Institute for Clinical Excellence (NICE) in the UK.

The costs were adjusted to 2002, although the method was not reported. Estimations of the quantities and total costs were derived using modelling and from published literature. The resource quantities and the costs were reported separately. The source of the cost data was published medical and government literature. The costs were discounted but the rate was not explicitly reported.

Statistical analysis of costs
In the analysis that used data from the EVBI study (reporting final hospital outcome analysis), the difference in costs and the 95% CIs were calculated using the nonparametric bootstrap method.

Indirect Costs
The indirect costs were not reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
The effects of changes in cost assumptions, length of stay, discounting, utility and hospital mortality were examined for both analyses (i.e. 28-day all-cause hospital mortality and the final observed all-cause hospital mortality). A two-way sensitivity analysis of utility and absolute risk reduction was presented graphically. The method used to select the ranges was not reported.

Estimated benefits used in the economic analysis
The undiscounted mean life expectancy of hospital survivors was similar in both analyses. For the analysis based on 28-day outcomes, the results in LYs per survivor (discounted) were 17.88 (14.05) for placebo and 18.10 (14.18) for drotrecogin alfa (activated). The corresponding results for the analysis based on final hospital outcome were 18.23 (14.32) LYs per survivor for placebo and 18.45 (14.38) LYs per survivor for drotrecogin alfa (activated).

The LYs were 9.38 for the placebo arm and 10.49 for the drotrecogin alfa (activated) arm, accounting for 1.12 years gained in the analysis based on 28-day outcomes. The LYs were 9.03 (placebo) and 9.73 (drotrecogin alfa, respectively, accounting for 0.71 years gained (95% CI: 0.49 - 1.89) in the analysis based on final hospital outcome.
The QALYs were 6.47 for the placebo arm and 7.24 for the drotrecogin alfa (activated) arm, accounting for a gain of 0.77 QALYs gained in the analysis based on 28-day outcomes. The QALYs were 6.23 (placebo) and 6.72 (drotrecogin alfa), accounting for a gain of 0.41 additional QALYs (95% CI: 0.34 - 1.30) in the analysis based on final hospital outcome.

**Cost results**
The total costs were 18,132 for the placebo arm and 23,271 for the drotrecogin alfa (activated) arm in the analysis based on 28-day outcomes, and 17,110 (placebo) and 22,496 (drotrecogin alfa), respectively, in the analysis based on final hospital outcome. These figures represented incremental discounted costs of 5,139 in the analysis based on 28-day outcomes and 5,387 (95% CI: 4,779 - 6,012) in the analysis based on final hospital outcome, mainly due to the drotrecogin alfa (activated) cost.

**Synthesis of costs and benefits**
The cost per QALY was 6,679 in the analysis based on 28-day outcomes and 11,051 in the analysis based on final hospital outcome. The costs per LY gained were 4,608 (28-day outcomes) and 7,625 (final hospital outcome), respectively.

Bootstrapping of the final hospital outcome analysis yielded the cost-effectiveness acceptability curves which were reported graphically. The probability that drotrecogin alfa (activated) was cost-effective in comparison with standard care alone was almost 80% at the widely conjectured limit of 30,000 per QALY for cost-effectiveness in the UK.

The greatest sensitivity of cost-effectiveness was to discounting or the downward adjustment of quality-adjusted life expectancy. A two-way sensitivity analysis of utility and absolute risk reduction showed that drotrecogin alfa (activated) remained cost-effective even at much lower absolute risk reductions than those observed in the follow-up study, so long as the quality-adjusted life expectancy remained reasonably good. Equally, with larger absolute risk reductions, drotrecogin alfa (activated) remained cost-effective in patients with sharply reduced quality-adjusted life expectancy. The analysis indicated that whilst the cost per QALY rose with lower utility estimates, the ratios remained well within the limits of acceptable cost-effectiveness ratios currently discussed in the UK.

**Authors’ conclusions**
The study showed the treatment of severe sepsis in the UK to be cost-effective. Although the cost of treatment with drotrecogin alfa (activated) appeared to be high, the cost per quality-adjusted life-year (QALY) was modest. Thus, drotrecogin alfa (activated) represented a cost-effective option for treatment.

**CRD COMMENTARY - Selection of comparators**
The authors gave a justification for the comparators. The European Commission had approved drotrecogin alfa (activated) for the treatment of adult patients with severe sepsis and multiple organ failure on the basis of the PROWESS study, which compared drotrecogin alfa (activated) with a placebo. You should judge whether these treatment strategies are relevant in your own setting, or whether other comparators from other drugs could also be relevant.

**Validity of estimate of measure of effectiveness**
The authors did not state that a systematic review of the literature had been undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors used data from the available studies selectively. One cannot be sure that all the relevant literature was identified, although large clinical trials and follow-up studies were used to derive the effectiveness, and were applied to local databases to derive locally relevant results. In addition, few authors’ assumptions were made.

The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, experts’ opinions and their own assumptions. The effectiveness evidence was derived from a clinical trial,
which is an adequate source for estimating effectiveness. The authors justified their assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses using ranges from the literature, but the authors did not justify the ranges selected and reported.

Validity of estimate of measure of benefit
The authors used QALYs as a measure of benefits. The QALYs were derived by modelling. This measure of benefit enables comparisons across health technologies. The methods used in the literature to derive the utility weights were not reported. Sensitivity analyses over adjusted QALYs were conducted, although the method used to select the ranges was not reported.

Validity of estimate of costs
The authors reported that the study had been conducted from the perspective of the National Health Service. Only in-hospital medical direct costs were included, but they were not reported in sufficient detail. Costs after discharge were not included. The resource quantities and the prices were reported separately, which enhances the reproducibility of the results. The unit costs were taken from published sources, and the authors calculated the costs of drug vials using published literature. A statistical analysis of the costs was undertaken when possible. Sensitivity analyses of selected direct costs were conducted and were reported to have assessed the robustness of the estimates used. A discount rate for the costs was not explicitly reported, but the authors stated that the incremental costs were discounted. A revaluation of the costs was carried out and the price year was reported, which will aid any future reflation exercise.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. They explicitly addressed the generalisability of the results and considered assessing the impact of population heterogeneity. The authors' conclusions reflected the scope of the analysis. The authors did not state any limitations explicitly but they reported that they estimated QALYs on the basis of a single utility estimate for survivors of severe sepsis, applied over the remaining lifetime of all patients. They also reported that they did not have data on the costs relating to severe sepsis that were incurred after discharge from the hospital, which ideally would have been included in the analysis. In addition, some criteria to identify patients in the parent studies were different from those used in the local data studies, although these were more appropriate for modelling UK cost-effectiveness.

Implications of the study
The introduction of drotrecogin alfa (activated) into clinical practice was one of the five new and effective treatment modalities that have recently advanced the care of the critically ill. Even the most conservative estimate of cost per QALY (11,051) was well below the 20,000 - 30,000 range at which NICE begins to look more carefully at the economic justification for approval of technologies.

Following its appraisal of drotrecogin alfa (activated), which included consideration of this analysis and that of a similar model used by the independent assessment group with very similar results, NICE has recommended that drotrecogin alfa (activated) is used in the treatment of “adult patients who have severe sepsis that has resulted in multiple organ failure (that is, two or more major organs have failed) and who are being provided with optimum intensive care support”.

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Other publications of related interest


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