Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis

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 drotrecogin alfa (activated), a recombinant form of human activated protein C (Xigris, Eli Lilly).

Type of intervention
Treatment.

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

Study population
The study population comprised adults presenting with severe sepsis. Severe sepsis was defined as suspected or proven infection, evidence of systematic inflammation (3 or more systemic inflammatory response syndrome criteria), and sepsis-induced dysfunction of one or more organ systems. Patients excluded were those at high risk of bleeding, pregnant or breast-feeding women, and those weighing in excess of 135 kg. Also excluded were those who were expected to die of a non-sepsis-related disease within one month and those with severe human immunodeficiency virus.

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

Dates to which data relate
The economic evaluation was performed alongside the clinical trial, which reported results in 2001 (study enrolment July 1998 to June 2000). The costs were reported in US dollars for the year 2000.

Source of effectiveness data
The effectiveness data were from the related clinical trial (the PROWESS study), the methods and results of which were reported elsewhere (Bernard et al., see Other Publications of Related Interest).

Link between effectiveness and cost data
The effectiveness parameters on mortality were from the associated clinical trial. These data were used to model the long-term mortality or survival effects. Differences in cost over the first 28 days were from the clinical trial data. The study used a cost cohort, which was a sub-set of the trial patients, comprising 552 of the 705 US patients. Other sources of cost data were used for the cost-effectiveness analysis.

Study sample
The authors did not report whether a sample size was determined in the planning phase of the PROWESS study. The
clinical trial enrolled patients with known or suspected infection on the basis of clinical data at the time of screening. Of the 1,728 patients who underwent randomisation (1:1), 1,690 received the study drug (n=850) or placebo (n=840).

**Study design**
This was a multi-centre, randomised placebo-controlled trial (phase III). It involved 164 centres across 11 countries. No information was provided on how the participants were allocated to the groups, or if any blinding was carried out. The collection of clinical data in the trial was limited to 28 days after randomisation. The authors made reference to the clinical paper by Bernard et al (see "Other Publications of Related Interest" below).

**Analysis of effectiveness**
The analysis of effectiveness was conducted on an intention to treat basis. The primary clinical end point was 28-day all-cause mortality. At baseline, the demographic characteristics and severity of disease were similar in the placebo and treatment groups.

**Effectiveness results**
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 report any differences in effectiveness across the sub-groups.

**Clinical conclusions**
Treatment with drotrecogin alfa activated significantly reduced mortality in patients with severe sepsis, but may be associated with an increased risk of bleeding.

**Modelling**
A model was used to extrapolate the life time benefits and costs from the outcomes of the clinical trial.

**Measure of benefits used in the economic analysis**
The base-case analysis reported the incremental effect as the difference in the primary clinical end point of 28-day all-cause mortality, and estimated cost per life saved. The reference case analysis estimated the incremental effect as the number of life-years and quality-adjusted life-years (QALYs) gained. A model was used to calculate the number of life-years gained (LYG), generating an age- and gender-specific life expectancy for each 28-day survivor, from US life tables. There was an adjustment of life expectancy to allow for the increased risk of death for survivors of severe sepsis. The QALYS were estimated using general population values from the Beaver Dam Health Outcomes Study, a longitudinal cohort study. These values were adjusted to allow for the reduced quality of life in survivors of severe sepsis compared to general population norms.

**Direct costs**
The cost categories included in the analysis were unclear. The health care costs were for hospital, physician, drug and post-discharge costs. The post-discharge costs included acute hospital care, care in a nursing home, and formal or informal care. Therefore, the health service costs and some patient or patient relatives' costs were included.

Differences in health care costs between the treatment and placebo groups were estimated using a cost cohort of trial patients, comprising 552 of the 705 US patients (those patients for whom billing data were available prior to unblinding of the dataset). The costs of the study drug were estimated using dose data from the trial and the price per vial. The post-discharge costs up to day 28 were estimated by assigning a daily rate depending on location and summing over all days. Daily rate data were from published sources. The post-day 28 costs were estimated using age-specific annual health care costs form the 1987 National Medical Expenditure Survey projected to year 2000 costs by the National Centre for...
Health Statistics. There was some additional adjustment (using a published source) to allow for nursing home costs. An age-specific cost was estimated, based on the predicted remaining years of life. This made an allowance for the fact that sepsis survivors incurred higher costs in comparison with age-matched general population data.

The base-case analyses used institution-specific charges. The cost estimates were adjusted to year 2000 US dollars, using the Consumer Price Index, with adjustment for physician costs. Hospital stay and cost data were reported separately. The reference case analysis used day 1 to 28 costs (base-case costs), plus post-day 28 lifetime costs for survivors. The future costs were discounted at a rate of 3%. In the cost-effectiveness analysis, the study adjusted the cost estimates to correct for imbalances between the make-up of the cost cohort and the overall trial cohort, by deriving an average cost adjusted to the proportions of survivors and nonsurvivors and the proportions of surgical and nonsurgical patients.

**Statistical analysis of costs**
To estimate distributions around the mean cost-effectiveness findings, the study generated simulations using bootstrapping with replacement. Simulations were conducted using Datadesk and SAS software.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Various sensitivity analyses were undertaken. A one-way sensitivity analysis was undertaken on the base-case estimates of hospital costs, post-discharge to day-28 costs, intervention drug costs, lifetime survival and utilities. All were varied by 25% each way. The physician costs were varied from half to double the original estimate. The reference cost-effectiveness analysis was undertaken without long-term costs, and all the parameters were varied and presented in a tornado diagram. For the reference case, a two-way sensitivity was undertaken on life expectancy estimates and average annual utility estimates. The analysis was undertaken on US patients only. A sensitivity analysis was also undertaken on the discount rates, and adjustment to the risk of death in survivors of severe sepsis. A sub-group analysis was also undertaken for a wide range of groupings, with the cost-effectiveness results presented using confidence ellipses.

**Estimated benefits used in the economic analysis**
The PROWESS clinical trial reported mortality rates of 30.8% for placebo and 24.7% for drotrecogin alfa (activated), (p=0.005). This survival benefit was used for the base-case cost-effectiveness analysis.

The survival effect was 0.061 (0.022 lives saved per treated patient).

For the reference case analysis, the average 28-day survivor was 58.1 years old and was projected to live an additional 12.3 years at an average utility of 0.68, yielding 8.5 QALYS.

The incremental LYG were 0.48 (+/- 0.29) and the incremental QALYS were 0.33 (+/- 0.21) per treated patient.

The future benefits were discounted at a rate of 3%.

**Cost results**
In the short-term base-case analysis, drotrecogin alfa (activated) increased the costs by $9,800 (+/- 2,900).

In the lifetime reference case analysis, drotrecogin alfa (activated) increased the costs by $16,000 (+/- 4,200) per treated patient; $6,200 of this cost was attributed to long-term post-day 28 costs.
The total intervention costs and comparator costs were reported for all patients (mean per patient costs, without a measure of distribution), but these did not reflect the costs used in the cost-effectiveness ratios. The costs used in the ratios were adjusted cost estimates to correct for imbalances between the cost cohort and the overall trial cohort.

The future costs were discounted at a rate of 3%.

**Synthesis of costs and benefits**

The costs and benefits were combined by calculating a cost-effectiveness ratio for the cost per life saved (base-case analysis), plus the cost per LYG and cost per QALY gained in the reference case analysis.

The base-case analysis reported a cost of $160,000 per life saved, with 84.7% and 97.9% probabilities that the ratio was less than $250,000 and less than $500,000 per life saved, respectively.

Under the lifetime reference cost analysis, the cost per LYG was $33,300, with an 89.1% probability that the ratio was less than $100,000. The cost per QALY was $48,800, with an 82% probability that the ratio was less than $100,000.

The study reported that the base-case and reference case cost-effectiveness results were generally robust to assumptions and estimates of costs and effects.

The reference case cost-effectiveness was most sensitive to changes in effects.

The results for the US-only analysis were better than for the overall trial cohort.

In the sub-group analyses, the cost-effectiveness ellipses tended to overlap, indicating no difference. However, older patients had worse cost-effectiveness findings due to fewer projected life-years. In addition, drotrecogin alfa (activated) was indicated to be more cost-effective in patients with higher APACHE II scores, at $27,400 per QALY for the upper two APACHE II quartiles (score ≥ 25). Treatment with drotrecogin alfa (activated) appeared cost-ineffective in the lower two APACHE II quartiles (score < 25), with negative QALY findings.

**Authors’ conclusions**

The use of drotrecogin alfa (activated) in patients with severe sepsis was associated with a favourable cost-effectiveness profile, especially if restricted to the Food and Drug Administration approved use (i.e. in more severe patient groups, such as those with an APACHE II score of at least 25).

**CRD COMMENTARY - Selection of comparators**

The comparator was placebo, as detailed in the clinical trial (PROWESS), and the rationale for this was clear.

**Validity of estimate of measure of effectiveness**

The measure of effectiveness was based on a large, international randomised controlled trial. The authors did not report the methodology of the trial in detail, referring instead to the clinical paper by Bernard et al (see “Other Publications of Related Interest” below). For this reason it is not possible to assess the internal validity of this trial from the information given in the present paper.

**Validity of estimate of measure of benefit**

The measure of effect was lives saved in the base-case analysis and life-years or QALYs gained in the reference case. The base-case directly applied the mortality results from the clinical trial. Therefore, the validity of the estimate was robust. Data on health state values applicable to survivors of severe sepsis were not available, so the study used values from an earlier experimental exercise, which modelled values for the US general population. There remain some methodological questions in relation to this exercise. The analysis then made assumptions about which values to use in the derivation of QALYs gained, making allowances for the expected reduced quality of life and survival in survivors of severe sepsis, compared to matched population norms. Such assumptions may be valid, but there are methodological...
issues that remain uncertain in this approach.

Validity of estimate of costs
The perspective of the study was stated to have been societal. Given this perspective, productivity costs and possibly patient costs other than informal care costs could have been included in the analysis, but were not. The base-case costs were limited to a 28-day cost estimate, using trial data for the intervention and a cost cohort for hospital cost estimates. The cost cohort comprised US patients with billing data. The methods used in the cost-effectiveness analysis indicated that the cost cohort had a different clinical profile to the broader trial population. This gives rise to some uncertainty over the validity of the cost estimates. The unit costs and the quantities were reported separately in some cases.

The reference cost analysis used the base-case 28-day cost estimate, therefore the above applies equally to the reference case analysis. Further, for the reference cost analysis, assumptions were made about the make up over longer-term costs for survivors of severe sepsis. These assumptions lead to uncertainty over the cost estimates used, especially since the post-day 28 costs constituted around 70% or more of the total cost for the treatment and placebo groups.

The study did not report the actual disaggregated total costs for each group that were used in the cost-effectiveness findings. An adjustment was made in the cost-effectiveness analysis to correct for imbalances between the cost cohort and the trial population.

The reference case cost-effectiveness analysis used long-term health care costs for survivors of severe sepsis, and this issue may be open to some methodological debate. However, the authors did report cost-effectiveness findings excluding the long-term costs.

Other issues
The authors did not compare their results with those of other studies. The issue of generalisability was addressed. The authors noted that the results were applicable to a patient population in the controlled environment of a randomised controlled trial. The authors also thought that the range of patient characteristics was not sufficiently broad to be representative of the target population. The study results were appropriately reported and the conclusions reflected the scope of the analysis.

Implications of the study
The findings from this study suggested that drotrecogin alfa (activated) is cost-effective. However, it may be reasonable to restrict the use of drotrecogin alfa (activated) to patients with APACHE II scores of at least 25. The study indicated that treatment may best be targeted to patients with greater severity of illness (APACHE II score ≥ 25), and a reasonable life expectancy if they survive the episode of severe sepsis. This has equity implications in relation to age and severity of illness.

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