Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis with multiple organ failure

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 addition of drotrecogin alpha (activated) (DAA) to best standard care (BSC) for the treatment of severe sepsis with multiple organ failure (MOF) was examined. DAA was administrated as a continuous intravenous infusion at a rate of 24 microg/kg per hour for 96 hours.

Type of intervention
Treatment.

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

Study population
The study population comprised a cohort of patients with MOF requiring treatment for severe sepsis.

Setting
The setting was an intensive care unit (ICU). The economic study was carried out in France.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1997 and 2003. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A decision tree model was developed to assess the costs and benefits of DAA in patients with severe sepsis and MOF. The time horizon of the analysis was the patients' lifespan. Other details of the decision model were not provided.

Outcomes assessed in the review
The outcomes estimated from the literature were:
characteristics of the patients,
treatment effectiveness and adverse events,
life expectancy, and

quality of life after ICU stay.

Study designs and other criteria for inclusion in the review
The primary estimates appear to have been identified selectively rather than through a systematic review of the literature. Data on treatment effectiveness came from the recombinant human activated PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS) study results (1,271 patients with MOF), while patient characteristics (including length of stay and mortality) were obtained from the CubRea (Intensive Care Database User Group), a database gathering data of 9,948 hospital stays in the Parisian area. Age- and gender-specific life expectancy of the general population were estimated from French life tables from 1997 to 2000. Limited information on the other sources of clinical data was provided.

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 clinical data used in the decision model were derived from 6 primary studies.

Methods of combining primary studies
The primary estimates were not combined since each source was used to derive a specific clinical estimate.

Investigation of differences between primary studies
Data from PROWESS were matched to those from the CubRea. It was observed that patients in the PROWESS trial were more severely ill than those in the CubRea database.

Results of the review
In the PROWESS trial, the absolute risk reduction (ARR) of death with DAA compared with placebo was 6.13% (95% confidence interval, CI: 1.86 to 10.39), while the relative risk (RR) of death of DAA compared with placebo was 0.80 (95% CI: 0.69 to 0.94).

Mortality for patients with severe sepsis with at least two organ failures was 33.9% (95% CI: 30 to 38) in the PROWESS trial and 43.5% (95% CI: 42 to 45) in the CubRea database.

The mean length of survival in the ICU was 21 days.

The primary serious adverse event with DAA was bleeding. The proportion of patients with bleeding at 28 days was 3.5% for DAA and 2% for placebo, (p=0.06).

Life expectancy of ICU survivors was estimated to be half of that estimated for the general population.

Quality of life after the ICU was 0.6.
Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs) gained with DAA added to BSC in comparison with BSC alone. Discounting was not performed in the base-case. The utility weights were based on a Canadian cost-effectiveness study, but no details of this study were reported.

Direct costs
The perspective chosen for the analysis of the costs was not stated. The direct costs associated with hospitalisations were included in the analysis. These were for investigations, consumables, care staff, hotel services, laundry, pharmacy and administration. The costs were incurred in both the ICU and normal wards. The costs associated with the treatment of adverse events were not considered in the base-case. The unit costs and the quantities of resources used were not presented separately. The resource use data and costs appear to have been mainly derived from the French database. Discounting was not relevant since the costs were incurred during a short timeframe. The price year was not reported.

Statistical analysis of costs
A multiple linear regression was developed to predict the patient's ICU costs. The independent factors used were the length of stay in the ICU, the Simplified Acute Physiology Score, the Omega score, and the status of the patient when leaving the ICU (deceased or alive).

Indirect Costs
The indirect costs were not considered.

Currency
French francs (FFR) were converted into US dollars ($) at a conversion rate of 0.98316 in 2002.

Sensitivity analysis
A univariate sensitivity analysis was carried out to assess the robustness of the cost-effectiveness and cost-utility ratios to variations in key model inputs, the ranges for which were presumably based on authors' opinions and published data. A probabilistic sensitivity analysis (Monte Carlo simulation) was also performed by running 5,000 iterations of the 385 model parameters.

Estimated benefits used in the economic analysis
When all patients were considered, the incremental LYs gained with DAA over BSC were 0.64 per patient. These ranged from 0.42 for patients requiring less than two-organ support to 1.04 for patients requiring three-organ support (circulatory, renal and respiratory). The incremental QALYs were not reported.

Cost results
When all patients were considered, the incremental costs of DAA were $7,545. These ranged from $7,333 for patients requiring two-organ support to $8,187 for patients requiring three-organ support (circulatory, renal and respiratory).

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of DAA over BSC.

The incremental cost per LY gained was $11,812 for all patients. This ranged from $7,873 for patients requiring three-organ support to $17,704 for patients requiring less than two-organ support.
The incremental cost per QALY gained was $19,686 for all patients. This ranged from $13,122 for patients requiring three-organ support to $29,507 for patients requiring less than two-organ support.

The sensitivity analysis showed that the results of the analysis were sensitive to the RR of death. When using the upper (0.93) and lower (0.66) bounds of the 95% CI for the RR of death for patients with MOF in the PROWESS trial, the incremental cost per LY gained ranged from $6,450 to $33,894. The use of the ARR of death instead of the RR led to an incremental cost per LY gained of $14,413.

Variations in other model inputs, or the inclusion of costs for the treatment of adverse events, did not alter the conclusions of the analysis. The probabilistic sensitivity analysis suggested that for a willingness to pay of $50,000 per QALY, the probability that DAA is cost-effective was 85% (71% for patients requiring less than two organ supports, 82% for those requiring two organ supports, and 91% for those requiring three organ supports).

**Authors’ conclusions**
The addition of drotrecogin alpha (activated) (DAA) to best standard care (BSC) was a cost-effective strategy for the treatment of severe sepsis in intensive care unit (ICU) patients with multiple organ failure (MOF).

**CRD COMMENTARY - Selection of comparators**
The rationale for the selection of the comparator was clear. DAA was added to BSC, which represented the standard approach for the treatment of severe sepsis in ICU patients with MOF. Dosages of DAA were reported. You should decide whether BSC is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was derived from published sources, but it was not stated whether a systematic review of the literature was undertaken. Indeed, the primary studies appear to have been identified selectively. The characteristics of the patients included in the PROWESS and CubRea databases were provided. The design of the PROWESS study, which was the main source of the effectiveness data, enhances the internal validity of the analysis. The issue of the homogeneity of the studies was implicitly addressed and the two patient groups (in the PROWESS trial and in the CubRea database) were quite different, especially with respect to disease severity. The authors noted that this issue deserves particular caution. Sensitivity analyses were performed on key clinical data. Some country-specific data were used.

**Validity of estimate of measure of benefit**
QALYs and LYs are the most appropriate benefit measures because they capture the impact of the intervention on quality of care and survival, which are the most relevant dimensions of health for ICU patients with severe sepsis. Utility was derived from the literature, but the instrument used to assess the utility weights was not described. The use of QALYs allows comparisons with the benefits of other health care interventions. Discounting was not applied.

**Validity of estimate of costs**
The perspective adopted in the study was not explicitly stated. A detailed breakdown of the cost items was not provided since only macro-categories of costs were reported. There was limited information on resource consumption and the unit costs were not given. This limits the possibility of replicating the cost analysis in other settings. Both the costs and resource use data were specific to the French setting, thus caution is required when extrapolating these estimates to other settings. Some statistical analyses of the costs were performed in the sensitivity analysis, where probabilistic distributions were assigned to all items. The impact of altering some cost items was investigated in the sensitivity analysis. The price year was not reported, which will make reflation exercises in other time periods difficult. The authors noted that the costs of conventional care were estimated from a population of ICU patients; it is possible that the use of data from patients with severe sepsis would have led to different estimates of the total costs.
Other issues
The authors stated that their findings were comparable with those from a Canadian study when a 5% annual discount rate was applied. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the use of a probabilistic sensitivity analysis to some extent enhances the external validity of the study. The analysis referred to ICU patients with MOF who required treatment for severe sepsis, and this was reflected in the authors’ conclusions.

Implications of the study
The study results appear to support the use of DAA for the treatment of ICU patients with severe sepsis. The authors pointed out that the introduction of this new treatment would increase ICU costs.

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Other publications of related interest


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