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

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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 health intervention examined in the study was drotrecogin alpha (activated) (DAA) for the treatment of severe sepsis. DAA was given in 5mg vials based on a 12 hourly dosage.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised both the whole group of patients with severe sepsis and the subgroup of patients with severe sepsis and 2 or more organ dysfunctions.

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

Dates to which data relate
Effectiveness data were derived from studies published between 1997 and 2001. Resource use data came from a study published in 2002. Costs were estimated using 1998/1999 values.

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

Modelling
A decision tree model was constructed to assess the costs and benefits of DAA plus standard care in comparison with standard care alone for the treatment of severe sepsis. The model considered the survival rate by day 28 after start of treatment. Surviving patients could still be in hospital after day 28 or have already been discharged. The structure of the decision tree was reported graphically. The proportion of patients surviving at 28 days (inpatient or discharged) with DAA or standard care was then used to extrapolate survival rates over patients' lifetime.

Outcomes assessed in the review
The outcomes assessed from the literature were 28-day mortality with DAA or standard care and life expectancy.
Study designs and other criteria for inclusion in the review
The effectiveness data came from studies that were identified selectively. Most of the evidence came from the PROWESS trial. This included 850 patients in the DAA arm (634 with 2 or more organ dysfunctions) and 840 in the standard care group (637 with 2 or more organ dysfunctions). Mean age was 60.5 +/- 17.7 years and 60.6 +/- 16.5 years, respectively, while the percentage of men was 56.1% and 58.0%, respectively. Life expectancy was estimated from German life tables. Adjustments for life expectancy (due to prolonged ICU stay, severe sepsis, and comorbidities) were derived from a published study that estimated the relative hazard ratio relating to long-term survival between patients with severe sepsis and the general population. No details of this study were given.

Sources searched to identify primary studies
Not relevant.

Criteria used to ensure the validity of primary studies
The use of data from a large, randomised, clinical trial ensures a high internal validity.

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

Number of primary studies included
Three primary studies were used in the review.

Methods of combining primary studies
It appears that each outcome measure was obtained from a single study, thus effectiveness results were not combined.

Investigation of differences between primary studies
Not stated.

Results of the review
The absolute risk reduction (ARR) in 28-day hospital mortality was 6.0% for all patients (30.1% with standard care versus 24.1% with DAA), and 7.3% for patients with 2 or more organ dysfunctions (33.3% with standard care versus 26.0% with DAA).

ARR remained at 6.0% at final patient discharge (7.3% in patients with 2 or more organ dysfunctions).

The application of German life-table data to the marginal age and sex profile from the PROWESS study led to a mean life expectancy of 19.4 years for each additional survivor.

The hazard ratio for long-term survival between patients with severe sepsis and general population was 0.51. Thus, adjusted life expectancy was 9.9 years for post discharge mortality (7.8 years after discounting at 3%).

In the subgroup of survivors with two or more organ dysfunctions, the mean life expectancy was 23.5 years for each additional survivor, which gave an adjusted life-expectancy of 12.0 years for post discharge mortality (9.5 years after discounting at 3%).

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic evaluation was the expected number of life-years (LYs) gained with DAA in comparison with standard care. Results were reported, both undiscounted and discounted at 3%.
Direct costs
The analysis of costs took the perspective of the German health care payer and included all hospital costs associated with severe sepsis, such as inpatient stay in ICU or hospital ward, DAA, and specific therapies (including ventilation support, renal support, vasodilator support, and blood therapy without antithrombin III). Post-discharge costs were not considered. Unit costs were presented separately from quantities of resources used. Most resource use data were estimated from the PROWESS clinical trial. Hospital costs came from a published German cost of illness study of 385 severe sepsis patients in 3 ICUs in Germany. Discounting was not relevant as costs were incurred over a short time frame. Costs referred to the fiscal years 1998/1999.

Statistical analysis of costs
Statistical analyses of costs were not performed.

Indirect costs
Indirect costs were not considered in the economic evaluation.

Currency
Euros (EUR).

Sensitivity analysis
Extensive sensitivity analyses were carried out to address the issues of the robustness and validity of the study results. Univariate and multivariate sensitivity analyses were carried out on the following model inputs: cost of DAA, assumptions regarding survival, discount rate, and hospital mortality. Ranges for sensitivity analyses appear to have been set by the authors. Alternative assumptions for resource use consumption in the subgroup of patients with multiple organ failure were also taken into account. For example, the impact of the type of organ support received was investigated. Moreover, local resource use data were used as an alternative to the PROWESS-based data.

Estimated benefits used in the economic analysis
The undiscounted (discounted) LYs gained per patient with DAA over standard care were 0.59 (0.47) in the whole group and 0.87 (0.69) in the subgroup of patients with multiple organ failure.

Cost results
Total hospital costs per patient were EUR 18,125 with standard care and EUR 26,455 with DAA (difference: EUR 8,330).

In the subgroup of patients with multiple organ failure, total hospital costs per patient were EUR 18,469 with standard care and EUR 27,356 with DAA (difference: EUR 8,887).

Total ICU costs and other hospital ward costs were similar between the two groups, thus the cost difference was mainly driven by the cost of DAA.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine costs and benefits of the two treatment strategies.

The incremental cost per LY gained with DAA over standard care was EUR 14,119 (EUR 17,723 when discounted).

In the subgroup of patients with multiple organ failure, the incremental cost per LY gained with DAA over standard care was EUR 12,880 (EUR 17,723 when discounted).
The sensitivity analysis showed that the use of data reflecting a local observed pattern of care rather than trial-based data led to lower cost-effectiveness ratios for the subgroup of patients with multiple organ failure in comparison with base case results. Furthermore, it was found that the cost of DAA was the key driver of cost-effectiveness ratios. The range of cost-effectiveness ratios resulting from the multivariate sensitivity analysis was EUR 3,700 (10% decrease of DAA cost and maximum ARR) to EUR 23,500 (10% increase of DAA cost and minimum ARR).

Authors' conclusions
The authors concluded that DAA treatment added to standard care for the management of patients with severe sepsis was cost-effective in Germany. A key aspect of the cost-effectiveness of DAA was patient selection. DAA appears more cost-effective as the severity of the disease increases, in particular in the case of patients with 2 or more organ dysfunctions.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was appropriate as DAA was compared with the standard treatment. However, no details on the definition of usual care were provided. You should decide whether they are valid interventions in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a synthesis of published studies. Most of the clinical evidence came from a multicentre, randomised, clinical trial, which usually has a high internal validity due to the robust design. Expected life expectancy for surviving patients was estimated using German statistics. The characteristics of the third study used as source of evidence for the reduction in survival due to severe sepsis were not reported. However, extensive sensitivity analyses were carried out to assess the impact of variations in clinical estimates on the results of the analysis.

Validity of estimate of measure of benefit
The use of LYs as the summary benefit measure is appropriate as survival represents the most relevant dimension of health for patients with sepsis. Both discounted and undiscounted LYs were reported, and the impact of using alternative discount rates was investigated in the sensitivity analysis. LYs can be compared with the benefits of other health care interventions.

Validity of estimate of costs
The analysis of costs was consistent with the perspective adopted in the study. A justification for the exclusion of some categories of costs was provided. Extensive information on unit costs, quantities of resources used, price year, and source of data was provided, thus enhancing the possibility of replicating the results of the analysis in other settings and facilitating reflation exercises in other time periods. Costs reflected national tariffs, which were the costs relevant from the perspective of the national health care payer. The uncertainty surrounding some cost estimates was addressed in the sensitivity analysis, in which alternative scenarios for resource use were taken into account. Discounting was not applied as it was not relevant.

Other issues
The authors stated that the cost-effectiveness ratios of DAA, as observed in the current study, were comparable to those of other health care interventions implemented in Germany. It was also noted that the analysis was based on data coming from similar types of hospital involved in both the PROWESS trial and the cost of illness study (i.e., large university teaching hospitals), thus, caution is required when extrapolating the results of the analysis to other types of providers. The issue of the generalisability of the findings of the analysis was addressed in the sensitivity analysis, which enhances the external validity of the study.

Implications of the study
The study results support the use of DAA added to conventional care for the treatment of severe sepsis. The authors stated that the current findings need validation following further use of DAA in real-world clinical settings. Future studies should also investigate aspects related to quality of life.

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**Other publications of related interest**


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