Drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults

Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Severe sepsis and septic shock are life-threatening systemic responses to infection and are the most common cause of death in intensive care units. The incidence of severe sepsis in the first 24 hours in intensive care in the UK is estimated to be 27.1%, equivalent to 21,191 cases in England and Wales per annum. Despite successful early resuscitation, overall 20–56% of patients with severe sepsis will die from their disease.

Current treatment of severe sepsis involves both treatment of the underlying infection, primarily with antibiotics and surgical débridement, and supportive treatments according to the signs and symptoms exhibited by the patient. Attempts to reduce mortality rates have focused on the use of anti-inflammatory therapies, with large randomised controlled trials (RCTs) targeting mediators such as tumour necrosis factor alpha (TNF-α), TNF-α receptor, interleukin-1 (IL-1), the IL-1 receptor and prostaglandins and bradykinins, as well as using large-dose corticosteroids. However, RCTs have generally failed to show any improvement in survival.

Drotrecogin alfa (activated) (Xigris®), a recombinant human activated protein C (rhAPC), is a new treatment for patients with severe sepsis. It has been licensed in the European Union for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. The recommended standard treatment regimen for drotrecogin alfa (activated) is for 24 μg kg^{-1} body weight per minute for a period of 96 hours, and the mean acquisition cost per 70-kg patient, for a full 96-hour course, is estimated to be £4905 excluding VAT.

Objectives

To assess the clinical and cost-effectiveness of drotrecogin alfa (activated) for the treatment of adults with severe sepsis in a UK context.

Methods and results

A systematic review of the literature and an economic evaluation were undertaken. Data on the clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) were synthesised through a narrative review with full tabulation of results from included studies.

Number and quality of studies

Two RCTs assessing the effectiveness of drotrecogin alfa (activated) were identified; one Phase II RCT and one Phase III RCT (PROWESS study). The results of the Phase III RCT (PROWESS) have been published in five subsequent papers. A review on the safety of drotrecogin alfa (activated) was informed by the two identified RCTs, plus three otherwise unpublished prospective open-label studies. Data from the commercial use of the drug up to April 2002 also formed part of the review.

Quality assessment of the two RCTs was conducted according to the guidelines of the Cochrane Infectious Diseases Group, with addition of some topic-specific items relevant to the trials conducted in severe sepsis. Based on a quality assessment of the internal validity of the two RCTs, they may be regarded as being of good quality. It was not possible to assess the quality of the unpublished open-label studies.

Three published cost-effectiveness studies were identified, together with six published abstracts and two unpublished abstracts. The cost-effectiveness analysis submitted to the National Institute for Clinical Excellence (NICE) by the manufacturer of drotrecogin alfa (activated) has also been used to provide information on the cost-effectiveness of the technology.

Summary of benefits

The evidence on the effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis came primarily from one large pivotal RCT, the PROWESS study. This study demonstrated a statistically significant absolute reduction in 28-day mortality of 6.5% [95% confidence interval (CI) –10.7 to –2.2], equivalent to a relative risk of death of 0.79 (95% CI 0.68 to 0.92). Longer term follow-up of PROWESS patients showed that the survival benefit was maintained to 90 days (p = 0.048). By 9 months, the trend towards increased median survival was non-significant ▶

(log-rank $p = 0.097$), although the survival curves did not cross.

A priori subgroup analyses showed a progressive reduction in the relative risk of death with increasing number of organ failures, from 0.92 (95% CI 0.63 to 1.35) in patients with one organ failure at baseline to 0.60 (95% CI 0.33 to 1.11) in those with five organ failures. Results presented by the number of organ dysfunctions were not statistically significant, but when mortality rates for those with two or more organ failures were combined, the relative risk of death was significantly lower in those treated with drotrecogin alfa (activated) compared with placebo (0.78, 95% CI 0.66 to 0.93). However, this report highlights a number of considerations relevant to the subgroup analyses reported for the PROWESS study.

To estimate the cost-effectiveness of treatment with drotrecogin alfa (activated) it was necessary to extrapolate from effectiveness data from the PROWESS trial (i.e. short-term 28-day survival data) to longer term outcomes reflecting life-years and quality-adjusted life-years (QALYs) gained. To do this it was necessary to estimate the life expectancy of the additional survivors of severe sepsis, following treatment with drotrecogin alfa (activated). Published cost-effectiveness studies have applied a range of methods to the estimation of benefits, estimating an incremental gain per treated patient of between 0.38 and 0.68 life-years (for patients with severe sepsis). Analysis from the manufacturer (Eli Lilly) estimated an incremental gain of 1.115 life-years per treated patient, in patients with severe sepsis and multiple organ dysfunction. The Southampton Health Technology Assessments Centre (SHTAC) analysis estimated an incremental gain of 1.351 life-years per treated patient, in those patients with severe sepsis and multiple organ dysfunction. These latter UK analyses are based on a patient group that is more severely affected by disease, where effectiveness is greater and the baseline risk of all-cause mortality is much higher (SHTAC analysis); these factors are associated with the noted difference in effect.

Costs

The additional costs associated with drotrecogin alfa (activated) in patients with severe sepsis comprise the acquisition cost of the drug, an additional cost associated with an increased risk of severe bleeding episodes, hospitalisation costs associated with additional survivors of severe sepsis and, where deemed appropriate, the long-term healthcare costs associated with additional survivors of severe sepsis. There are variations in estimates of cost in the published literature. The three published cost-effectiveness studies report cost for US and Canadian patient groups; for those patients with severe sepsis they report the additional cost per patient treated in a range around $10,000–16,000.

The manufacturer's submission reports analysis for the UK, based on 28-day survival data in patients with severe sepsis and multiple organ dysfunction (the European licence indication), with the additional mean cost per treated patient estimated to be £5106. The analysis undertaken by SHTAC, for a UK group of patients with severe sepsis and multiple organ dysfunction, estimate an additional mean cost per patient treated of £6661.

Cost-effectiveness

Estimates of cost per life-year and cost per QALY in the published literature were from US and Canadian economic evaluations and ranged from $15,801 to $33,000 per life-year gained, and from $20,047 to $48,800 per QALY. These estimates were for patients eligible for inclusion in the PROWESS study (i.e. severe sepsis). For those US and Canadian patients regarded as having more severe disease, as indicated by an APACHE II score of 25 or more, the cost-effectiveness profile was more attractive (i.e. costs per life-year and per QALY are lower). For those patients with an APACHE II score of less than 25, published studies (USA and Canada) reported that drotrecogin alfa (activated) was generally regarded as cost-ineffective.

Patients with severe sepsis and multiple organ failure formed the relevant patient group for European analysis. The manufacturer's submission to NICE presented cost-effectiveness estimates for drotrecogin alfa (activated) in the UK, in patients with severe sepsis and multiple organ dysfunction, at £6637 per QALY based on 28-day effectiveness data, and £10,937 per QALY based on longer term follow-up data. SHTAC developed an independent cost-effectiveness model and estimated a base-case cost per QALY of £8228 in patients with severe sepsis and multiple organ failure (based on 28-day survival data). Simulation results indicated that where the NHS is willing to pay £20,000 per QALY, drotrecogin alfa (activated) is a cost-effective use of resources in 98.7% of cases.

Sensitivity analyses: cost-effectiveness analysis

Published economic evaluations reported various sensitivity analyses, with results sensitive to ▶

changes in the measure of treatment effect (i.e. variations in the absolute or relative risk measure used), but otherwise studies reported that results were robust to variations in most assumptions used in the cost-effectiveness analysis. Where multiple changes were made to the base-case assumptions in the SHTAC cost-effectiveness model, the cost per QALY increased towards the estimates reported in the published US and Canadian economic analysis, but the intervention remained at a level that would be regarded as cost-effective to most decision-makers.

Conclusions

Limitations of the review and generalisability of the findings

The key limitation of the two RCTs was in the generalisability of the findings to the UK. The definition of severe sepsis used in the pivotal RCT (PROWESS) was stricter than applied in practice in the UK, and the trials included only patients developing severe sepsis within the first 24 hours of screening (intensive care). Drotrecogin alfa (activated) is licensed in Europe for treatment of patients with severe sepsis and two or more organ dysfunctions, with no further restrictions on its use. It may be that in practice it is used in a wider patient group than those included in the PROWESS study.

Cost-effectiveness analysis was generally limited by a lack of data on longer term survival and quality of life in patients surviving severe sepsis. The published literature on the cost-effectiveness of treatment with drotrecogin alfa (activated) was dominated by studies from USA and Canada, with limited generalisability to the UK. Furthermore, the cost-effectiveness analysis undertaken by SHTAC uses UK data on patients with severe sepsis as defined in the PROWESS study, as a baseline population, but it did not apply the exclusion criteria from the PROWESS study. This may be regarded as both a strength and a limitation of the model, as the in-practice use of these exclusion criteria, which do not form part of the European licence indication, is uncertain.

Other important issues regarding implications

The introduction of drotrecogin alfa (activated) would involve a substantial additional cost to the NHS. The treatment-eligible population in England and Wales may comprise up to 16,570 patients, with an estimated annual drug acquisition cost of over £80 million, excluding VAT.

Recommendations for research

Further research is required on the longer term impact of drotrecogin alfa (activated) on both mortality and morbidity in UK patients with severe sepsis, on the clinical and cost-effectiveness of drotrecogin alfa (activated) in children (under 18 years) with severe sepsis, and on the effect of the timing of dosage and duration of treatment on outcomes in severe sepsis.

Publication

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NHS R&D HTA Programme

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The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

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