Cost-effectiveness of ancrod treatment of acute ischaemic stroke: results from the Stroke Treatment with Ancrod Trial (STAT)

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 ancrod, a defibrinogenating agent, for the treatment of patients with acute ischaemic stroke within 3 hours after the event. The patients received ancrod as a continuous 72-hour infusion, followed by infusions lasting approximately 96 hours (range: 90 - 102) and 120 hours (range: 114 - 126) after treatment initiation. Ancrod was administered at initial infusion rates of 0.167, 0.125 and 0.082 IU/kg per hour on the basis of pre-treatment fibrinogen levels of more than 13.23, 10.29 to 13.20, and 2.94 to 10.26 micromol/L, respectively.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised adult patients with ischaemic stroke (any vascular territory) with symptoms lasting at least 30 minutes and treatment starting within 3 hours of stroke onset. Several exclusion criteria were reported. For example, evidence of brain haemorrhage of potentially progressive lesion, very mild stroke, coma, prior stroke within 6 weeks, deficit from transient ischaemic attack within 3 hours, recent or anticipated surgery, ipsilateral neurological deficit from prior stroke interfering with evaluation, deficit attributed to migraine, hypoglycaemia, or sequelae of recent seizure.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered between August 1993 and January 1998. The price year was 1996.

Source of effectiveness data
The effectiveness evidence was derived from a single published study, the Stroke Treatment with Ancrod Trial (STAT; see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was performed prospectively on the same patient sample as that used in the effectiveness study.
**Study sample**
Power calculations were conducted on the basis of an absolute difference in favourable functional outcomes of 15% and a placebo rate of 34%, with 90% power and a 2-sided significance level of 0.05. Of the 2,613 patients screened in the study centres, 500 were included in the study sample. Exclusions were mainly due to inability to treat patients, mild stroke or transient ischaemic attack, or haemorrhage on pre-treatment computed tomography. No patient was excluded for any reason from the initial study sample.

**Study design**
This was a multicentre, parallel-group, double-blind, randomised placebo-controlled study, which was carried out at 48 centres in the USA and Canada. Randomisation was conducted using sequentially numbered pre-packs of infusions at each site, following a 1:1 programme in block sizes of 4 generated by a statistician. The follow-up lasted 3 months. Four patients in the ancrod group and one in the control group were lost to follow-up. To preserve the blinding, the patients' allocation to the study groups was known only by the supplier's clinical packaging group.

**Analysis of effectiveness**
The basis of the analysis of the clinical study was intention to treat. The primary health outcome used in the analysis was favourable functional status. This was defined as survival to follow-up day 90 with a Barthel Index (BI) score (range: 0 (worst) - 100 (best)) of 95 or more (implying a need for little or no help in daily activities) or at least equal to the pre-stroke value. Statistical analyses were conducted to evaluate the impact of specific factors on the estimated outcome. Safety variables, such as death, adverse events within 3 months and laboratory measurements, were also evaluated in the original trial, although they were not relevant in the present economic evaluation. The study groups were comparable at baseline in terms of their demographic and clinical characteristics.

**Effectiveness results**
Ancrod treatment resulted in a significantly, (p=0.04) greater proportion of patients (102 cases, 41.1%) with favourable function outcomes than placebo (89 cases, 35.3%). The odds ratio was 1.55 (95% confidence interval: 1.02 - 2.36).

The safety profile was comparable in the treatment and placebo group.

**Clinical conclusions**
The effectiveness study showed that ancrod treatment increased significantly the proportion of patients with ischaemic stroke who achieved favourable functional status at 3 months in comparison with placebo.

**Modelling**
The Stroke Policy Model (SPM), as developed by the Stroke Patient Outcomes Research Team, was used to describe the natural history of stroke. Published methodologies were used to populate the decision model. The model was used to extrapolate long-term data on the basis of clinical short-term data coming from the STAT. The simulations used 50,000 iterations each.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the quality-adjusted life-year (QALY). This was calculated using the area-under-the-curve approach. The authors made a survey-based assessment of the relationship between BI and utility, using the procedure of Samsa et al. (see Other Publications of Related Interest). The utility values were assumed to be constant from the time of the stroke until day 7. The utility values between day 7 and 90 (or death) were derived by linear interpolation.

**Direct costs**
Discounting was relevant since the long-term costs were evaluated in the decision model, but no discount rate was
mentioned in the analysis. The unit costs were only reported separately from the quantities of resources used for some items. The health services included in the economic evaluation were drugs, inpatient stay, rehabilitation, nursing home, physical and occupational therapy, and home care nursing. The cost/resource boundary adopted was not clearly defined since the authors stated that the perspective of the study was societal, but the indirect and non-medical costs were not included in the analysis. Resource use was generally estimated alongside the clinical trial. Most of the unit costs were derived from Medicare rates. To estimate missing data on resource use and the unit costs required in the decision model, the authors made some assumptions and statistical regression analyses were conducted. The price year was 1996.

Statistical analysis of costs
No statistical analyses of the costs were conducted in the base-case.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
The authors addressed the issue of the variability of data in terms of both trial-based variability and imprecision in the SPM parameter estimates. A bootstrapped analysis was also performed.

Estimated benefits used in the economic analysis
The trial QALYs were 0.09 with both ancrod and placebo. The SPM QALYs were 2.02 with ancrod and 1.94 with placebo (difference: 0.08). The long-term QALYs were 2.12 with ancrod and 2.03 with placebo (difference: 0.09).

Cost results
The trial costs were $17,424 with ancrod and $17,618 with placebo (difference: -$194). The SPM costs were $108,129 with ancrod and $119,592 with placebo (difference: -$11,463). The long-term costs were $125,553 with ancrod and $137,211 with placebo (difference: -$11,658).

Synthesis of costs and benefits
An incremental analysis was conducted to combine the costs and benefits of the ancrod treatment over placebo. However, a cost-utility ratio was not calculated because ancrod dominated placebo, being more effective and less expensive. This conclusion was robust to any sensitivity analysis performed.

Authors' conclusions
Ancrod proved to be slightly more effective than placebo and led to a cost-saving. Even a modest improvement in effectiveness was likely to result in substantial cost-saving for the population of patients with stroke.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected because it was the comparator in the primary effectiveness study. Moreover, the aim of the economic evaluation was to assess the active value of ancrod. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a multicentre, parallel-group, double-blind, randomised placebo-controlled study, which was appropriate for the study question. The internal validity of the analysis was further enhanced by the performance of power calculations, the use of intention to treat as the basis for the clinical study, and the minimal loss to follow-up. Statistical analyses were also conducted to estimate covariates affecting the primary outcome. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
QALYs were used as the benefit measure in the economic analysis. The utility values were based on authors' estimates, which had already been published. The authors made some assumptions to calculate the QALYs. The use of QALYs permits the benefits of ancrod treatment to be compared with those associated with other treatments.

Validity of estimate of costs
The perspective adopted in the study was not clearly defined. The authors stated that a societal perspective was adopted, but the indirect costs were not included. It appears more likely that the cost/resource boundary was that of the third-party payer, as most of the cost estimates were based on Medicare reimbursement rates. The unit costs were only reported separately from the quantities of resources used for a few cost items. The costs and the quantities were treated deterministically in the base-case, but sensitivity analyses were conducted on key economic variables. Resource consumption was mainly evaluated alongside the clinical trial, but assumptions were also required due to missing data. The source of the unit costs was reported.

Other issues
The authors compared their findings with those from other published studies. However, they did not address the issue of the generalisability of the study results to other settings. Sensitivity analyses were conducted, but the overall external validity of the analysis was low. The study enrolled patients with stroke and this was reflected in the conclusions of the analysis. The authors stated that the main limitation of the analysis was the need for assumptions, due to a lack of data estimated alongside the clinical trial.

Implications of the study
The study results suggest that ancrod may represent a cost-effective treatment for patients with acute ischaemic stroke, within 3 hours after the event.

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Other publications of related interest

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