The influence of clinical study design on cost-effectiveness projections for the treatment of Gram-negative sepsis with human anti-endotoxin antibody

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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
Using human anti-endotoxin antibody (HA-1A) in patients with sepsis and suspicion of gram-negative bacteremia (GNB).

Type of intervention
Treatment.

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

Study population
Patients older than 18 years with sepsis and suspicion of gram-negative bacteremia (GNB).

Setting
University medical centre. The economic study was carried out in Pittsburgh, USA.

Dates to which data relate
The effectiveness data related to the single study based open-label protocol were collected between December 1990 to June 1992. The effectiveness data related to the RCT were extracted from a paper published in 1991. Resource utilisation was not reported. The price dates were not specified.

Source of effectiveness data
The sources of effectiveness data were a single study and a previously conducted RCT by Ziegler et al.

Link between effectiveness and cost data
It was implicitly stated that the costing was performed on the same patient sample as that used in the effectiveness analysis although it was not clear whether the costing was carried out prospectively or retrospectively.

Study sample
Power calculations were not used to determine sample size. A total of 131 University of Pittsburgh Medical Centre (UPMC) patients who received HA-1A were included in the study. The number of HA-1A recipients in the RCT study was 262.

Study design
The study was a case series, the outcomes of which were compared with the outcomes of a previously published multicentre RCT. The case series study was performed in a single centre. The duration of the follow-up period was until discharge or death in hospital. No loss to follow-up was reported.

**Analysis of effectiveness**

It was not clearly specified whether the effectiveness analysis was based on intention to treat or treatment completers only. The primary health outcomes were the percentage of patients with GNB, patient survival with GNB, and toxicity. The comparison between the UPMC patients and RCT patients showed that the patients chosen to receive HA-1A at UPMC “were significantly sicker at enrolment than the HA-1A subgroup with GNB in the RCT”.

**Effectiveness results**

The percentage of patients with GNB was 40% in the RCT versus 32.8% in the UPMC cohort (not statistically significant). Patient survival with GNB at day 28 was 47% in the UPMC cohort versus 69% in the RCT intervention group, (P<0.05). When the UPMC patient survival was compared with the RCT placebo group with 51% of survival the difference was not statistically significant. No minor or major side effects were observed at UPMC.

**Clinical conclusions**

The authors concluded that the failure to demonstrate significant efficacy with MAb therapy in patients at UPMC compared with control patients in the RCT could be because the drug is ineffective, because the patient population were different, or because of both conditions. The CHESS findings suggest that the UPMC results may be attributable to a lack of efficacy of HA-1A.

**Measure of benefits used in the economic analysis**

The measure of benefits was lives saved or expected survival.

**Direct costs**

Resource quantities were not reported separately from the costs. The cost items were not reported separately. The cost analysis was performed within the framework of three different economic models used in previously published studies. The UPMC data were compared with RCT data in the model of Schulman et al (1991), which was reported to consist of the cost of acquisition of HA-1A and cost of acute care. The perspective adopted in the above framework was that of society. A comparison of a model by Barriere (1992) for gram-negative septic shock using RCT data with the same model using UPMC data was performed. The perspective adopted in this model was cost to an institution. Based on the model of Chalfin et al (1994), a cost analysis was performed for patients with GNB and shock comparing UPMC and RCT HA-1A recipients with controls. The perspective adopted in the Chalfin analysis was that of patient (hospital charges). The date of the price data was not specified.

**Indirect Costs**

Not reported.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analysis was carried out on mortality rate by using favourable mortality estimates (lower bound of 95% confidence intervals), cost of HA-1A, cost of acute care, morbidity rate, and years of life gained.
Estimated benefits used in the economic analysis
Since no significant clinical efficacy was demonstrated for the UPMC HA-1A recipients, the use of HA-1A was regarded as ineffective according to the model of Schulman et al, and only sensitivity analysis was performed based on the assumption of 1 and 20 years of life gained. According to the Barriere model, number of lives saved for RCT was 13 versus 0 (and 2 in the favourable case) for UPMC. According to the Chalfin model, expected survival was reported to be 0.66 for RCT Mab against 0.42 for standard antibiotic regimen (controls) and 0.47 for UPMC MAb.

Cost results
Cost results were not reported for the Schulman and Barriere models. In the Chalfin model, the total expected charges for RCT were $51,005 versus $44,172 for standard antibiotic therapy and $47,252 for UPMC.

Synthesis of costs and benefits
The cost per year of life saved was $24,100 for RCT, using the model of Schulman et al, and $90,400 (in favourable case) for the UPMC. The cost per life saved was $37,465 for RCT and $124,625 (in favourable case) for UPMC using the Barriere model. The marginal cost-effectiveness ratios for UPMC and RCT in comparison with standard antibiotic therapy (controls) were $61,600 and $28,471 respectively.

Authors' conclusions
Extrapolating cost-effectiveness from RCT-derived analyses to open-label usage may yield widely inaccurate projections because of only small differences in patient population and the drug administration protocol.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator is clear.

Validity of estimate of measure of benefit
The internal validity of the UPMC study results may have been weakened by the lack of randomisation.

Validity of estimate of costs
Resource quantities were not reported separately from the costs. Adequate details of the methods of cost estimation were not given.

Other issues
In view of the lack of both randomisation and statistical analysis of the costs, the UPMC study results may need to be treated with some caution.

Source of funding
None stated.

Bibliographic details

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Other publications of related interest


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