Cost-effectiveness analysis of augmentation therapy for severe alpha1-antitrypsin deficiency
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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
Three strategies for alpha1-antitrypsin (AAT) deficiency were examined. Strategy 1 was not treating AAT deficiency with augmentation therapy (intravenous pooled human plasma antiprotease). Strategy 2 was treating AAT-deficient individuals who have indications for augmentation therapy for life. Strategy 3 was treating AAT-deficient individuals with augmentation therapy until the forced expiratory volume in 1 second (FEV1) is below 35% of that predicted.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population was a cohort of 30,000 46-year-old patients, of which 50% were men, who had a FEV1 of 49% predicted. The reason for choosing this base-case was to keep inline with the mean baseline characteristics of the NHLBI Registry participants.

Setting
The setting was secondary and tertiary care. The economic study was carried out in Cleveland, OH, USA.

Dates to which data relate
The effectiveness evidence was obtained from studies dating from 1998 to 2002. For the cost data, the studies were from 1995 to 2001. The price year was 2001.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on experts’ opinions.

Modelling
A Markov Monte Carlo (state transition) decision model was used. For each strategy, the patients were followed until death in a model consisting of five health states. The health states considered were FEV1 50 - 79% predicted, FEV1 35 - 49% predicted, FEV1 below 35% predicted, lung transplantation, and death. The model cycle length was 1 year. The time horizon was from the starting age (base-case 46 years) until death. Annual transitional probabilities to death were calculated on the basis of 5-year mortality rates derived from the Alpha-1-Antitrypsin Deficiency Registry Study (see Other Publications of Related Interest).

Outcomes assessed in the review
The parameters used in the model included:

- the progression of lung dysfunction on the basis of the mean annual FEV1 decline for each disease state;
- the annual transitional probabilities to death;
- the annual probability of death for patients with an FEV1 below 50%;
- disease-specific mortality rates;
- the mortality rates from causes other than AAT deficiency; and
- the lung transplantation rate.

**Study designs and other criteria for inclusion in the review**
No inclusion criteria for a review of any of the parameters were reported. The study was based on data coming from the Alpha-1-Antitrypsin Deficiency Registry Study (see Other Publications of Related Interest).

**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**
Although the authors reported that one primary study was the main source of the effectiveness evidence (see Other Publications of Related Interest), four other studies also provided selected outcome measures.

**Methods of combining primary studies**
A narrative method was used to combine the studies.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The parameters used in the model for the base-case were as follows.

For patients receiving augmentation therapy, the annual FEV1 decline mean +/- standard deviation, SD) was 73.7 (+/- 56.9) mL for FEV1 50 - 79% predicted, 66.4 (+/- 59.4) mL for FEV1 35 - 49% predicted, and 43.9 (+/- 63.5) mL for FEV1 below 35% predicted.

For patients not receiving augmentation therapy, the annual FEV1 decline (mean +/- SD) was 81.2 (+/- 56.3) mL for FEV1 50 - 79% predicted, 93.2 (+/- 56.6) mL for FEV1 35 - 49% predicted, and 46.5 (+/- 61.7) mL for FEV1 below 35% predicted.
The annual probability of death for those with an FEV1 above 50% predicted was 0.006.

The annual probability of death attributed to AAT deficiency for those with an FEV1 below 50% predicted and taking augmentation therapy was 0.02905. For those not taking augmentation therapy, this value was 0.07405.

Deaths from causes other than AAT deficiency were also included in the model using standard US life table mortality rates.

The probability of lung transplant when FEV1 was below 15% predicted was 0.19.

Methods used to derive estimates of effectiveness
The estimates were derived from published data, experts' opinions, and authors' assumptions.

Estimates of effectiveness and key assumptions
The disease-specific mortality rates (i.e. mortality attributed to AAT deficiency) were determined by adjusting all-cause mortality rates from the Registry by standard life table mortality rates. The AAT deficiency-specific mortality rate was added to the mortality rate from other causes to calculate the total annual mortality rate.

As in the Registry, since no significant difference in mortality rates was observed between patients receiving and not receiving augmentation therapy (for individuals with an FEV1 greater than 50%), they were assigned the same annual probability of death.

In the base-case analysis, the authors estimated that 19% of patients with an FEV1 below 15% predicted received lung transplantation.

The authors also reported they assumed several characteristics for AAT-deficient patients. Specifically, they assumed that all patients had the PI*ZZ phenotype, were current nonsmokers, and that the rate of lung function decline was the same in men and women. On the basis of the average characteristics of NHLBI Registry participants, they assumed that patients entering the model were 46 years old and had an FEV1 of 49% predicted. The analysis made further assumptions. First, that all patients received usual COPD therapy irrespective of augmentation therapy use. Second, that augmentation therapy is started immediately when patients enter the model. Finally, that lung transplantation is considered only when the FEV1 is below 15% predicted.

Measure of benefits used in the economic analysis
The authors used the quality-adjusted life-years (QALYs) as a measurement of benefit. The utility data were obtained through a prospective survey of pulmonologists experienced in treating AAT deficiency using the health utilities index (Mark III) (Feeny et al., see Other Publications of Related Interest). For each health state in the model, the 14 respondents completed the health utilities index to provide the estimated utility weights.

In the base-case analysis, utilities were defined for the health states. More specifically, 0.93 for Stage I chronic obstructive pulmonary disorder (COPD), 0.75 for Stage II COPD, and 0.26 for Stage III COPD. The ranges of state utilities were also reported for the sensitivity analysis.

An annual discount rate of 3% was applied.

Direct costs
Medical direct costs were included in the analysis conducted from the perspective of the health care system. These costs were for medication, augmentation therapy infusion, managing patients with AAT deficiency other than augmentation therapy (including the cost of medications, oxygen therapy, laboratory and diagnostic tests, clinic and emergency department visits, and hospitalisations), transplantation, and post-transplantation care.

The base-case analysis assumed a 70-kg individual who receives weekly 1-hour augmentation therapy infusions of 60
mg/kg. The costs of augmentation therapy with Prolastin (Bayer) were estimated using the 2001 average wholesale price and Medicare reimbursement rates for a 1-hour infusion, where a 500-mg vial of the drug (as the smallest dispensing unit) required a weekly use of 4,500 mg. The cost of managing patients with AAT deficiency other than augmentation therapy was estimated using data from a retrospective analysis of the cost of managing COPD. The costs of transplantation and post-transplantation care were derived from published pharmacoeconomic studies of lung transplant patients.

The authors reported some examples of the process followed to derive the costs for the model base-case, but they did not report the quantities and the costs separately. The quantities and the total costs were estimated using modelling.

The costs from previous years were converted to year 2001 dollars using the medical care services component of the Consumer Price Index. All the costs were discounted at an annual rate of 3%.

**Statistical analysis of costs**

No statistical analysis of the costs was reported.

**Indirect Costs**

No indirect costs were included in the study.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analyses were used to investigate areas of uncertainty relating to variability in the data. A one-way sensitivity analysis was conducted for all variables in the model. The sensitivity ranges for annual FEV1 decline and probability of death were determined by the 95% confidence intervals. The costs and the utility weights were both halved and doubled. Extensive sensitivity analyses were conducted for the length of treatment and the duration of clinical benefit of augmentation therapy. Other effects investigated were:

- changing the discount rate to 0%;
- setting the utility weights equal to 1 for all health states;
- the potential impact of a systematic bias of health state utilities by simultaneously halving and doubling all utilities in the same direction; and
- changing all the costs simultaneously.

A threshold analysis was also conducted to determine the annual cost of augmentation therapy at which the incremental cost-effectiveness ratio (ICER) of augmentation went below $100,000 and $50,000 per QALY, respectively.

**Estimated benefits used in the economic analysis**

The base-case results showed that treating patients with augmentation therapy for life led to 7.19 QALYs. Treating patients until the FEV1 falls below 35% produced 6.64 QALYs, while the no treatment strategy produced 4.62 QALYs.

**Cost results**

In the base-case, the cost of treating patients with augmentation therapy for life produced the highest cost, $895,243. Treating patients until the FEV1 falls below 35% predicted cost $419,839, while the no treatment strategy cost $92,091.
Synthesis of costs and benefits
The estimated benefits and costs were combined using an ICER. This was calculated as the difference in cost divided by the gain in QALYs. The ICER was $207,841 for treating patients until the FEV1 falls below 35%, and $696,933 for treating patients with augmentation therapy for life. In comparing directly the treatment for life with the no treatment strategy, the ICER for the treatment for life strategy was $312,511 per QALY.

Authors' conclusions
According to the authors, the main finding of this study was that the incremental cost-effectiveness ratio (ICER) of intravenous augmentation therapy for individuals with severe alpha1-antitrypsin (AAT) deficiency exceeded prior estimates. They stated that their estimates of the cost per quality-adjusted life-year (QALY) gained for augmentation therapy suggested that augmentation therapy was not as cost-effective as therapies reported in earlier analyses. In the scenario in which augmentation therapy was for life, the yearly cost of augmentation therapy would need to be reduced from over $50,000 to $4,900 to reach an ICER below $50,000 per QALY gained.

CRD COMMENTARY - Selection of comparators
The authors gave a justification for the comparators. Intravenous augmentation therapy with pooled human plasma alpha1-proteinase inhibitor is currently the only available Food and Drug Administration approved specific therapy for AAT deficiency. You should judge whether these strategies are relevant in your setting, or whether other comparators or other drugs could also be relevant.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used. The authors used data from the available studies selectively. As such, one cannot be sure that all the relevant literature was identified, although the main source appears to have been a valid one for this rare disease. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, experts' opinions and their own assumptions. The effectiveness evidence was derived from a prospective cohort study, which is an adequate source for this disease type. The authors justified their assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses, with some of the ranges determined by 95% confidence intervals and some varied selectively. The authors did not provide a justification for the ranges selected and reported.

Validity of estimate of measure of benefit
The authors used the QALYs as a measure of benefits. These were derived from a Markov model. This measure of benefit enables cross health technology comparisons. The methods used to derive the utility weights were reported. The utility weights relied on experts who are known to have systematic difference in comparison with patients or the general public. Sensitivity analyses of the utility weights, in which the values were halved and doubled to produce the ranges used, were conducted.

Validity of estimate of costs
The authors reported that the study had been conducted adequately from the perspective of a health care system, considering only the direct medical costs. Although all the costs were taken from different sources and years, discounting was appropriately carried out since the time horizon exceeded two years. The price year was reported, which will aid any future reflation exercise. The prices were taken from published sources, but not all resource use quantities were reported separately. Sensitivity analyses of resource quantities or prices were not reported separately. The annual costs were halved and doubled to determine sensitivity ranges, and the discount rate was varied from 0 to 7%.

Other issues
The authors compared their findings with those from other studies which, in general, showed that augmentation therapy
conferred a high cost per QALY. The issue of the generalisability of the results to other settings was not addressed. The authors' conclusions reflected the scope of the analysis. The authors acknowledge some limitations of their study. First, they were unaware of incidence data of transplantation for AAT deficiency to guide their estimates. Second, the indirect costs were not assessed in the study.

**Implications of the study**
The authors stated that the unfavourable cost-effectiveness estimates of this study should be considered in the context that intravenous augmentation therapy with pooled human plasma AAT remains the only specific therapy currently available for individuals with severe AAT deficiency. They stated that their findings should encourage the evaluation of alternative treatments under development, which are both more clinically effective and more cost-effective than existing specific therapy, such as using alternate routes of administration (e.g. inhalation) or recombinant-produced AAT.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
alpha 1-Antitrypsin Deficiency /diagnosis /drug therapy /economics; Comparative Study; Cost-Benefit Analysis; Drug Administration Schedule; Female; Humans; Long-Term Care; Male; Markov Chains; Protease Inhibitors /administration & dosage /economics; Quality-Adjusted Life Years; Registries; Respiratory Function Tests; Sensitivity and Specificity; Severity of Illness Index

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