rhDNase therapy for the treatment of cystic fibrosis patients with mild to moderate lung disease

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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
rhDNase therapy for the treatment of cystic fibrosis patients with mild to moderate lung disease.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Cystic fibrosis patients aged 5 years or over with mild to moderate lung disease.

Setting
Hospital. The study was set in the UK.

Dates to which data relate
Effectiveness and resource use data were collected from studies published between 1992 and 1998 and from clinical expert opinion. Cost data were collected from 1996-1998 sources. The price year was not reported.

Source of effectiveness data
Effectiveness data were derived from a literature review.

Modelling
A decision analytic model, based on one of the randomised controlled trials (RCTs) identified in the review, was used to determine the cost-effectiveness of rhDNase therapy.

Outcomes assessed in the review
The review assessed the short-term and long-term effectiveness of rhDNase therapy in patient subgroups, including its effect on forced expiratory volume (FEV), forced vital capacity (FVC), pulmonary function, and adverse effects.

Study designs and other criteria for inclusion in the review
The data on the short-term efficacy of rhDNase therapy were derived from a large, multi-centre, randomised, double-blind, placebo controlled trial over a 24-week period. Inclusion criteria were RCTs and cost-effectiveness analyses comparing rhDNase with placebo in CF patients with mild to moderate lung disease. RCTs of very short duration (14
days or less) were excluded. Open label extensions providing information on longer term outcomes were included. Evidence on the efficacy of rhDNase therapy in patient subgroups was derived from a retrospective case series.

**Sources searched to identify primary studies**


**Criteria used to ensure the validity of primary studies**

Studies were appraised using a standardised checklist from the Critical Appraisal Skills Programme.

**Methods used to judge relevance and validity, and for extracting data**

Results were extracted by one of the authors.

**Number of primary studies included**

At least 20 studies were included.

**Methods of combining primary studies**

Narrative method.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

Administration of rhDNase reduced the age-adjusted risk of respiratory exacerbation by 28% if used once daily and by 37% if used twice daily. FEV in one second improved by a mean of 5.8% (+/- 0.7%) from baseline for once daily treatment, and by 5.6% (+/- 0.7%) for twice daily treatment, (p<0.01). FVC improved by 3.8% (+/- 0.6%) from baseline for once daily treatment and by 3.0% (+/- 0.6%) for twice daily treatment, (p=0.01). Improved pulmonary function was maintained in 32% of patients and was maintained over a 2-year period. rhDNase did not appear to have serious adverse effects, other than voice alteration, pharyngitis, laryngitis, rash, chest pain and conjunctivitis. The response to rhDNase was highly variable, and there was no predictive marker at baseline for a good response. Early improvement was the best predictive marker for long-term benefit.

FEV declined at a rate of 4.2% per year from 100% of predicted value at birth to the age of 13 years, then the rate of decline diminished to 2.77% per year. The initial FEV of patients starting treatment was 61.1% of the predicted value. Once FEV fell to this level all patients would be started on rhDNase. Patients receiving rhDNase would have a FEV 5.8% higher than they would have otherwise had throughout the course of treatment. Death would occur in the year that FEV fell below 28% of the predicted value.

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

The number of life years gained was used as the measure of benefits. Benefits were not discounted in the base case analysis.

**Direct costs**

Direct costs were discounted at an annual rate of 6%. Quantities and costs were not reported separately. Direct costs
included drug costs and hospitalisation costs. The quantity/cost boundary adopted was that of the hospital. The estimation of quantities and costs was based on actual data. Cost information was identified from the British National Formulary and from the Extra Contractual Referral tariffs within the (NHS) South and West Region for 1996/1997. The price year was not reported.

Statistical analysis of costs
No statistical analysis of costs was reported.

Indirect Costs
Indirect costs were not included.

Currency
UK pounds sterling ( ).

Sensitivity analysis
Sensitivity analyses were conducted on the rate of decline in FEV, the initial FEV at start of treatment, the percentage improvement in FEV with rhDNase, the length of treatment, and the discount rate.

Estimated benefits used in the economic analysis
The continued use of rhDNase over the lifetime of a CF patient might extend their life expectancy by 2 years. The continued use of rhDNase over the lifetime of a CF patient whose FEV fell below 70% of predicted value might extend their life expectancy by 7 years. This result was sensitive to changes in the improvement in FEV with rhDNase.

Cost results
Treatment for one year at 2.5 mg daily costs about 7,442 per patient. A saving of 1,746 per patient responding to rhDNase was achieved in terms of hospitalisation costs.

Synthesis of costs and benefits
The discounted cost per life year gained for all patients was 52,500, which ranged from 25,000 to 57,000 in the sensitivity analysis. For patients whose FEV fell below 70% of the predicted value, the discounted cost per life year gained was 16,000 (range: 18,000 - 36,600 in the sensitivity analysis).

Authors' conclusions
Although there is short-term evidence that the use of rhDNase improves lung function and decreases the risk of respiratory exacerbation, there is no evidence to indicate whether this effect is sustained over a longer time period, or whether rhDNase is associated with a reduction in mortality.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used, namely placebo. Placebo was used in the RCT which met the authors' inclusion criteria, and which was used to construct the model to determine cost-effectiveness.

Validity of estimate of measure of benefit
The authors appear to have undertaken a systematic review of the literature but more details could have been provided about the design of the review, and the method of combining primary effectiveness estimates. Unpublished studies and those in languages other than English were not considered. Estimation of benefits was obtained directly from the
effectiveness analysis.

**Validity of estimate of costs**
All relevant cost categories appear to have been included. Any savings resulting from the decreased use of antibiotics could not, however, be generalised to the UK, and hence were not considered. Quantities and costs were not reported separately. Sensitivity analyses were conducted on some quantities, but not on costs. Some cost estimates were based on tariffs. The price year was not reported.

**Other issues**
The issue of generalisability to other settings was discussed in terms of the RCT from the United States used in the model and its limitations in terms of generalising the results to a UK setting. The authors did not present their results selectively. The study examined CF patients aged 5 years or older with mild to moderate lung disease, and this was reflected in the authors' conclusions. It is unlikely that FEV will decline at a steady rate over the course of a lifetime or that the use of rhDNase will improve FEV by an equal amount each year.

**Implications of the study**
Further long-term research is needed, with economic analysis to evaluate the long-term cost-effectiveness of rhDNase. Research is also needed to identify, in advance, which patients would benefit most from this expensive treatment.

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