Effects of hypertonic saline, alternate day and daily rhDNase on healthcare use, costs and outcomes in children with cystic fibrosis


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
Daily recombinant human deoxyribonuclease (rhDNase) was compared with nebulised hypertonic saline (HS) in the treatment of children with cystic fibrosis (CF). The treatment options compared were 2.5 mg rhDNase administered daily, alternate day 2.5 mg rhDNase, or 5 mL 7% HS administered twice daily.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children aged between 5 and 18 years who had CF. To be included in the trial, children had to be able to undergo spirometric tests and to be either currently on rhDNase or have a forced expiratory volume in 1 second (FEV1) of less than 70% predicted. Exclusion criteria were the inability to take the trial medication, known hypersensitivity to rhDNase or HS, isolation of Burkholderia cepacia in the sputum, pregnancy and breastfeeding. To ensure the patients were enrolled when they were clinically stable, they had to be free of lower tract infections requiring a change in antibiotics, steroids or bronchodilator treatment 14 days before randomisation.

Setting
The study took place in two postgraduate hospitals. The economic analysis was carried out in London UK.

Dates to which data relate
The effectiveness data were collected for patients treated between April 1999 and March 2000. The data on resource use were collected during the same time. The costs used were based on 1999 to 2000 prices.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study. The costing from a district general hospital was also presented, to represent care provided by that type of institution.

Study sample
Power calculations were calculated on the basis of change in FEV1 (primary clinical outcome). A total of 48 children
were randomised, 8 to each of the six treatment orders. One child dropped out due to prolonged illness and 8 children were unable to complete all three treatment periods. Therefore, 43 children were included in the comparison of daily and alternate day rhDNase, and 40 in the comparison of daily rhDNase and HS. Patients already on rhDNase or HS discontinued the treatment at least 2 weeks before the study, in order for a complete washout to occur for both rhDNase and HS.

Study design
The study was a prospective open, randomised crossover trial carried out in multi-centres. Each patient was allocated to receive, in random order, consecutive 12-week treatments of 2.5 mg rhDNase once daily, 2.5 mg rhDNase on alternate days, and 5 mL 7% HS twice daily. There was a 2-week washout period between the treatments. The patients were followed for a minimum of 40 weeks.

Analysis of effectiveness
The basis of the analysis of the clinical study was intention to treat. The primary health outcome was the change in FEV1. The secondary outcomes included quality of life and the number of pulmonary exacerbations, which were defined using an outlined protocol for respiratory tract infection. Adherence to treatment was monitored in two ways. The patients were asked to return all unused bottles of HS and used vials of rhDNase, and they also recorded the treatment doses taken for each trial drug in a patient diary.

Effectiveness results
There was a mean increase in FEV1 from baseline of 16 (25%) for patients receiving daily rhDNase, 14 (23%) for patients receiving alternate rhDNase, and 3 (21%) for patients receiving HS.

Comparing the mean FEV1, there was a mean advantage of 8% (95% confidence interval, CI: 2 - 14; \( p=0.01 \)) for daily rhDNase over HS, but none for daily rhDNase compared with alternate day rhDNase (2%, 95% CI: -4 - 9; \( p=0.55 \)).

There were variations to individual responses to treatments. Twenty-six of the 40 children responded better with daily rhDNase than with HS.

There was no evidence of differences in the quality of life, or in the occurrence of pulmonary exacerbations, between the treatments.

Clinical conclusions
The authors concluded that their study found that daily rhDNase was more effective than HS. In addition, administering rhDNase on alternate days was as effective as administering it on a daily basis.

Measure of benefits used in the economic analysis
The primary outcome measure in the economic analysis was the change in FEV1. The secondary outcome measures included quality of life and the number of pulmonary exacerbations. Quality of life was measured using the quality of well-being scale. The number of exacerbations was defined using an outlined protocol for respiratory tract infections.

Direct costs
Discounting was not carried out since the costs were incurred less than 2 years. The costs and the quantities were reported separately. All health care resources including hospital contacts (inpatient, outpatient and ward review), radiological investigations, blood tests, drug use and the use of community services (including community nurse, physiotherapist and general practitioner) were assessed. The study was conducted from a health service perspective. The quantities were estimated from actual data. The source of the resources used was the patients' hospital notes and diaries. The cost data were collected from the relevant departments. The finance departments at the three hospitals also provided information on the total costs of consumables and overheads on the ward or department where CF patients
were treated. All the costs were adjusted to 1999 to 2000 prices using the hospital and community health services price index.

**Statistical analysis of costs**
The costs were treated in a stochastic manner. Pairwise comparisons were carried out on the mean differences between the treatments. Due to skewed cost distributions, the 95% CIs around the total mean cost differences between the two groups were calculated using non-parametric bootstrapping techniques.

**Indirect Costs**
No indirect costs were considered.

**Currency**
UK pounds sterling (GBP).

**Sensitivity analysis**
A one-way sensitivity analysis was carried out on the price of rhDNase, which might be lower than that quoted in the British National Formulary. Also, on the cost per hospital bed, which could have varied depending on the setting. The cost of rhDNase was reduced by 10% and 30%, while the cost per bed was varied from 187 to 120. No justification for the choice of ranges was reported.

**Estimated benefits used in the economic analysis**
The estimated benefit use in the economic analysis was the change in FEV1.

**Cost results**
Over the 12 weeks, the mean drug cost was 1,755 for rhDNase versus 37 for HS. This difference in the intervention cost was not offset by lower hospital and community care costs.

The total health service cost was 5,694 for daily rhDNase compared with 4,285 for HS. The mean difference was 1,409 (95% CI: 440 - 2,318).

In the comparison of daily and alternate rhDNase, the mean costs were 5,711 (daily) and 5,198 (alternate), respectively. The mean difference was 513 (95% CI: -546 - 1,510).

Compared with HS, the mean additional costs of rhDNase fell to 1,234 (95% CI: 264 - 2,204) when the price of rhDNase was reduced by 10%, and to 884 (95% CI: -85 - 1,885) when it was reduced by 30%. The mean additional costs of daily compared with alternate day rhDNase were 425 (95% CI: 594 - 1,443) and 246 (95% CI: -771 - 1,262).

**Synthesis of costs and benefits**
The estimated benefits and costs were not combined.

**Authors' conclusions**
Daily recombinant human deoxyribonuclease (rhDNase) was more effective than hypertonic saline (HS), but it increased the costs by 1,409 over 12 weeks. Administering rhDNase on alternate days, rather than on a daily basis, was as effective and had potential cost-savings of 513 over a 12-week period.
The authors justified their choice of the comparator since it represented a valid treatment option in their setting. You should decide if the comparator represents a valid option in your setting.

**Validity of estimate of measure of effectiveness**
The analysis used a prospective randomised controlled crossover design, which was appropriate for the study question. The study sample appears to have been representative of the study population. The internal validity of the study is likely to be quite high due to the randomisation process. The authors indicated that there was evidence that the period between the treatments was sufficient for a complete washout. If the washout period was insufficient it would be difficult to establish the effectiveness of each separate treatment. Power calculations were conducted to ensure that the sample size was large enough to detect statistical significance.

**Validity of estimate of measure of benefit**
The measure of benefit was obtained directly from the effectiveness analysis. The authors indicated that the details of the health economic assessment were in a study reported elsewhere (see Other Publications of Related Interest).

**Validity of estimate of costs**
All the categories of costs relevant to the perspective adopted (the health service) appear to have been included in the analysis. The resource use quantities were taken from a single study and statistical analyses of the quantities were undertaken. The indirect costs were not included as the perspective of the study only considered the direct costs. The authors highlight the fact that taking a societal perspective (i.e. including indirect costs) would be unlikely to change the results. Both statistical and sensitivity analysis were undertaken on the costs. Discounting was not undertaken since all the costs were incurred in a period of 12 months. The dates to which the prices related were reported. In addition, the costs and the quantities were reported separately. These factors enhance the reproducibility of the results in other settings.

**Other issues**
The authors made appropriate comparisons of both the effectiveness and study results with those from other studies. In addition, the issue of generalisability was addressed. The authors do not appear to have presented their findings selectively and their conclusions reflect the scope of the analysis. The authors reported a shortcoming of their study in that it would have required about four times as many patients for the observed difference in cost to have been found statistically significant. Power calculations were conducted to ensure that the study was powered to detect differences in the effectiveness measures, but not in the costs.

**Implications of the study**
The authors indicated that there is a need for further research to assess the long-term costs and consequences of the respective strategies. In particular, to examine the relative use of hospital resources for larger groups of patients over a longer period of time. They also highlighted the fact that further studies may benefit from stating in advance what constitutes an important differential in the total cost, and then using a measure of variability from the study to perform sample size calculations.

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**Bibliographic details**

**PubMedID**
Other publications of related interest

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