Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial


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 health technologies studied were alternate-day, or daily recombinant human deoxyribonuclease (rhDNase) (2.5 mg once daily) or hypertonic saline (HS) for the treatment of children with cystic fibrosis. The human enzyme rhDNase was cloned and sequenced in 1990 and has been shown to improve lung functions. The enzyme works by cleaving extracellular DNA in airway secretions, thereby aiding expectoration of sputum.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children with cystic fibrosis. Inclusion criteria were: age between 5 and 18 years; ability to carry out spirometry; and either current treatment with rhDNase or a forced expiratory volume in 1 second (FEV1) of less than 70% of predicted. Exclusion criteria were: inability to take the trial medication; known hypersensitivity to rhDNase of HS; isolation of Burkholderia cepacia in the sputum; pregnancy; and breastfeeding. Patients had to have no lower-respiratory-tract infection during the 14 days before the start of the study.

Setting
The setting was hospital and community. The economic study was carried out in the UK.

Dates to which data relate
The dates during which the effectiveness and resource use data were collected were not reported, and the price year was not reported. Unit costs were gathered in 1999 and 2000.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were performed in the planning phase: it was estimated that a sample of 40 subjects would have ensured a power of more than 90% to detect, at the 5% significance level, an average difference of 8% (0.1L of FEV1).
in the final measurements between any two treatments. The authors aimed to recruit 50 patients to allow for withdrawals and non-adherence. Sixty-two patients were eligible for the study. However, 14 were excluded (4 were clinically unstable and 10 declined to participate). Forty-eight patients were enrolled in the study, but one subject dropped out immediately, therefore the study sample comprised 47 patients (mean age 12.6 years, 40% male). Baseline characteristics were also given by current treatment at enrolment and lung microbiology.

Each patient was allocated to consecutive 12-week treatments of once-daily 2.5mg rhDNase, alternate-day 2.5mg rhDNase, and twice-daily 5mL 7% HS. Children were then aggregated in six groups, corresponding to the six possible treatment orders. Of the 48 patients enrolled, 45 subjects completed the first treatment (3 withdrawn), 44 patients completed the second treatment (1 withdrawn), and 40 completed the third treatment (1 withdrawn and 3 ineligible for HS). Overall, 43 patients were included in the comparison of daily and alternate-day rhDNase and 40 children in the comparison of daily rhDNase and HS.

**Study design**
The study was an open, cross-over, randomised, controlled trial. Blinding was not possible due to the readily apparent differences between HS and rhDNase. The study was carried out in two centres: Great Ormond Street Hospital for Children NHS Trust and Royal Brompton and Harefield NHS Trust in London. Patients were allocated randomly to the various groups. Randomisation was co-ordinated by an independent unit and was then stratified by hospital. A two-week washout period was considered between treatments and patients were assessed at the start and end of each 12-week treatment period.

**Analysis of effectiveness**
The effectiveness analysis was based on intention to treat. The primary health outcome used in the study was FEV1. Secondary health outcomes were forced vital capacity (FVC), number of pulmonary exacerbations, weight gain, exercise tolerance, and quality of life. FEV1 and FVC were measured in accordance with the guidelines of the American Thoracic Society. Pulmonary exacerbation was defined for the specific purpose of the study, and quality of life was assessed through the quality of well-being-scale self-administered form 1.04, based on a questionnaire which produced a score between 0 (death) and 1 (symptom-free full function). Statistical analyses of results (multiple regression) were conducted to adjust for the role of some factors (age of the children, treatment period, and quarterly season of the year). Subgroup analyses were conducted to investigate whether disease severity (initial FEV1) affected the treatment-group differences.

**Effectiveness results**
The effectiveness results were as follows:

With respect to FEV1, the mean percentage change was 16% (SD = 25) for daily rhDNase, 14% (SD = 22) for alternate-day rhDNase, and 3% (SD = 21) for HS.

There was an 8% advantage of daily rhDNase over HS (95% CI: 2 - 14; p=0.01) but the 2% advantage of daily rhDNase over alternate-day rhDNase was not statistically significant (95% CI: -4 - 9; p=0.55).

Adjustments for age of the children, treatment period, and quarterly season of the year confirmed the results.

There were no statistically significant differences among the treatments with respect to secondary outcomes, the authors referring to the office of the Lancet for this data.

**Clinical conclusions**
The effectiveness analysis indicated that there was no statistically significant difference between daily rhDNase and alternate-day rhDNase. However, HS was statistically significantly much less effective than daily rhDNase.
Measure of benefits used in the economic analysis
Health outcomes were left disaggregated and no summary benefit measure was used, therefore a cost-consequence analysis was carried out.

Direct costs
Discounting was not relevant because costs were incurred over a period of time shorter than two years. Quantities and unit costs were not reported separately. The resource/cost boundary adopted was that of the hospital and of the community health system. The cost analysis included intervention costs (professionals’ time, consumables, and overheads), hospital costs (inpatient, outpatient, and day-use), and community services (visits to general practitioners, district nurses, and physiotherapists). The estimation of costs was based on actual data mainly derived from the finance departments of the two hospitals involved in the study and from a district general hospital. Drug and community costs were taken from the British National Formulary and from some published studies. Unit costs were gathered in 1999 and 2000. However, the dates during which resource use data were gathered and the price year were not reported.

Statistical analysis of costs
A statistical test of difference of costs was reported.

Indirect Costs
No indirect costs were included.

Currency
UK pounds sterling (£).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See effectiveness results above.

Cost results
The cost results were as follows:

In the comparison of daily rhDNase and HS, intervention costs were 1,755 versus 37, other drug costs amounted to 2,271 versus 2,364, and hospital and community costs were 1,668 versus 1,883, respectively.

Total costs were 5,694 for daily rhDNase and 4,285 for HS.

In the comparison of daily rhDNase and alternate-day rhDNase, intervention costs were 1,749 versus 857, other drug costs amounted to 2,367 versus 2,349, and hospital and community costs were 1,595 versus 1,992, respectively.

Total costs were equal to 5,711 for daily rhDNase and 5,198 for HS but the difference (513) was not statistically significant.

Synthesis of costs and benefits
Not applicable.
Authors’ conclusions
The authors concluded that the analysis indicated that there was no evidence of a difference between daily and alternate-day rhDNase either in terms of costs or effectiveness. Although HS was less costly, it was also substantially less effective than daily rhDNase.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of comparators was clear as, based on established practice and prior research, they are considered to be potential alternatives. You should consider whether they are widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the study is likely to be high given that the study design was a randomised clinical trial. In addition, power calculations were performed in the planning phase to detect significant differences among the health outcomes and statistical analyses were conducted to take into account the role of potential confounding factors. The measures of effectiveness appeared to be appropriate to the technologies studied and covered a wide range of patient experience. It is unfortunate that the complete results were not published.

Validity of estimate of measure of benefit
Since there was no summary measure of benefit, please refer to the commentary on effectiveness above.

Validity of estimate of costs
Quantities and unit costs were not reported or analysed separately and the price year was not reported. Furthermore, the cost estimates were quite specific to the study setting. Only a few details relative to the resources used were reported, although statistical analyses of costs were carried out. Generally, these failings result in reduced transparency, and hence difficulty in testing for possible biases or generalisability.

Other issues
The authors compared their findings with those of other studies, and their results appeared to confirm previous analyses. However, sensitivity analyses were not performed, thus the generalisability of the results to other settings appears to be limited. As the authors acknowledged, it would be interesting to adopt a societal perspective and include also patients’ costs, which were likely to be substantial due to the high intensity of care needed by the treated children. The authors also acknowledged that the sample size may have been insufficient to test whether there was a significant difference in total costs between the treatment groups.

Implications of the study
The main implication of the study was that “rhDNase given on alternate days has similar efficacy to a daily regimen”. This result implies that the drug could be administered less frequently, thus reducing both the time and resources necessary for drug administration.

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