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

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Authors' objectives
To assess the short- and long-term effectiveness of rhDNase therapy for the treatment of patients with cystic fibrosis (CF), with mild to moderate lung disease.

Searching
The following databases were searched (search terms not stated): MEDLINE from 1992 to January 1999, the Cochrane Library (Issue 1, 1999), HealthSTAR from 1992 to 1998, EMBASE from 1989 to January 1999, PREMEDLINE and NHS EED. Additional studies were identified by contacting clinical experts within the field and the product manufacturer, and by examining the reference lists of retrieved studies. The cost of rhDNase was obtained from the British National Formulary, and the cost-saving was identified from the Extra Contractual Referral tariffs within the South and West Region (UK) for 1996 to 1997.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and economic analyses were eligible for inclusion. Trials of very short duration, i.e. 14 days or less, were excluded. Open label extensions providing information on longer term outcomes were included. For the subgroup analysis, the authors included relevant literature in the form of clinical trials, cohort studies, case-control studies and case series, to determine whether any evidence for the use of rhDNase in selected subgroups could be found.

Specific interventions included in the review
For inclusion, the intervention had to be rhDNase (Pulmozyme) therapy compared with placebo.

Participants included in the review
For inclusion, the participants had to be adults, or children aged at least 5 years or more, with CF and with mild to moderate lung disease. Trials of CF patients with severe lung disease were excluded.

Outcomes assessed in the review
No a priori outcome measures were stated. The review presented data for the outcomes of age-adjusted risk of respiratory exacerbations, forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and adverse effects.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Relevant studies were evaluated using the standardised checklist from the Critical Skills Appraisal Programme (see Other Publications of Related Interest). The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
One of the authors extracted the data. Review data were extracted for the following categories: study identification, main research question addressed, study designs included, search strategy, main findings and recommendations. Data
extracted for the RCTs included: identifier, number of patients, inclusion criteria, study length, dosage, and main outcome measures.

**Methods of synthesis**

*How were the studies combined?*

Only one trial was included, so a synthesis of studies was irrelevant. The authors then constructed a simplified model to estimate the decline in lung function for patients treated with rhDNase, compared with those who were not treated.

*How were differences between studies investigated?*

The authors did not assess heterogeneity. They did, however, assess the clinical and cost data for a subgroup of patients with moderate lung disease who responded to treatment.

**Results of the review**

Nine RCTs were identified, but only one with 968 participants met the inclusion criteria.

Administration of rhDNase once or twice daily reduced the age-adjusted risk of respiratory exacerbations by 28 and 37%, respectively. The FEV1 improved by on average 5.8% (plus or minus 0.7%) from baseline for once-daily treatment, and by 5.6% (plus or minus 0.7%) for twice-daily treatment (P<0.01). The FVC improved by on average 3.8% (plus or minus 0.6%) from baseline for once-daily treatment (P<0.01), and by 3.0% (plus or minus 0.6%) for twice-daily treatment (P=0.01).

**Adverse effects.**

Data from the trial suggested that rhDNase was well tolerated and did not appear to be associated with any serious adverse events, although less serious side-effects were reported. These side-effects included voice alteration (principally hoarseness), pharyngitis, laryngitis, rash, chest pain and conjunctivitis. At the end of the RCT, antibodies to rhDNase were measurable in 3% of the patients treated once daily, compared with 0% of the placebo group. It is unknown whether this will be a concern with long-term treatment lasting many years.

From the model, it appeared that the continued use of rhDNase over the lifetime of a CF patient might extend their life expectancy by 2 years. If treatment is limited to a subgroup of patients with moderate lung disease who respond to treatment, the continued use of rhDNase might extend their life expectancy by 7 years.

**Cost information**

The authors used the model constructed for clinical effectiveness to also assess the cost-effectiveness. The discounted cost per life-year gained for all patients was estimated to be £52,500; the sensitivity analysis showed this ranged from approximately £25,000 (9 years of treatment) to £57,000 (39 years of treatment). For the subgroup of patients, the discounted cost per life-year gained was estimated to be £16,000, with the sensitivity analysis showing a range of approximately £18,000 to £36,600.

**Authors’ conclusions**

The authors stated that treatment with rhDNase therapy (1 RCT) over a 6-month period improved lung function, and decreased the risk of respiratory exacerbations. Expert opinion suggests that there are identifiable subgroups of patients showing improvement, little or no change, and deterioration, after treatment with rhDNase therapy. RCTs have yet to provide evidence for the long-term impact of rhDNase therapy.

**CRD commentary**

The authors stated the research question and the inclusion and exclusion criteria. The literature search was thorough, although it was not stated whether the search was restricted to English language publications. The authors attempted to find unpublished or grey literature and contacted other researchers. There were no tests for publication bias.

The quality of the included studies was assessed using a recognised scale but the authors did not report how the articles
were selected, or who performed the selection or validity assessment of the included studies. Only one of the authors extracted the data.

The data extraction was reported in tabular format and was discussed briefly in the text of the review. The characteristics of the participants were missing from these details. The studies were not statistically combined since only one trial was included; it would also have been inappropriate to assess heterogeneity. A model was also constructed to predict longer-term outcomes but, as the authors state, this is a simplified version of reality and should be interpreted with caution.

The authors' conclusions appeared to follow from the results but, as stated, should be viewed with caution because of the limitations in the review process.

**Implications of the review for practice and research**

Practice: The authors state that it has been suggested that limiting the treatment to certain groups of patients may be a more reasonable approach in practice, given the high drug cost and varied treatment response.

Research: The authors state that further long-term research is needed, with economic analyses 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.

**Bibliographic details**


**PubMedID**

10651974

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

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