Two years experience with recombinant Human DNase I in the treatment of pulmonary disease in cystic fibrosis

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Recombinant human DNase I (rhDNase) has been shown to improve pulmonary function in patients treated for up to 6 months. A cohort of 52 cystic fibrosis patients with a FVC > 40% predicted were enrolled into an open label study in order to evaluate longer-term effects of rhDNase. They received 2.5 mg rhDNase twice daily for 6 months followed by a 2-week wash-out period, and for the subsequent 18 months were treated with rhDNase once daily. Twenty-six male and 26 female patients with a mean FVC of 2.94 l and FEV$_1$ of 1.47 l were recruited. Thirteen patients did not complete the study; there were seven deaths, three patients withdrew consent and three patients were lost to follow-up. Improvement in pulmonary function was seen following treatment and changes were evaluated as mean percent change from baseline. The maximum improvement occurred in the first month followed by a plateau at a lower level of improvement. The mean improvement in FEV$_1$ over the first month was 13.3% (range 12-14.1%), followed by a plateau at around 7.1% (range 4.6-11.0%) for the subsequent 23 months. Mean FVC was improved by 12.03% (range 9.0-14.3%) over the first month and subsequently 4.2% (range -2.2-10.2%). The effects on pulmonary function were similar for both treatment doses of rhDNase. There was also a steady improvement in weight from a mean of 54.2 kg to 55.7 kg at the end of the study. Analysis of the results of only those patients who completed the full 2-yr treatment period show that changes in pulmonary function and weight were similar to those observed for the whole group. The death rate and adverse event profile were consistent with that seen in a cystic fibrosis population. This study confirms that longer-term treatment with rhDNase maintains the improvement in lung function, is associated with weight gain and has a good safety profile.

Introduction

Bronchopulmonary complications are responsible for much of the mortality and morbidity in cystic fibrosis (CF) (1,2). The chronic occlusion of airways by highly viscoelastic secretions, accompanied by bacterial colonization and persistence promotes the self perpetuating, neutrophil dominated, local immune response. The aggregating neutrophils release neutrophil elastase and oxygen radicals. These products are responsible for much of the lung damage and perpetuate the immune response by inducing chemoattractants, stimulating mucus secretion, and impairing ciliary clearance further. The neutrophil death that accompanies the process termed as ‘frustrated phagocytosis’ contributes to the extracellular deoxyribonucleic acid (DNA) in CF sputum (3). The DNA is present in concentrations of 3–14 mg ml$^{-1}$ (4,5) and the interaction of polymerized DNA and mucous glycoproteins further exacerbates the abnormal rheology of airway secretions in CF. The viscoelastic secretions progressively impair pulmonary function by this pathogenic mechanism and also by occluding the bronchial tree per se.

Current therapies in CF are aimed at promoting clearance of airway secretions, improving nutrition and reducing both inflammation and infection. The role of mucolytic agents aimed at mucous glycoproteins has been controversial (6). Nebulized therapy may cause bronchospasm in some individuals (7) and the use of oral mucolytic agents has produced inconsistent results (8–10). Recombinant human DNase I (rhDNase) depolymerizes extracellular DNA and reduces the viscoelasticity of purulent airway secretions. Initial Phase I studies have been encouraging (11,12) and two Phase II studies have confirmed that rhDNase effectively improves pulmonary function and that short-term treatment is safe (13,14). In the U.K. Phase II study (14), 71 stable CF patients with
mild to moderate pulmonary disease were randomized to receive either placebo or 2.5 mg rhDNase twice daily. FEV₁ was improved by 13.3% on rhDNase compared to a mean change of −0.2% for placebo. The Phase III double-blind placebo controlled study was conducted in 51 centres in North America (15). Nine hundred and sixty-eight CF patients older than 5 years of age with a FVC>40% predicted were randomized to receive either placebo, 2.5 mg rhDNase once daily, or 2.5 mg rhDNase twice daily for 6 months. A modest reduction in the risk of exacerbations of respiratory symptoms requiring parenteral antibiotics was observed (reduction of 22% in the rhDNase once daily group and 34% in the rhDNase twice daily group). Pulmonary function was also improved by about 6% over the 6-month treatment period.

The objectives of the present study were to evaluate the longer-term results of treatment with rhDNase. We have observed a cohort of 52 patients who had participated in the Phase II U.K. study who have received rhDNase over a 2-yr period and report the findings.

Methods

 Fifty-two CF patients with mild to moderate pulmonary disease were treated with 2.5 mg rhDNase twice daily for 6 months followed by a 2-week wash-out period. Subsequently for the remaining period, patients received 2.5 mg rhDNase once daily. The patients were reviewed at regular intervals at a similar time of the day, and pulmonary function was performed at a similar time of the day according to American Thoracic Society Guidelines (16). Height and weight was also measured at each visit. Any adverse events, patient hospitalizations, or changes in medications were recorded.

STATISTICAL ANALYSIS

The results for pulmonary function are presented as mean percentage changes from baseline as mean (with range of means) unless otherwise stated. Conversion of pulmonary function variables to mean percentage changes from baseline allowed an assessment of the effect of treatment in a population with heterogeneous values for pulmonary function as suggested by the American Thoracic Society (17). Changes in lung function for the last 18 months on 2.5 mg rhDNase once daily are calculated from the new baseline values (at 26 weeks) at the end of the 2-week wash-out period. Descriptive statistics are used for the remaining parameters recorded and data that was found to have significant deviations from normality presented as medians (with inter-quartile ranges).

Results

 Twenty-six male and 26 female CF patients with a mean FVC of 2.94 l and FEV₁ of 1.47 l were observed over a 2-yr period. The age range for this cohort was 16–55 years. Treatment with rhDNase improved pulmonary function (Fig. 1). FEV₁ was improved by 13.3% (range 12.1–14.1%) and FVC improved by 12.0% (range 9.0–14.3%) in the first month. Subsequently, there was a plateau at 6.2% (range 4.6–7.8%) for FEV₁ and FVC at 7.2% (range 5.1–10.2%) for the remaining 5 months on 2.5 mg rhDNase twice daily. Two weeks after discontinuation of rhDNase, FEV₁ was 5.7% and FVC 5.9% below baseline. Pulmonary function improved when the patients were recommenced on rhDNase. The mean change for FEV₁ over the last 18 months when patients received 2.5 mg rhDNase once daily was 8.0% (range 5.1–11.0%) and FVC was improved by 1.2% (range −2.2–4.4%). A gradual improvement in weight was observed over the treatment period. Prior to therapy, mean weight was 54.2 (SEM ± 1.2) kg and at the end of the 2-yr period was 55.7 (SEM ± 1.48) kg (Fig. 2). Analysis of the results for only those patients who completed the 2-yr treatment period demonstrates that the relationship for both pulmonary function and weight are maintained, and not an artefact due to the loss of patients who did not respond to treatment or lighter patients.

Respiratory tract infective exacerbations were the major adverse event recorded and there were 157 such events. The data is skewed by four patients who
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In the first month and was then maintained at a mean of 7.1% above baseline for the subsequent 23 months. Improvements in FVC were 12.0% for the first month and 4.2% for the remaining 23 months. Analysis of only those patients who completed the 2-yr treatment period shows that the changes are maintained and are not due to the possible artefact of losing patients who did not respond to therapy. Despite the limitations of an open-label study, these improvements which were maintained for up to 2 yr are considered important especially as lung function declines by 3-4% annually in patients with established pulmonary infection (18,19). In adult CF patients, weight gain is difficult to achieve and is a good indicator of patient well-being. In this cohort, an improvement in weight was observed following treatment with rhDNase.

The incidence of respiratory tract infective exacerbations and other pulmonary complications were consistent to those observed in a CF population (1,2), and comparable to the events observed in the North American Phase III placebo controlled study (15). However, the cohort of patients in the current study were older than those in the Phase III study and had more severe pulmonary disease. The Phase III study had also shown that there was no increase in serious respiratory adverse events such as haemoptysis, dyspnoea and pneumothorax. The incidence of death was also comparable in the control and treatment groups of the Phase III study. There were no unexpected serious respiratory adverse events in our cohort followed for 2 yr. The seven deaths occurred in patients with advanced lung disease (baseline FEV₁ <30%). Baseline FEV₁ for the whole group was 41% predicted and the estimated mortality of patients with a FEV₁ <30% is above 50% within 2 yr (20). Further observation is important to see if survival and morbidity are influenced by therapy.

The long-term results are encouraging as improvements in pulmonary function were maintained above baseline, an increase in weight was observed and drug treatment appeared to be safe.

References


