rhDNase in cystic fibrosis

Chronic pulmonary sepsis is the main cause of morbidity and mortality in cystic fibrosis. It has long been recognised that purulent bronchial secretions contain large amounts (3–14 mg/ml) of deoxyribonucleic acid (DNA) derived from the breakdown of inflammatory cells, particularly neutrophils. DNA concentrations in cystic fibrosis are higher than in other supplicative lung diseases and entanglement of long polymerised chains of DNA within the sputum matrix causes increased sputum viscosity, and may decrease the efficacy of aminoglycoside antibiotics.

In the 1950s bovine pancreatic DNase was first purified. This enzyme, responsible for the breakdown of extracellular DNA, was shown in vitro to reduce the viscosity of purulent sputum and was subsequently approved for human use in 1958. Several uncontrolled clinical trials ensued in patients with bronchitis and cystic fibrosis. Although a degree of efficacy was demonstrated, several severe adverse reactions occurred, possibly as a consequence of other protease impurities in bovine DNase. As a result DNase did not become a widely accepted method of treatment and its use was largely abandoned.

The successful cloning and sequencing of human deoxyribonuclease using genetic recombinant technology in 1990 caused a resurgence of interest in the use of DNase in cystic fibrosis, culminating in the launch of aerosolised recombinant human deoxyribonuclease or rhDNase (Pulmozyme) in 1994. Early studies showed that rhDNase reduced sputum viscosity in patients with cystic fibrosis, was well tolerated, and produced useful short term improvement in forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) of about 10–15%. Having shown that rhDNase was safe and produced useful short term spirometric improvement, longer term studies were needed to determine if the spirometric improvement was maintained.

A report by Shah and colleagues on pages 333–338 of this issue of Thorax has addressed this question. This open study examined the efficacy and safety of 2.5 mg rhDNase given twice a day for six months to 59 adult cystic fibrosis patients with an FVC of over 40% of predicted normal. Over this period there was a mean improvement in FEV₁ and FVC of 6.2% and 7.2% respectively, when compared with the patients’ own baseline values. Small improvements in general wellbeing, symptoms related to cystic fibrosis, and perception of dyspnoea were also shown, although these did not reach statistical significance. The results of the study by Shah and colleagues are broadly similar to a much larger double blind study of over 960 adults and children in the USA. This compared placebo, 2.5 mg rhDNase once daily, and 2.5 mg twice daily over six months in a parallel group design. Both treatment arms demonstrated a mean improvement of FEV₁ by 6% over baseline values when compared with placebo which was sustained over the six month period. The improvement seen in this study and that of Shah et al is less than the improvement seen in the earlier short term studies, although the reason for this is not clear.

The US trial also examined the effect of rhDNase treatment on the risk of developing an infective exacerbation. The use of parenteral antibiotics for respiratory exacerbations was reduced by 28% and 37% in those patients given 2.5 mg rhDNase once or twice daily, respectively. This effect was mirrored by a small reduction in the number of hospital inpatient days during the study, as well as an improvement in the patients’ perception of dyspnoea and overall wellbeing. The fact that the changes in subjective status were significant in this study, but not in the study by Shah et al, probably reflects the difference in study power. There is no evidence to date that rhDNase prevents the development of progressive lung damage. In the study by Shah et al there was a 6% reduction in spirometric values below baseline following cessation of six months treatment with rhDNase. Long term follow up studies are required to address this question properly.

Several questions about the use of rhDNase remain unanswered: should all patients have rhDNase or would selected groups be more likely to benefit? Most studies to date have examined the efficacy of rhDNase in patients with mild to moderate pulmonary disease. Given its mode of action there seems little justification for the use of rhDNase in patients with no evidence of active pulmonary inflammation. More recently the use of rhDNase in cystic fibrosis patients with more severe lung disease has been reported in preliminary form.

In patients with FVC measurements of less than 40% of predicted a similar modest improvement in spirometric values has been demonstrated. The US study showed a heterogeneous response to rhDNase in individual patients, despite the overall mean improvement in spirometric values. It would seem important to record spirometric data before and after initiation of treatment to measure objectively any response, but the criteria on which to base continued treatment are not clear. In the studies so far rhDNase has been administered in addition to existing treatment and, though no interactions have been reported, the optimum combination of rhDNase with other therapies such as nebulised antibiotics, other mucolytics, bronchodilators, and physiotherapy needs to be addressed. The doses of rhDNase studied have ranged from 1.2 to 40 mg per
day; the results suggest that the optimum dose is 2-5 mg once daily, with selected patients benefiting from 2-5 mg twice daily.

A major consideration with this new treatment is its cost, in excess of £20 per day for once daily treatment. This is in addition to the current, not inconsiderable, cost of optimum cystic fibrosis care. It is unclear, given the present NHS funding system, who should pay for this treatment. Hospital provider units may be reluctant to fund continuous outpatient therapy, whilst general practitioners may object to the cost of such a specialised treatment. This question needs to be urgently addressed if treatment is not to be withheld from patients who might benefit. Patient compliance with this additional treatment in a disease already overburdened with time consuming remedies may also be a problem which prevents the full benefit of rhDNase being realised. rhDNase should, however, be a useful additional weapon in the armament of doctors caring for patients with cystic fibrosis, and its selective use would seem justified.

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