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Annotation

Recombinant human DNase (rhDNase) in cystic fibrosis: is it cost effective?

Almost simultaneously with a request to prescribe any novel treatment for our patients, the bellowing voices of the Mr Bumbles, to be found inhabiting our drug and therapeutic committees and our local family health services authorities, will be heard to exclaim, 'More! after he has prescribed the drugs already allotted by the pharmacy!'¹ Thus those of us committed to the care of patients with cystic fibrosis should not have been surprised to encounter a wall of resistance to the introduction of recombinant human DNase (rhDNase) at an estimated cost of £7500 per patient per year. Even after multicentre, international studies conducted by most respected colleagues we were asked to make the case again, and to prove its efficacy and cost effectiveness.

What is cost effectiveness in cystic fibrosis?

The concept of cost effectiveness is fraught with difficulties for clinicians committed to the care of patients with cystic fibrosis. There is no easily defined starting point and no clearcut finishing tape. The cost effectiveness of treatment for cystic fibrosis cannot be assessed in the same way as, for example, the immunisation campaign to eradicate poliomyelitis, which has a well documented preintervention scenario and easy to record end points, both economic (less decimation of the workforce, less money spent on longterm care, no need for further vaccine manufacture), and social (less human suffering). In cystic fibrosis there are no such clear 'beginnings' or 'ends'. We must arbitrarily define clinical stability before introducing and assessing any new treatment, and a patient clinically stable today may not be so tomorrow. Our end points must be changes in respiratory function tests, which several independent variables can affect on any particular day, the incidence of respiratory exacerbations, themselves an ill defined entity, laboratory changes in sputum qualities, which may or may not be clinically relevant, and the subjective observations of our patients.

From the phase 1 trials²⁻³ onwards, patients have reported subjective benefits from treatment with rhDNase: less dyspnoea, less chest congestion, less tenacious sputum,

and easier sputum expectoration.⁴⁻⁵ The value of these outcomes to patients and families is not quantifiable, but is likely to be significant. But what financier ever gambled on subjective evidence?

When given optimal treatment the annual decline in lung function in patients with cystic fibrosis is minimal, and in a substantial number of patients close to zero. Thus any effect that rhDNase has on slowing this rate of decline will take years of monitoring many patients to produce significant results.

Cost effectiveness in cystic fibrosis also means different things to different people: to the patients, if a treatment makes them feel better, it is cost effective whatever the cost; to the budget holder, only if the treatment reduces the need for other medications and for hospital admission *and* has a positive impact on the disease process, is it cost effective; to the clinician, if a treatment improves the patient's clinical condition and quality of life, and potentially prolongs life, *and* if someone is willing to fund it, it is cost effective whatever the cost.

Clinical studies—efficacy

We know that rhDNase is safe and effective in patients over 5 years of age. Early studies in moderate to mild cystic fibrosis showed a mean increase from baseline forced expiratory volume in one second (FEV₁) of about 9–14% within days of starting treatment.^{2-3,6,7} With continued rhDNase use improved respiratory function was maintained, but at a plateau of about 6%. The changes were similar for forced vital capacity (FVC). Improvement in respiratory function with rhDNase was independent of age, sex, or other treatments. In the 24 week phase 3 study, the risk of respiratory exacerbations requiring parenteral antibiotics was reduced by 28–37% in treated patients. As a consequence, these patients had 1.4 fewer hospital days and 2.7 fewer days on parenteral antibiotics. Interestingly, even those patients showing less than 5% increase in FEV₁ during the first two weeks of the phase 3 study, acquired protection against respiratory exacerbations requiring parenteral antibiotics.

Subgroup analysis showed benefit even in children aged 5 to 10 years and in the most mildly affected patients; FVC greater than 85% predicted normal. Subsequent work has also shown a positive, but sometimes late, response in more severely affected patients.⁸

We know that the benefits of treatment are maintained in the medium term. The reduced frequency of respiratory tract infection seen in the 24 week phase 3 study continued throughout a further 24 week open label extension period. Shah *et al* documented a 7% increase from baseline FEV₁ maintained after two years of rhDNase treatment.⁹ Patients also showed a steady increase in mean weight from 54.2 kg to 55.7 kg. This suggests that longer term treatment was associated with a downgrading both of the inflammatory response to lung infection and its catabolic effects. The better sense of wellbeing reported by patients may also have resulted in a better appetite.

We must carefully monitor longer term responses. McColley *et al* analysed 3115 maximum expiratory flow volume curves of 188 patients who had been followed up between 1976 and 1995.¹⁰ Regression analysis showed significant rhDNase effects for FVC, FEV₁, forced expiratory flow FEF₂₅₋₇₅, and FEF₇₅, but suggested a persistent beneficial effect at age 25 years only for FVC of 9% of predicted, and FEV₁ of 5% of predicted.

Clinical studies—cost

The use of healthcare services by the 968 patients in the phase 3 study was prospectively documented.¹¹ The main outcome measures were the number of hospital admissions, days of outpatient antibiotic treatment, and total costs of other care resulting from respiratory tract infections. Patients receiving rhDNase in the standard, once daily, 2.5 mg dose averaged over the 24 week study 0.15 fewer hospital admissions related to respiratory tract infections and 1.5 fewer days of outpatient intravenous antibiotic treatment. These results translate to an annual saving of between \$1800 and \$3700, that is up to 38% of the cost of the drug. The majority of this saving is the reduced cost of inpatient care,¹² and is a conservative estimate as the study did not include differences in doctor visits or frequency of physiotherapy, or the amount of work missed by adult patients or parents of the children with cystic fibrosis during respiratory exacerbations. Thus rhDNase treatment may be cost effective even on a simple credit/debit ledger, taking no account of improvement in patient wellbeing or its potential for prolonging patient survival.

Potential poor compliance with rhDNase treatment

It is generally agreed that rhDNase should be used in addition to existing drug regimens. There is some concern that patient adherence to yet another nebulised therapy might be poor.¹³ Our experience in the Leeds paediatric and adult units is that patients will only request continued rhDNase treatment if they perceive it to be beneficial.

Clinical experience

Although as a group 65 children at the Brompton and Great Ormond Street Hospitals in London treated with rhDNase under field conditions for six months showed an increase in FEV₁ of 14%, there was a wide scatter of responses.¹⁴ Fifteen children had increases greater than 20%, but 15 had worse lung function. After six months a 100 patient, multicentre, Italian study showed the same variability in response with changes in FEV₁ ranging from -17% to +26%.¹⁵ Adult patient experience is similar. In the

Key messages

- rhDNase is an effective additional treatment for a subgroup of patients with cystic fibrosis
- These patients should be monitored for objective evidence of continuing response
- At least one third of the cost of treatment will be recouped from the decreased need for intravenous antibiotic courses
- Conclusive judgments on cost effectiveness depend on the results of longer term studies which are now in process
- All such judgments must be made in the context of the effects of rhDNase on a disease which is fatal, on average, at about 30 years of age

Leeds unit over a mean treatment period of 15 months, 45 (76%) of 59 patients showed a mean improvement in FEV₁ of 15% that was maintained throughout rhDNase treatment. Four had no change and 10 deteriorated.¹⁶ Almost all patients report improved wellbeing during rhDNase treatment, but changes in spirometry do not always reflect patients' subjective impressions of the effects of treatment.^{14 16} Nor are there any clinical parameters associated with a positive spirometric response.¹⁶⁻¹⁸ Careful individual assessment of patients during rhDNase treatment is the only way to identify non-responders and avoid ineffective and expensive prescribing.

After one year of treatment, compared with the year before starting rhDNase, the Leeds patients had received a mean five days fewer of intravenous antibiotics. In the Brompton and Great Ormond Street Hospitals' paediatric group the intravenous antibiotic use fell by a mean of five days over six months. These data represent a considerable cost saving, in keeping with the results of the phase 3 study.

Our uncontrolled clinical experiences of rhDNase use in very severe cystic fibrosis strongly indicate that it plays an important part in preserving both survival and quality of life. Patients with very low respiratory function (FEV₁ less than 20%) can survive, with substantial periods at home, seemingly almost indefinitely with an intensive cocktail of treatments. They are often receiving in conjunction with rhDNase, daily intravenous, nebulised, and oral antibiotics, bronchodilators, inhaled and/or oral steroids, and intensive nutritional support. It is not possible to tease out the percentage contribution to this successful prolongation of reasonable quality life made by rhDNase, but the experience of our unit suggests that it is large. Many such patients can now survive the wait for lung transplant without daily and longterm nasal ventilation. In our unit this was needed more frequently as a 'bridge to transplant' before the availability of rhDNase. We have also used rhDNase successfully in some patients who have deteriorated despite maximal other treatment. We recognise that such anecdotal experiences are not substantive data, but in the early experience of this new treatment believe they are important indicators of the drug's potential cost effectiveness.

Conclusion

rhDNase is still undergoing assessment. It should only be prescribed by major, or established satellite, cystic fibrosis centres where non-responders will be identified by following simple and agreed protocols. In Leeds we have negotiated a hospital funded two week treatment trial for patients with moderate to mild respiratory impairment. In all the early studies a positive effect on lung function was seen

within a few days in this patient group. Those with more severe disease are given a six week trial. Patients are only assessed when in a stable state. Both changes in respiratory function and the patient's subjective impression of the drugs effects are monitored. We are looking for a minimum 10% increase in FEV₁ or FVC from baseline. If there is no improvement in any parameter, treatment is stopped. If the patient feels better but shows no rise in lung function, the trial is extended for a further month. Treatment is stopped if, after that time, there is no objective evidence of a beneficial effect. If the respiratory function improves during the trial period we request that the purchasers fund the continued prescription of rhDNase for that patient.

We still need to know whether improved respiratory function is maintained long term, and whether rhDNase exerts a longterm protective effect against respiratory infection. If continuing benefit is apparent we need to know if this is universal for all responders, or whether the global statistics hide a subgroup of patients who continue to receive an expensive treatment that no longer benefits them. It is essential that these studies are begun now, using those patients involved in the phase 1, 2, and 3 trials. Only future research will tell us if rhDNase improves patient survival.

rhDNase will improve the respiratory health of between one and two third of patients with cystic fibrosis. Some will show dramatic increases in FEV₁ in excess of 20%. Questioning of its cost effectiveness must be seen in the context of a disease that has a mean survival of around 30 years. Sensible but proper medicine dictates an approach as recommended by the USA Consensus Committee—all patients should be considered eligible for a trial of rhDNase therapy if deemed so by their cystic fibrosis specialist. Proper monitoring of patients on treatment will ensure that there is no wastage. In 1997, within this context and these guidelines, rhDNase should satisfy the cost effective criteria of all involved parties. Only additional anticipated studies directed to determining whether rhDNase (1) has a beneficial effect on the underlying pathophysiology of cystic fibrosis and (2) prolongs survival,

will allow us to make final and confident judgments on its true cost effectiveness.

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