

# How do we choose a therapeutic regimen in cystic fibrosis?

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As the range of treatments for cystic fibrosis increases and the costs rise, the clinician is faced with an increasingly complex dilemma to develop a treatment schedule that provides optimal benefit, given financial restraints and the impact of an increasingly complex therapeutic regimen on patient adherence.

Over the past 20 years there has been an exponential increase in research to develop new treatments for the management of cystic fibrosis—particularly following the identification of the CFTR protein and its impact on the composition and function of the surface epithelial cell airway surface liquid. While early progress was achieved in gene therapy, it is the pharmacological modulation of function of the CFTR protein and the airway surface liquid that is more likely to be translated into treatment.

One of the major consequences of the defect in CFTR production is alteration of the airway surface liquid to impair mucociliary clearance and promote infection. There have been several attempts to alter the properties of the airway surface liquid and to reduce the viscosity of the mucus to improve mucociliary clearance. Agents investigated include recombinant human rhDNase,<sup>1</sup> hypertonic saline,<sup>2</sup> dry powder mannitol,<sup>3</sup> amiloride,<sup>2</sup> and 5'-uridine triphosphate.<sup>4</sup> Each has shown a modest benefit and rhDNase has been successfully introduced into the therapeutic routine of many cystic fibrosis centres.

The role of rhDNase was reviewed in *Thorax* some years ago.<sup>5</sup> It has been subjected to two prolonged randomised placebo controlled trials in cystic fibrosis.<sup>6,7</sup> The first compared administration twice daily with once daily and placebo over a 24 week period.<sup>6</sup> The drug produced an initial improvement in lung function and a reduced risk of respiratory exacerbations. The study failed to show a benefit for twice daily administration over that of single dose administration and the rate of decline in lung function after the initial improvement was not different from placebo. In fact, the initial 9% improvement in FEV<sub>1</sub> after 2 weeks had fallen to 5% above placebo at 24 weeks. A similar study of once daily treatment over 24 months in young children with

mild disease showed an initial improvement in lung function which was sustained over a 2 year period and a reduced risk of respiratory tract exacerbation. However, the rate of decline in lung function after the initial improvement was no different from that with placebo.<sup>7</sup> This benefit comes at a considerable cost of approximately £7500 per annum<sup>8</sup> yet, despite the clear initial benefits, it remains unclear whether rhDNase has a positive outcome on the long term outcome in cystic fibrosis.

Hypertonic saline has been shown to improve mucociliary clearance and, in short term studies,<sup>9</sup> results in a similar improvement in lung function to that observed with rhDNase.<sup>10</sup> The mechanism by which hypertonic saline is thought to achieve its benefit is by its favourable effect on mucus rheology and altering the osmotic composition of the airway surface liquid.<sup>11</sup> The lung has the ability to rapidly render inhaled solutions isotonic so the effect of any hyperosmolar aerosol will be dependent on the dose and rate of delivery.

Development costs of new pharmaceutical agents determine their high cost to the consumer. In a study reported in this issue of *Thorax* Suri *et al*<sup>8</sup> have attempted to compare the cost and the effectiveness of daily administration of rhDNase with that of alternate day administration and hypertonic saline. The authors were able to show that alternate day rhDNase was equally as effective as daily treatment and had a moderate cost advantage. Hypertonic saline was found not to be as effective as rhDNase in improving lung function but offered a considerable cost advantage.

Previous clinical trials that showed inhaled mucociliary clearance and improvement in lung function used a dose of 10 ml of either 6% or 7% saline delivered via ultrasonic nebuliser.<sup>2,9</sup> The ultrasonic nebuliser delivers a large volume over a short period of time and has a small residual volume ensuring delivery

of approximately 9 ml per dose. The jet nebuliser used in the current study was filled with a loading dose of 5 ml and would deliver approximately 4 ml over the same time period. As the proposed mechanism of effect for hypertonic saline is dependent on dose and rate of delivery of the hyperosmolar aerosol,<sup>11</sup> the lack of benefit from hypertonic saline observed in this study may be a result of the low dose delivered. It is disappointing that the methodology which had been shown to be effective in earlier clinical trials was not used in the currently reported comparative study. So the question regarding the effectiveness of hyperosmolar aerosols used over a longer period of time remains unanswered.

Cystic fibrosis is a lifelong disease with an extremely variable outcome. In an era when the range of pharmaceuticals available for the management of cystic fibrosis is expanding and where each conveys a modest benefit to the patient, difficult decisions have to be made. Judgements of the benefits of new treatments on long term outcome must be extrapolated from relatively short term clinical trials. The clinician is faced with an increasingly complex dilemma to develop a treatment schedule that provides optimal benefit, given financial restraints and the impact of an increasingly complex therapeutic regimen on patient adherence. Furthermore, as costs of pharmaceuticals escalate, the clinician may be faced with capping of healthcare expenditure. When limited to a fixed sum per patient per year for comprehensive health care, how should the clinician best spend it in a patient with cystic fibrosis? Suri *et al*<sup>11</sup> have clearly shown that alternate day treatment with rhDNase is equally as effective as daily treatment, not only providing a cost advantage but simplifying the therapeutic regimen and reducing the burden for the patient.

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