# Dornase alpha and survival of patients with cystic fibrosis

*Ann-Marie McIntyre*

***Dornase alpha can offer substantial clinical benefits to cystic fibrosis patients, but its long-term impact is as yet unknown. This article attempts to model the impact of continuous dornase alpha use on patient survival and its cost implications for the health-care provider.***

In 1960, the median survival of cystic fibrosis (CF) patients was only 6 years (Tullis and Guyatt, 1995). Babies born in the 1990s with CF are now expected to survive into middle age (Fogarty, 1996). This improvement in survival can be attributed to an improved understanding of the disease and improved treatments. Nevertheless, declining lung function remains the main cause of morbidity and mortality, with the accumulation of thick mucus in the lungs limiting pulmonary function and often leading to recurrent infections and lung damage (Menzin et al, 1996). Obstructive pulmonary disease accounts for over 90% of CF fatalities (Ramsey, 1996).

Dornase alpha (Pulmozyme, Roche Products Ltd, Welwyn Garden City) successfully reduces the viscoelasticity of purulent lung secretions, through the hydrolysis of DNA in the sputum. For the CF patient responding to treatment this can lead to a number of subsequent effects. For example, there is a statistically significant improvement in lung function as shown by the forced expiratory volume ($FEV_1$) and forced vital capacity (FVC), a reduction in the incidence of respiratory tract infections (RTIs) requiring parenteral antibiotics, fewer days in hospital for RTIs and improved wellbeing and quality of life.

These aspects have health economic consequences: the reduced cost of RTI care and improved quality of life, but the increased total cost of care for the CF patient. To estimate the true cost-effectiveness of dornase alpha it is necessary to consider the long-term consequences such as delayed disease progression and longer patient survival. While data for long-term analysis are being collated they are not yet available; this study therefore aims to model the potential long-term health economic benefits of dornase alpha from the perspective of the health-care provider.

**Dr Ann-Marie McIntyre** is Health Economist in Healthcare Management, Roche Products Ltd, Welwyn Garden City, Hertfordshire AL7 3AY

## THE IMPACT OF DORNASE ALPHA USE

Over 12 months the administration of dornase alpha at a dose of 2.5 mg once daily significantly improved pulmonary function, reduced the incidence of RTIs and improved quality of life parameters for CF patients who were clinically stable (patients with a FVC >40% predicted) (Fuchs et al, 1994; Schidlow, 1994).

From a health economic viewpoint such clinical data were found to result in cost savings from reduced RTI-related care, increased total cost consequences and improved quality of life in the short term.

### RTI-related care

Oster et al (1995) found that once-daily dornase alpha reduced the rate of RTIs over 24 weeks, with 73% of patients in the placebo group compared to 78% in the dornase alpha once-daily group remaining free of protocol-defined RTIs (*Table 1*). This had significant resource usage implications. Patients on once-daily dornase alpha were found to have an incidence of RTI-related admission of 41% compared to 56% for placebo patients. It was also noted by Fuchs et al (1994) that these patients spent on average 2.7 fewer days on parenteral antibiotics, 1.3 fewer days in hospital and 1.5 fewer days at home as a result of CF-related illness. A number of studies translated these resource savings into cost savings (*Table 2*) over a 24-week period. The evidence suggested that over a 24-week period, anything from US $700 to US $1682 might be saved on RTI-related care as a result of the use of dornase alpha.

### Total cost implications for dornase alpha

Including the acquisition cost of dornase alpha, Oster et al (1995) found that the cost savings associated with RTI-related care offset approxi-

mately 18.3–37.5% of the acquisition costs of dornase alpha. The question is, therefore, whether this overall cost increase is cost-effective.

As Conway (1997) noted, cost-effectiveness can mean different things to different people. To the patient 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 admissions and has a positive impact on the disease process is it cost effective; to the clinician, if it 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.

### Quality of life

Questionnaires were developed in phase II clinical studies to evaluate the general wellbeing (general feeling, energy, physical activity, appetite and sleep) and CF-related symptoms (sputum production, frequency and severity of cough, chest congestion). Oster et al (1995) noted that, compared to the placebo group, there was significantly less dyspnoea, a significant improvement in overall wellbeing and significantly fewer CF-related symptoms.

## DISEASE PROGRESSION AND SURVIVAL MODEL

### Background

It has been suggested that the recurrent infections of CF patients lead to progressive lung damage and, ultimately, death. Anaokar (1996) suggested that a reduction in RTI exacerbations and improved lung function might halt the progress of the disease or at least delay it. Cramer and Bosso (1996) and Schidlow (1994) suggested that the use of dornase alpha might delay the progression of pulmonary disease in those in whom pulmonary function is declining, especially as the improvement in pulmonary function appears to be sustained as long as treatment is continued. McCoy et al (1996) noted that the use of dornase alpha might even prolong the survival of CF patients.

Long-term evidence to support such claims is not yet available, therefore this study attempts to model the delayed progression of lung function and the possible increased survival time of a patient who positively responds to dornase alpha using Microsoft Excel 97.

### Assumptions

A study by Konstan et al (1995) found that before the age of 13 years, lung function in CF patients declined at a rate of 4.2% per annum and from the age of 13 years by 2.77%. This estimate was used as the default within the model.

**TABLE 1.**
**Phase III clinical trial results**

| | Source | Placebo | Once-daily dornase alpha | Difference |
|---|---|---|---|---|
| Incidence of protocol RTIs (24 weeks) | Oster et al (1995) | 27% | 22% | 6% |
| Incidence of any RTIs (24 weeks) | Oster et al (1995) | 43% | 34% | 9% |
| Change in $FEV_1$ from baseline | Oster et al (1995) | 0 | 5.8% | 5.8% |
| Incidence of hospitalization | Oster et al (1995) | 56% | 41% | 15% |
| Days on parenteral antibiotics | Fuchs et al (1994) | 11.2 | 8.5 | 2.7 |
| Days in hospital | Fuchs et al (1994) | 6.9 | 5.6 | 1.3 |
| Days at home as a result of CF-related illness | Fuchs et al (1994) | 4.8 | 3.3 | 1.5 |
| Dyspnoea scale (change from baseline) | Fuchs et al (1994) | 0.4± 0.6 | −2.1 ± 0.7 | |
| Overall wellbeing score (change from baseline) | Fuchs et al (1994) | −0.058±0.22 | 0.019±0.024 | |
| CF-related symptoms score (change from baseline) | Fuchs et al (1994) | −0.001±0.22 | 0.126±0.025 | |

CF= cystic fibrosis; $FEV_1$= forced expiratory volume in 1 second; RTI = respiratory tract infection

**TABLE 2.**
**Cost of RTI-related care: placebo *vs* dornase alpha**

| | | Placebo | Once-daily dornase alpha | Savings |
|---|---|---|---|---|
| Menzin et al (1996) | UK | – | – | £434 |
| | France | – | – | FF7011 |
| | Germany | – | – | DM1970 |
| | Italy | – | – | ItL1285000 |
| Fuchs et al (1994) | | $6443 | $4761 | $1682 |
| Oster et al (1995) | | $6443 | $4761 | $1682 |

RTI = respiratory tract infection

Even with dornase alpha use this rate of decline was assumed to remain unaltered as there is no clinical evidence to suggest otherwise.

Shah et al (1995) found a mean sustained improvement in $FEV_1$ over 18 months with once-daily dornase alpha of 8%; this was used as the default dornase alpha improvement. The starting point for prescribing dornase alpha was assumed to be $FEV_1$ 70% of predicted, approximately 8 years of age given the rate of decline assumed above. Provided a response is noted the patient will be maintained on dornase alpha until death.

In a study by Kerem et al (1992), it was found that patients with $FEV_1$ <30% had a 50% chance of dying within 2 years. For the model this finding was simplified, assuming that once $FEV_1$ dropped below 28% death would occur.

### Results

Given these simplifying assumptions, *Figure 1* illustrates the decline in lung function for a CF

patient from birth until death comparing standard treatment with standard treatment plus dornase alpha. This treatment is started at the age of 8 years and $FEV_1$ 70% of predicted, with an expected improvement of 8% in $FEV_1$. The model suggests a delay in transition from mild ($FEV_1$ >70%) to moderate disease ($FEV_1$ 40–70%), from moderate to severe ($FEV_1$ <40%) and eventually, an additional 3 years of life for the patient (age at death 41 years with dornase alpha *vs* 38 years without dornase alpha).

### Cost considerations

Robson et al (1992) noted that the average annual cost of treatment for a CF patient was £8241 (£2 792–19 955). It was assumed within the model that the annual cost of treatment for a mild CF patient would be £2 792, for a moderate patient £8 241 and for a severe patient £19 955. All future costs must be discounted so that they do not weigh as heavily in programme decisions (Drummond et al, 1993), therefore all future costs were discounted at 6%. The discounted lifetime cost for a CF patient in this model was estimated at approximately £151 264. This estimate fell within the range of previous estimates from Wildhagen et al (1996) of between £72 166 and £164 365.

Obviously, administration of dornase alpha reduces RTI-related costs as shown by the clinical trials. It was estimated that the cost savings from RTI-related care would offset between 18.3 and 37.5% of the acquisition cost of dornase alpha (Oster et al, 1995). Offsetting the cost of dornase alpha (£7200 per annum) by 18.3%, the discounted lifetime cost for the CF patient would be £233 070 including the acquisition cost of dornase alpha and the additional cost of treatment for 3 extra years of life. The cost per life year gained is £27 269 and the additional cost of dornase alpha treatment per year is £2 479 (*Table 3*).

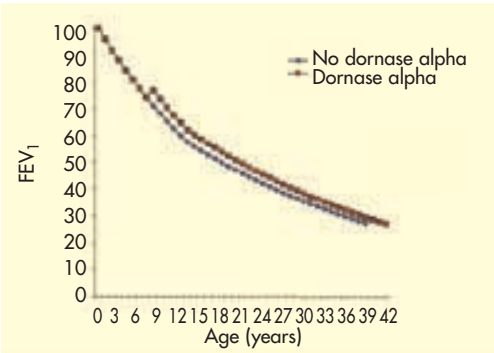


***Figure 1. Forced expiratory volume in 1 second ($FEV_1$) decline until death ($FEV_1$ <28%).***

**TABLE 3.**
**Sensitivity analysis I: lifetime costs and cost per life year gained (£) varying $FEV_1$ improvement as a result of dornase alpha, and the cost offset possible with dornase alpha use**

| | | No dornase alpha | Improvement with dornase alpha | | |
|---|---|---|---|---|---|
| | | | 8% | 4.3% | 20% |
| Lifetime costs | 18.3% cost offset | 151 264 | 233 070 | 241 731 | 223 440 |
| | 37.5% cost offset | | 212 218 | 221 093 | 201 845 |
| Age at death | | 38 | 41 | 40 | 45 |
| Life years gained | | | 3 | 2 | 7 |
| Cost per life year gained | 18.3% cost offset | | 27 269 | 45 234 | 10 311 |
| | 37.5% cost offset | | 20 318 | 34 915 | 7 226 |
| Additional cost of dornase alpha per year | 18.3% cost offset | | 2 479 | 2 827 | 1 951 |
| | 37.5% cost offset | | 1 847 | 2 182 | 1 367 |
| Difference in days in hospital (lifetime) | | | –65 | –76 | –20 |
| Difference in days on parenteral antibiotics (lifetime) | | | –154 | –171 | –86 |
| Difference in days at home as a result of CF-related illness (lifetime) | | | –94 | –101 | –68 |

CF = cystic fibrosis; $FEV_1$= forced expiratory volume in 1 second

### Patient impact

In addition to the cost impact of dornase alpha use, the model attempts to give some idea of the possible impact on factors affecting the patient. Published evidence of the mean days in hospital, days on parenteral antibiotics and days at home as a result of CF-related illness over a 24-week period (*Table 1*) were multiplied to give a yearly estimate. While these figures will undoubtedly vary with the stage of disease, no other data were available. Given the assumptions within the model and despite an additional 3 years of life for the patient administered dornase alpha, the model predicted approximately 65 fewer days in hospital, 154 fewer days on parenteral antibiotics and 94 fewer days at home as a result of CF-related illness over their lifetime (*Table 3*).

### Sensitivity analysis

The potential variations within this model are numerous and can be fully explored in the interactive Excel computer model (available upon request, Roche Products Ltd, Welwyn Garden City), however, for the purposes of this paper only the following were considered — the possible improvement associated with the administration of dornase alpha (4.3–20%), the possible cost offset with reduced RTI care as a result of dornase alpha (18.3–37.5%), and an increase in the cost of annual care for CF for severe patients ($FEV_1$<40%) of up to £30 000 (Fogarty, 1996). The upper limit of $FEV_1$ improvement as a result of dornase alpha (20%) was based on published evidence (Davies et al, 1997) and the lower limit of 4.3% taken from the product monograph.

From this analysis the increase in life expectancy varied between 1 and 7 years, with the cost per life year gained ranging between £6 084 to £45 234, dependent upon the variation in identified factors (*Tables 3* and *4*).

## CONCLUSION

From the clinical evidence dornase alpha works, with statistically significant improvements in lung function and prevention of RTI exacerbations evident in specific patients. Such efficacy has implications for the cost of RTI-related care with considerable savings possible. However, including the acquisition costs of the therapy, dornase alpha increases total expected health-care expenditure and brings in the complicated issues of whether or not the drug is cost-effective.

In many instances cost-effectiveness is a subjective issue. This modelling exercise suggests that under certain circumstances dornase alpha use may be considered cost-effective in the long run. In the best case scenario it might maintain a patient in the mild state of disease for an additional 4 years and extend their life by up to 7 years at a cost of £6 084 per life year gained. This delay in disease progression may also be an important factor in sustaining the patients' health until such time as gene therapy or other potentially curative treatments have been perfected.

There are a number of other aspects associated with dornase alpha that must also be considered. A delay in the onset of moderate and severe disease might improve the educational opportunities for the young CF patient, improving the chance of obtaining educational qualifications and possibly obtaining employment as an adult. Furthermore, the time required by parents, carers or potentially social services to look after such patients may be reduced, which would have economic implications for society in general.

For health-care providers the decision to allow dornase alpha to be prescribed is a difficult one because of the additional costs associated with its prescription. However, given this modelling exercise the additional cost associated with dornase alpha does not seem as significant as may have previously been thought. Taking into consideration the potential long-term benefits dornase alpha may yet prove to be cost-effective. **HM**

**TABLE 4.**
**Sensitivity analysis II: lifetime costs and cost per life year gained (£) associated with increased annual cost of severe cystic fibrosis (£30 000 for $FEV_1$ <40% predicted)**

| | | No DA | Improvement with DA | | |
|---|---|---|---|---|---|
| | | | 8% | 4.3% | 20% |
| Lifetime costs | 18.3% cost offset | 182 539 | 259 329 | 272 886 | 245 720 |
| | 37.5% cost offset | | 238 477 | 252 248 | 225 126 |
| Age at death | | 38 | 41 | 40 | 45 |
| Life years gained | | | 3 | 2 | 7 |
| Cost per life year gained | 18.3% cost offset | | 25 597 | 45 173 | 9 169 |
| | 37.5% cost offset | | 18 646 | 34 854 | 6 084 |
| Additional cost of DA per year | 18.3% cost offset | | 2 327 | 2 823 | 1 735 |
| | 37.5% cost offset | | 1 695 | 2 178 | 1 151 |

DA = dornase alpha; $FEV_1$= forced expiratory volume in 1 second


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## KEY POINTS

- It has been suggested that long-term use of dornase alpha in cystic fibrosis patients may be cost-effective, delaying the progression of disease and increasing patient survival.
- Modelling the long-term benefits of dornase alpha suggests that life expectancy may be increased by up to 7 years for those patients who respond.
- Modelling also suggests that the progression of disease might be delayed with possible implications on quality of life.
- The cost per life year gained within the model parameters ranged from £6 084 to £45 234.
- Decisions on dornase alpha use for cystic fibrosis patients must consider both short-term benefits and possible long-term benefits.