

The Role of Dornase Alfa in the Treatment of Severe Cystic Fibrosis

Jennifer J. Newman, Charles D. Bayliff, Brian D.B. Lyttle, and Nigel A.M. Paterson

Aggressive antibiotic regimens, chest physiotherapy, and pancreatic enzyme therapy have become standard treatments for cystic fibrosis and have helped to increase the life expectancy of patients with this disease. Recently, dornase alfa (recombinant human deoxyribonuclease I, also known as rh DNase I) has received attention as a useful treatment in cystic fibrosis.¹⁻⁴ Dornase alfa is a recombinant enzymatic product designed to produce the same effects as native human DNase through selective digestion of extracellular DNA. *In vitro*, dornase alfa hydrolyzes extracellular DNA in patients' purulent sputum, thereby reducing sputum viscoelasticity. Its mechanism of action *in vivo* may be related to a decrease in sputum viscoelasticity or a reduction in sputum adhesiveness (or both), either of which might enhance clearance of sputum.¹ Studies have demonstrated the clinical effectiveness of dornase alfa in patients with cystic fibrosis, and the drug is indicated in Canada for mild to moderate disease.³⁻⁹ In patients with more advanced disease, the role of dornase alfa is less clear. This paper evaluates its role in these patients.

Patients with severe pulmonary disease (forced vital capacity less than 40%) represent 7% of the cystic fibrosis population.⁵ The 1-year mortality rate for this group approaches 50%.⁵ Therefore, a therapeutic entity that improves pulmonary function and quality-of-life indicators in this patient population would be a welcome addition to the current therapeutic armamentarium. Only 2 studies^{10,11} have documented the effect of dornase alfa in this population.

In a randomized, double-blind, placebo-controlled trial conducted by Shah and others,¹⁰ the use of dornase alfa 2.5 mg bid for 14 days was studied in 70 patients. The primary end points for this trial included changes in

forced expiratory volume in 1 second, forced vital capacity, dyspnea, and quality of life in domains related to cystic fibrosis. No significant differences in any of these outcomes were observed between the dornase alfa and placebo groups. After the placebo-controlled phase, 64 of the patients entered a 6-month open-label phase of the trial. However, only 38 (59%) of them completed the open-label phase. Mean improvements in forced expiratory volume in 1 second and forced vital capacity relative to baseline were 9% and 18%, respectively, for all open-label participants. A subanalysis for the 38 patients who completed the trial demonstrated improvements of 11% in forced expiratory volume in 1 second and 23% in forced vital capacity.

In the double-blind portion of the study, the overall prevalences of adverse effects associated with dornase alfa and placebo were similar. The prevalence of dyspnea associated with dornase alfa (31%) was not significantly different from that in the placebo group (20%) ($p = 0.40$). All of the 13 patients in this trial who died were using dornase alfa at the time of death (2 during the placebo-controlled phase and 11 during the open-label trial). However, the trial clinicians reported that these deaths were unlikely related to the dornase alfa therapy. Trends toward greater rates of death and dyspnea in the dornase alfa group were not statistically significant.

In a second placebo-controlled, double-blind study evaluating dornase alfa in severely ill patients, McCoy and others¹¹ studied the effect of dornase alfa 2.5 mg once daily for 12 weeks in 320 patients. The primary end points for this trial were time to first pulmonary exacerbation and mean percentage change from baseline in forced expiratory volume in 1 second. Secondary end points included mean percentage change in forced vital



capacity, dyspnea, cumulative days of intravenous antibiotics, and cumulative length of stay in hospital.

At the beginning of the trial, patients in the dornase alfa group had significantly poorer lung function than those in the placebo group (forced expiratory volume in 1 second, $21.1\% \pm 5.3\%$ and $22.3\% \pm 5.5\%$, respectively, $p < 0.01$). However, the patients in the dornase alfa group experienced a significant improvement in mean forced expiratory volume in 1 second compared with patients in the placebo group ($9.4\% \pm 16.3\%$ and $2.1\% \pm 13.3\%$, respectively, $p < 0.001$), as well as improvement in forced vital capacity ($12.4\% \pm 18.6\%$ and $7.3\% \pm 16.5\%$, $p < 0.01$). There was no difference between the groups in terms of time to first pulmonary exacerbation or in intravenous antibiotic use.

Patients in the alfa dornase group experienced the following events with a frequency at least 3% greater than those in the placebo group: death, dyspnea, fever, decreased forced vital capacity (at least 10% of predicted), pharyngitis, rhinitis, voice alterations, and dyspepsia. The difference in the death rate (5.6% and 3.8% in the dornase alfa and placebo groups, respectively) was not statistically significant. Investigators labelled 3 of the deaths as "possibly remotely related" to the study drug, although one of the patients was actually receiving placebo. In total, 40 patients (12.5%) were unable or unwilling to complete the trial.

The 2 clinical trials discussed here provide the only available placebo-controlled data documenting the effect of dornase alfa in patients with severe pulmonary disease. However, they did not demonstrate a consistent benefit in lung function. Only McCoy and others¹¹ showed a statistically significant benefit in patients with severe pulmonary disease. These data are encouraging, given the expected decline in lung function that is normally observed in these patients. However, the results must be interpreted carefully, as they are at odds with the results of Shah and others,¹⁰ which showed no significant difference from placebo. In addition, neither trial demonstrated subjective improvement in dyspnea or quality-of-life parameters associated with dornase alfa in patients with severe disease. Furthermore, dornase alfa did not reduce the risk of infectious exacerbations. The effect of dornase alfa on survival is currently not known for any group of patients with cystic fibrosis. In fact, both trials in patients with severe pulmonary disease showed a nonsignificant trend toward increased mortality with dornase alfa therapy. Therefore, current clinical experience does not consistently support the use of dornase alfa in cystic fibrosis patients with severe pulmonary disease. Additional data demonstrating a beneficial effect in

severely ill patients are necessary to justify the routine recommendation of the drug for this population.

The annual cost of providing dornase alfa to all eligible persons in Canada is estimated at \$3.3 million.¹² To make appropriate decisions about resource allocation and to promote cost-effective utilization of dornase alfa, it is necessary to identify those patients likely to gain the most benefit from this therapy. Given the above results, a trial in individual patients might be considered. This concept has been promoted for people with less advanced disease, but could also be employed in those with more severe disease.¹³ Consideration should be given to the following factors. First, in view of the greater level of dyspnea associated with dornase alfa therapy, this therapy should not be instituted during an exacerbation and the patient should be clinically stable at the time of drug initiation. Should dyspnea increase, interruption of therapy is suggested. Second, given that the only trial that showed benefit employed dornase alfa 2.5 mg once daily,¹¹ that should be the initial dose. The use of twice-daily dosing was not associated with an improvement in spirometry and was associated with a high rate of dyspnea, possibly related to enhanced bronchorrhea.¹⁰ Third, spirometry data should be obtained before initiation of dornase alfa and should be reassessed at 6 weeks after initiation of therapy.¹³ In the absence of an increase of 10% in forced expiratory volume in 1 second, dornase alfa therapy should not be continued. In patients who tolerate the drug but do not respond to the once-daily dose, a trial at a higher dose could be pursued.

References

1. Bryson HM, Sorkin EM. Dornase alfa — a review of its pharmacological properties and therapeutic potential in cystic fibrosis. *Drugs* 1994;48:894-906.
2. Cramer GW, Bosso JA. The role of dornase alfa in the treatment of cystic fibrosis. *Ann Pharmacother* 1996;30:656-61.
3. Harms HK, Matouk E, Tournier G, von der Hardt H, Weller PH, Romano L, et al. Multicenter, open-label study of recombinant human DNase in cystic fibrosis patients with moderate lung disease. *Pediatr Pulmonol* 1998;26:155-61.
4. Witt DM, Anderson L. Dornase alfa: a new option in the management of cystic fibrosis. *Pharmacotherapy* 1996;16:40-8.
5. Hodson ME. Clinical studies of rhDNase in moderately and severely affected patients with cystic fibrosis — an overview. *Respiration* 1995;62(Suppl):29-32.
6. Ramsey BW, Astley SJ, Aitken ML, Burke W, Colin AA, Dorkin HL, et al. Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993;148:145-51.



7. Ranasinha C, Assoufi B, Shak S, Christiansen D, Fuchs H, Empey D, et al. Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993;342:199-202.
8. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331:637-42.
9. Genentech Canada Inc. Pulmozyme [product monograph]. In: Gillis MC, Welbanks L, Bergeron D, Cormier-Boyd M, Hachborn F, Jovaisas B, et al., editors. *Compendium of pharmaceuticals and specialties*. 33rd ed. Ottawa (ON): Canadian Pharmacists Association; 1998. p. 1403-4.
10. Shah PI, Bush A, Canny GJ, Colin AA, Fuchs HJ, Geddes DM, et al. Recombinant human DNase I in cystic fibrosis patients with severe pulmonary disease: a short-term, double-blind study followed by six months open-label treatment. *Eur Respir J* 1995;8:954-8.
11. McCoy K, Hamilton S, Johnson C. Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996;110:889-95.
12. Goa KL, Lamb H. Dornase alfa — a review of pharmacoeconomic and quality-of-life aspects of its use in cystic fibrosis. *Pharmacoeconomics* 1997;12:409-22.
13. Bollert FGE, Paton JY, Marshall TG, Calvert J, Greening AP, Innes JA. Recombinant DNase in cystic fibrosis: a protocol for targeted introduction through *n*-of-1 trials. *Eur Respir J* 1999;13:107-13.

Jennifer J. Newman, BScPhm, is a Staff Pharmacist at the London Health Sciences Centre, London, Ontario.

Charles D. Bayliff, PharmD, is Pharmaceutical Care Coordinator at the London Health Sciences Centre, London, Ontario.

Brian D.B. Lyttle, MD, FRCPC, is a Pediatric Pulmonologist at the London Health Sciences Centre, London, Ontario.

Nigel A.M. Paterson, MB, FRCPC, is a Respiriologist at the London Health Sciences Centre, London, Ontario.

Address correspondence to:
 Dr Charles D. Bayliff
 Pharmaceutical Care Coordinator
 London Health Sciences Centre
 375 South Street
 London ON
 N6A 4G5
 e-mail: charlie.bayliff@lhsc.on.ca

