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Dornase Alfa and Progression of Lung Disease in Cystic Fibrosis

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Summary. Obstruction, infection, and inflammation lead to progressive and irreversible lung destruction in cystic fibrosis (CF). Neutrophil-derived DNA contributes to thick, viscous secretions. Dornase alfa hydrolyzes DNA, reducing the viscosity of CF sputum. Clinical trials have shown that dornase alfa improves forced expiratory volume in one second (FEV_1). Immediate improvement is important, but long term survival requires slowing the rate of lung function decline. Demonstrating changes in rate of decline requires long term studies with many patients, which are impractical for clinical trials. Observational studies such as the Epidemiologic Study of Cystic Fibrosis (ESCF) can address rate of decline in lung function, and is being used to evaluate the long-term effectiveness of dornase alfa. CF patients age 8–38 years when initially treated with dornase alfa (index event) were compared to patients not treated (for 2 years before and 2 years after index). In a preliminary analysis, FEV_1 at index for the dornase alfa group ($n = 2,706$) was 80.5% predicted, and for the comparator group ($n = 3,991$) 86.7% predicted. The estimated rate of FEV_1 decline before index for the dornase alfa group was −2.81 and for the comparator group −0.85% predicted/year. After index, the rate of decline for the dornase alfa group was −1.53% predicted/year (46% reduction, $P < 0.001$), with no change in the comparator group. These preliminary results suggest that initiating dornase alfa is associated with both an acute improvement in FEV_1 and a slowing of the rate of FEV_1 decline. Analysis is ongoing to further evaluate this association. **Pediatr Pulmonol. 2008; 43:S24–S28.**

Key words: cystic fibrosis; dornase alfa; pulmonary function.

OVERVIEW OF THE LUNG DISEASE OF CF

Progressive pulmonary disease, resulting in lung destruction, continues to account for most of the morbidity and nearly all of the mortality in cystic fibrosis (CF).[1,2] The pulmonary disease of CF is characterized by airway obstruction along with chronic infection and inflammation.[3] These three factors act in a vicious cycle to slowly destroy the lung (Fig. 1). Airway obstruction occurs early in the disease process. Absent or deficient cystic fibrosis transmembrane conductance regulator (CFTR) protein at the apical surface of airway epithelia leads to abnormal salt and water transport, which results in an airway surface liquid height that is insufficient for normal mucociliary clearance. Decreased mucociliary clearance, coupled with mucus secretions that are biochemically altered by the basic defect of CF, lead to obstruction of the airways. Individuals with CF are prone to infection, with a special susceptibility to *Pseudomonas aeruginosa*. Failure to appropriately clear secretions, along with other factors related to the abnormal surface airway environment, is partly responsible for infection with pseudomonas and other organisms. Despite antibiotic treatment, infection becomes chronic. The inflammatory response to infection is quite vigorous in the CF lung, and becomes chronic as well. Inflammation in CF is characterized by persistent influx of neutrophils, which is quite different from other lung diseases that are characterized by inflammation. Normally neutrophil influx is an acute response, which resolves as inflammation becomes chronic, but in the CF lung neutrophil influx persists (Fig. 1). Whether inflammation can precede infection has been a long-standing debate in the CF community; some evidence links inflammation to the gene defect in CF. Regardless of the sequence for the onset of airway obstruction, infection, and inflammation in the CF lung, it is recognized that the disease process related to these factors usually begins early, often in early infancy.

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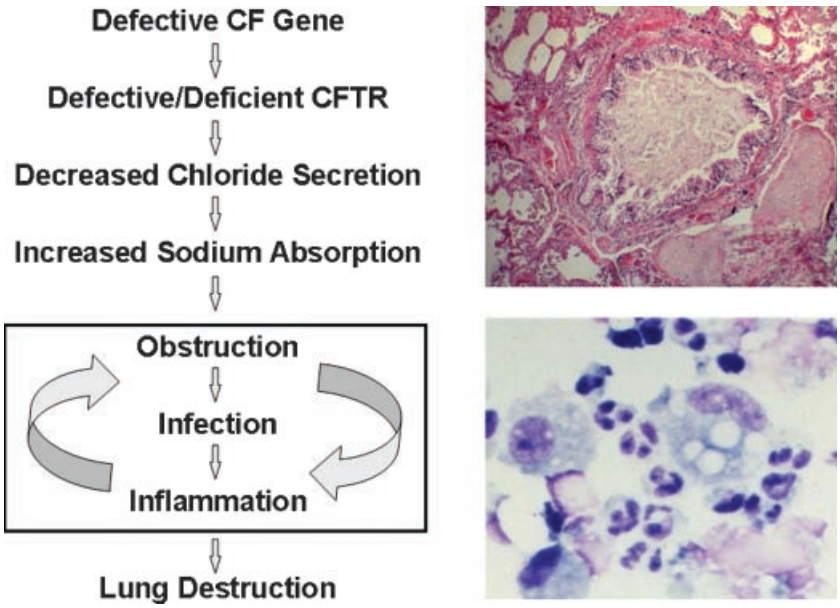

Fig. 1. Pathogenesis of CF lung disease. Airway obstruction, chronic infection, and persistent inflammation leads to lung destruction, and ultimately to death of the patient. Inflammation is characterized by persistent influx of neutrophils into the peribronchial and endobronchial space. Neutrophils release DNA, which contributes to the viscoelasticity of sputum, further worsening airway obstruction. Neutrophils and their products, including DNA, are major therapeutic targets in the CF lung (adapted from Ref. 3).

RATIONALE FOR DORNASE ALFA THERAPY IN CF

Although neutrophils help combat infection, when present in great excess they can cause more harm than good. As neutrophils decompose in the airways (in part due to failure to undergo normal apoptosis), intracellular constituents are released that harm the lung. Among these intracellular constituents is DNA, which thickens secretions by increasing their viscosity. Thickened secretions are more difficult to clear, and can plug small airways. Large amounts of DNA are found in the airways of individuals with CF, even at an early age, and in relatively asymptomatic individuals.[4] Bronchoalveolar lavage studies in infants identified through newborn screening demonstrate marked neutrophilia with elevated levels of DNA.[5] Thus, a reasonable approach to decreasing the viscosity of CF secretions would be to hydrolyze the neutrophil-derived DNA. DNases are capable of accomplishing just that, but are not present in sufficient quantity in the lung to exert this effect. Thus, exogenous administration of DNase seems like a reasonable treatment approach, and was actually prescribed in the 1950s and 1960s as a treatment for bronchopulmonary diseases, including CF.[6,7] However, the bovine-derived pancreatic DNase then available was often not well tolerated. In the early 1990s, recombinant human DNase (dornase alfa) was developed, and was shown to reduce the viscosity of CF sputum.[8]

DORNASE ALFA THERAPY RESULTS IN AN IMMEDIATE IMPROVEMENT IN LUNG FUNCTION

Clinical trials have shown that dornase alfa improves pulmonary function as measured by the forced expiratory volume in 1 second (FEV_1) in CF patients.[9,10] In the 24-week placebo-controlled phase III trial conducted at 51 US sites in CF patients (age >5 years; forced vital capacity [FVC] > 40% predicted; n = 968), once-daily administration of dornase alfa achieved a mean improvement of 5.8% in the FEV_1% predicted at the end of the 24-week treatment period.[9] The corresponding placebo group had no change in FEV_1% predicted. The increase in FEV_1 in the dornase alfa group was greatest after 2 weeks of initiating treatment, suggesting a fairly immediate effect of the drug on pulmonary function. A much longer placebo-controlled trial of once daily dornase alfa over 96 weeks in children with CF (age 6–10 years; FVC > 85% predicted; n = 474) conducted at 49 sites in the US, Canada, and Europe also demonstrated an initial increase in FEV_1, which was sustained above the baseline value during the nearly 2-year treatment period.[10] The FEV_1% predicted in the corresponding placebo group decreased over the treatment period, suggesting progression of lung disease. At 96 weeks, the treatment benefit for dornase alfa compared with placebo was 3.2 percent predicted points.

RELATIVE BENEFIT OF IMMEDIATE IMPROVEMENT IN LUNG FUNCTION VERSUS SLOWING THE RATE OF DECLINE

Immediate improvement in lung function as demonstrated by these two studies is important, but long-term survival for patients with CF requires slowing the rate of disease progression. Findings from previous studies suggest that the rate of FEV_1 decline is strongly associated with time to death in CF,[11,12] the ultimate outcome of disease progression. Thus, the long-term impact of a therapy that slows the rate of FEV_1 decline would be expected to have a much greater chance of extending the life of a patient than a therapy that improves FEV_1 quickly but does not alter the subsequent rate of FEV_1 decline (Fig. 2).

Demonstrating changes in the rate of lung function decline with a therapeutic intervention requires long-term studies with many patients, which are impractical for clinical trials.[13] Even the 2-year trial of dornase alfa in 474 patients was not sufficiently powered to assess the effect of dornase alfa on rate of FEV_1 decline,[10] and this trial was conducted in patients who are characteristically at greatest risk for FEV_1 decline (young age with high baseline FEV_1).[14] There is also a hint from a 3-year bronchoalveolar lavage study of dornase alfa conducted at five sites in Germany that once-daily dornase alfa may indeed slow the rate of FEV_1 decline.[15] Although this study was designed to assess the impact of dornase alfa on markers of inflammation in the lungs of CF patients with early lung disease (age >7 years; $FEV_1 > 80\%$ predicted), pulmonary function testing revealed a trend towards slowing FEV_1 decline over the 3-year treatment period. If this observation were to be confirmed in a controlled clinical trial, the claim could be made that dornase alfa not only improves pulmonary function over the short term, but also slows the rate of FEV_1 decline with long-term use, and thus could be considered as a therapy with a demonstrated effect on slowing disease progression.

The only clinical trial to date that demonstrates a significant effect of a therapy on slowing the rate of FEV_1 decline, and thus disease progression, was the 4-year trial of ibuprofen conducted at a single site in the US in 84 patients (age >5 years; $FEV_1 > 60\%$ predicted).[16] Ibuprofen-treated patients had a 40% slower rate of decline compared to placebo ($P = 0.02$), based on an average FEV_1 decline of -3.6% predicted/year for placebo-treated patients. Results from a 2-year trial of ibuprofen conducted at 12 sites in Canada in 142 patients (age 6–18 years; FEV1 $> 60\%$ predicted) were recently reported.[17] A significant reduction in the rate of decline in FVC, but not FEV_1, was observed. The study fell short of its recruitment goal of 440 patients required to demonstrate a significant reduction in the rate of FEV_1 decline. All of these studies substantiate the requirement that long duration of study and/or large numbers of patients are required to assess the effect of a therapy on disease progression (even large effects), which as previously stated is not practical for clinical trials.

USE OF OBSERVATIONAL DATA TO ASSESS THE ASSOCIATION OF A THERAPY WITH RATE OF DECLINE IN LUNG FUNCTION

Observational data from patient registries that monitor the safety and efficacy of therapies in clinical use may

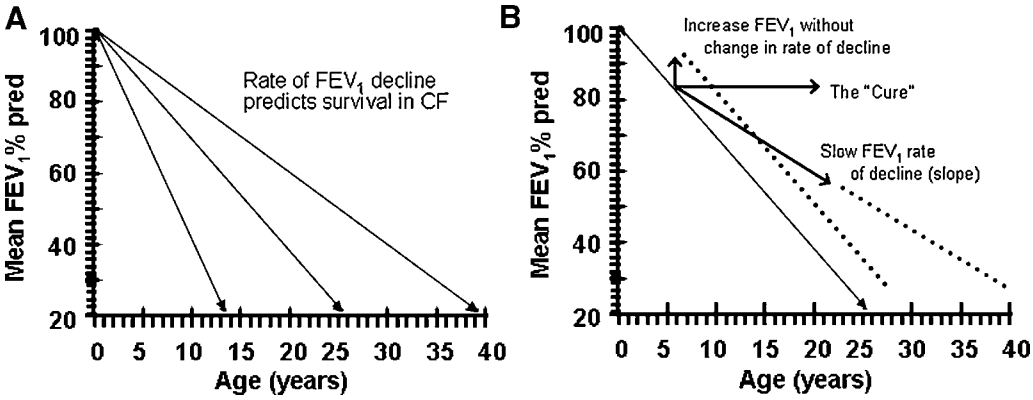

Fig. 2. A: Disease progression as measured by loss of lung function. The rate of decline in FEV_1 predicts survival in CF. Therapies that halt or slow progression of lung disease are highly sought after to improve the survival of CF patients (adapted from Refs.[11,12]). B: Benefit of increasing FEV_1 versus slowing the rate of decline of FEV_1. A therapy that slows the rate of FEV_1 decline would be expected to have a much greater chance of extending the life of a patient than would a therapy that increases FEV_1 but does not alter the rate of decline. Dornase alfa has been shown to increase FEV_1 in several short-term clinical trials in patients with CF. A key question is whether long-term treatment with dornase alfa can slow the rate of FEV_1 decline. If this can be demonstrated, dornase alfa could then be considered as a therapy that slows disease progression in patients with CF (adapted from Ref. 13).

provide another avenue for assessing the effect of a specific therapy on disease progression. The benefit of ibuprofen in slowing the rate of FEV_1 decline was recently demonstrated using the Cystic Fibrosis Foundation Patient Registry.[18] The rate of decline in FEV_1% predicted over 2–7 years among CF patients age 6–17 years with $FEV_1 > 60$% predicted who were treated with ibuprofen ($n = 1{,}365$) was compared to patients of similar age and disease severity who were not treated with this therapy ($n = 8{,}960$). FEV_1 declined less rapidly among ibuprofen-treated patients (difference, 0.60% predicted/year, $P < 0.0001$); a 29% reduction in slope based on an average decline of −2.08% predicted/year for patients not treated. The finding that the analysis of data from a patient registry (in this case, the Cystic Fibrosis Foundation Patient Registry) supports the results from a controlled clinical trial (the 4-year ibuprofen study) is an important one, suggesting that observational studies of CF patients may be robust enough to demonstrate the efficacy of a therapy used in clinical practice.

The Epidemiologic Study of Cystic Fibrosis (ESCF), a prospective encounter-based study designed to characterize the natural history of pulmonary disease and growth in a large population of patients with CF ($N = 24{,}863$) in the US and Canada,[19] may also be suitable for demonstrating the efficacy of a CF therapy. The study began in 1994, when dornase alfa became commercially available, and gathered data through 2005. Because of its primary focus on carefully gathering pulmonary function data and clinical use of dornase alfa, ESCF lends itself well to analyses evaluating the effectiveness of dornase alfa in clinical practice.[20] Thus, a preliminary analysis of ESCF data was performed to assess the association of dornase alfa use with FEV_1 decline.[21]

PRELIMINARY ANALYSIS OF THE ASSOCIATION OF DORNASE ALFA THERAPY WITH THE RATE OF FEV_1 DECLINE

For this analysis, patients age 8–38 years when initially treated with dornase alfa (index event) were selected if they had been enrolled in ESCF for the prior 2 years with no documented use of dornase alfa (baseline period), and remained on dornase alfa for ≥80% of the time for the following 2 years (follow-up period). A comparator group was selected who had never received dornase alfa or did not start dornase alfa for at least 4 years after enrollment in ESCF (to allow for assessment of two 2-year periods). Comparator index events were defined as the first encounter following the 8th or subsequent even-numbered birthday. Both groups had to have ≥1 encounter and ≥3 FEV_1 values spanning at least 6 months in each of the 2-year baseline and follow-up periods.

FEV_1 at the index event for the dornase alfa group ($n = 2{,}706$) averaged 80.5% predicted, and for the comparator group ($n = 3{,}991$) 86.7% predicted. An improvement in FEV_1 was observed for the dornase alfa group after the index event (2.66% predicted, $P < 0.001$), but not for the comparator group. For each patient, the rate of decline in FEV_1% predicted was estimated before and after the index event using a mixed-effects model, adjusted for age; gender; and the use of antibiotics (oral and inhaled), bronchodilators (oral and inhaled), corticosteroids (oral and inhaled), mast cell stabilizers, and nutritional supplements (oral, enteral, and parenteral). The estimated rate of FEV_1 decline before the index event for the dornase alfa group was −2.81% predicted/year, and for the comparator group −0.85% predicted/year. During the 2 years following the index event, the estimated rate of decline for the dornase alfa group was −1.53% predicted/year (46% reduction, $P < 0.001$), and for the comparator group −1.03% predicted/year (no significant change).

CONCLUSION

Preliminary results from this study demonstrate that, in addition to an immediate improvement in FEV_1, initiating dornase alfa therapy is associated with slowing the rate of lung function decline.[21] As discussed above, the only other CF therapy previously shown to have a beneficial effect on the rate of FEV_1 decline is high-dose ibuprofen.[16,18] Analyses are ongoing to determine if specific subsets of patients, for example, based on age or disease severity, are more likely to benefit from the clinical use of dornase alfa. While not evaluated in studies of ibuprofen or in this preliminary analysis of dornase alfa, slowing the progression of lung disease through a therapeutic intervention, as indicated by slowing the rate of FEV_1 decline, may ultimately result in improved survival. Use of observational data from patient registries such as those from the Cystic Fibrosis Foundation or from industry (where more detailed information on a specific therapy might be gathered) may be our only avenue to understanding the impact of CF therapies on disease progression and ultimately on survival.

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