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Dornase Alfa in Early Cystic Fibrosis Lung Disease

Philip J. Robinson, MD, PhD*

Summary. Leukocytes that infiltrate cystic fibrosis (CF) sputum as a result of infection have long been known to liberate large amounts of DNA, which increases sputum viscosity and promotes the cycle of chronic lung infection and inflammation that ultimately leads to respiratory failure and death. It was only recently recognized that this vicious cycle begins in infancy, and that architectural damage to CF lungs is detectable even in children with normal pulmonary function tests.

Dornase alfa cleaves DNA and improves sputum viscosity in CF. Although its efficacy in reducing the risk of acute infectious exacerbations and improving pulmonary function has been recognized for a decade, there is growing interest in its potential for long-term benefit in young patients with mild lung function abnormalities.

The Pulmozyme Early Intervention Trial (PEIT) study demonstrated that dornase alfa reduces the risk of pulmonary exacerbations requiring i.v. antibiotic treatment by 34% and improves forced expiratory flow at 25–75% of forced vital capacity (FEF_{25-75}), mid-expiratory flow at 50% of forced vital capacity (MEF), and forced expired volume in 1 sec (FEV_1) over a 2-year period in CF patients with almost normal lung function. A post hoc subgroup analysis suggests that the magnitude of pulmonary function test (PFT) changes may vary, depending on the initial degree of lung function impairment, but that the reduction in exacerbations appears to be a consistent benefit.

These results support the current view that CF patients benefit from intervention early in the course of their lung disease. **Pediatr Pulmonol. 2002; 34:237–241.** © 2002 Wiley-Liss, Inc.

INTRODUCTION

Despite the remarkable improvement in survival among cystic fibrosis (CF) patients that has already been achieved in past decades, in 1998 their median survival age in Europe was still only 32 years.[1] Since past progress has been largely due to better nutrition and success in treating the chronic pulmonary infections that plague CF patients throughout their lives, the focus is now shifting towards earlier intervention aimed at avoiding or postponing the onset of symptomatic disease.

Elsewhere in this issue, my colleagues have outlined the structural and functional abnormalities that are observed in the lungs of young CF patients,[2] and have reviewed the evidence supporting earlier initiation of antibiotic and other therapies.[3,4] Here, I will review the evidence that elevated DNA levels are intrinsic to CF sputum, and that recombinant human DNase (dornase alfa, Pulmozyme®, F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Genentech, Inc, South San Francisco, CA) improves pulmonary health even in young patients with well-preserved lung function. My focus will be on the recently completed Pulmozyme® Early Intervention Trial (PEIT).

STUDY RATIONALE

CF sputum is difficult to clear from the respiratory tract because of its unusually high viscosity. As early as 1959, DNA was identified as being present in significantly higher quantities in sputum from patients with CF as opposed to bronchiectasis,[5] and was subsequently confirmed to increase sputum viscosity.[6] The source of the DNA was identified in 1976 as primarily leukocytes infiltrating the sputum as a result of infection.[7] More recently, inflammation with or without infection has been recognized as fairly common in the lungs of infants with CF, and its frequency increases sharply with age, even among young children.[8–10] Elevated DNA concentrations have also been found in bronchoalveolar lavage fluid from infants with CF.[11,12]

Dornase alfa was developed specifically to cleave extracellular DNA into molecules of shorter length. As a result, it transforms CF sputum from a gel into a flowing liquid.[13] The efficacy of a nebulized formulation in

Department of Respiratory Medicine, Royal Children's Hospital, Parkville, Australia.

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*Correspondence to: Philip J. Robinson, M.D., Ph.D., Department of Respiratory Medicine, Royal Children's Hospital, Parkville 3052, Australia.

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improving lung function and reducing the frequency of pulmonary exacerbations was clearly demonstrated a decade ago, in a 6-month study of 968 patients over 5 years of age with forced vital capacity (FVC) $\geq 40\%$ predicted.[14] Subanalysis of the cohort of these patients with FVC $> 85\%$ predicted,[15] as well as a short-term study in 749 patients with FVC $\geq 70\%$ predicted,[16] confirmed that results in patients with mild lung function abnormalities may be expected to be similar to those in the larger CF population. This conclusion was supported by 2-year data from the Epidemiologic Registry of Cystic Fibrosis (ERCF),[17] an observational study that raised the hypothesis that younger and milder CF patients may even benefit most from dornase alfa treatment. A rationale for this hypothesis is that young patients with good lung health may be at increased risk of losing lung function.[18]

The fact that the intermediate-term benefits of dornase alfa had already been clearly demonstrated raised questions about the ethics of a randomized, double-blind, placebo-controlled trial to confirm its long-term benefits. However, despite the considerations above, there was evidence that it was being prescribed less frequently to patients with mild lung disease.[19] Therefore, young patients with early CF lung disease were chosen as subjects for the double-blind trial of long-term efficacy. The full results of the PEIT trial have been published.[20]

METHODS

Patients with CF were eligible for the trial if they were aged 6–10 years at enrollment, had FVC $\geq 85\%$ predicted, and were able to perform reproducible pulmonary function tests (PFTs) according to American Thoracic Society criteria.[21] Patients were excluded if they had been hospitalized for complications of CF within 2 months preceding the study or if they had used dornase alfa within the previous 6 months.

Study visits were scheduled for screening, baseline (two visits), and during treatment at weeks 4, 12, and every subsequent 12 weeks of the 96-week treatment period. Patients were randomized, by a call placed to an independent randomization center at the second baseline visit, to either dornase alfa 2.5 mg or matching placebo, administered once daily using a SideStream nebulizer and PortaNeb compressor.

The primary outcome measure was forced expired volume in 1 sec (FEV_1). Additional outcome measures were PFTs (FVC, FEF_{25-75}, and $MEF(V_{E50})$) and weight for age, which were recorded at all visits, as well as the number of respiratory tract exacerbations (RTEs) during treatment, and Brasfield score on chest X-ray at the beginning and end of the study. A respiratory tract exacerbation was defined as respiratory symptoms requiring treatment with intravenous antibiotics. Adverse events and comedications were also recorded.

Endpoints were expressed as the differences between groups in the frequency (for RTEs) or change in these measures (as percent of predicted values for PFTs) over the 96-week study period. Analysis was by intention to treat, using a repeated-measures model for PFTs to account for missing data and to adjust for any significant covariates. The relative risk of first exacerbation was analyzed using the Cox proportional hazards model.

RESULTS

The study was conducted at 49 sites in 12 countries (Australia, Belgium, Canada, Denmark, Germany, Ireland, Israel, The Netherlands, Norway, Spain, Switzerland, and the USA). Four hundred and seventy-four patients were randomized to treatment with either dornase alfa 2.5 mg (n = 239, 113 female) or placebo (n = 235, 114 female). Four patients (3 in the dornase group and 1 in the placebo group) withdrew before receiving treatment. Of the 470 treated patients, 87% (206 on dornase alfa and 204 on placebo) completed the scheduled 96 weeks of treatment (Fig. 1).

Patient characteristics were well-matched at baseline, and described a CF population with relatively mild lung disease (Table 1). Despite their almost normal PFTs at the start of the study, 39% of patients had a history of bronchial hyperreactivity, 34% of clubbing, 21% of nasal polyps, 18% of sinusitis, and 13% of daily sputum production, all of which were evenly distributed between groups.

Compared with placebo, dornase alfa improved PFTs starting at week 4 and continuing until the end of the study. When the repeated-measures model was applied to account for missing data, only baseline FEV_1 was found to be a significant covariate and so was included in the analysis. The raw data were not appreciably altered by application of the model, presumably because of the low dropout rate and the adequate balance between treatment groups (Fig. 2). The model indicated that the difference between groups at 96 weeks (mean $\pm$ SE) was: $3.2 \pm 1.2\%$

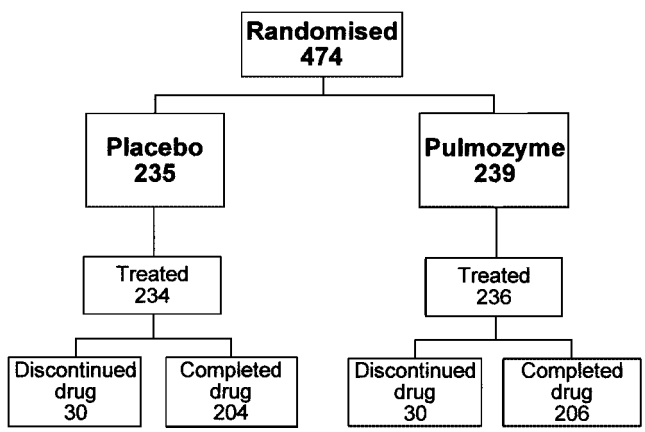

Fig. 1. Disposition of patients within PEIT study.[20]

TABLE 1—Characteristics of Study Population at Baseline[20]

Characteristic	Dornase alfa (N = 239)	Placebo (N = 235)
Age (years)	8.3 (1.4)	8.4 (1.5)
Sex (number of male/female)	126/113	121/114
Pulmonary function		
FVC (% predicted)	103 (12)	102 (12)
FEV_1 (% predicted)	96 (15)	95 (16)
FEF_{25-75} (% predicted)	85 (29)	85 (31)
MEF (% predicted)	87 (29)	87 (30)
Weight-for-age percentile (%)	47 (28)	43 (28)
Respiratory signs/symptoms (% of patients)		
Bronchial hyperreactivity/ashma-like symptoms	38	39
Clubbing	32	36
Daily sputum	12	14
Hemoptysis	0.4	2

Unless otherwise indicated, values are mean (SD).

predicted for FEV_1, $7.9 \pm 2.3\%$ for FEF_{25-75}, and $8.2 \pm 2.2\%$ for MEF (all $P < 0.01$) (Figs. 2 and 3). Notably, the results for both measures of peripheral flow were very similar. There were no differences in FVC ($0.7 \pm 1.0\%$ predicted), weight-for-age percentile, or Brasfield score.

Both the number of patients experiencing an RTE and the total number of RTEs were lower in the group treated with dornase alfa (Table 2). The relative risk of first exacerbation was 0.66 ($P = 0.048$) in the treated group compared with the placebo group. The Kaplan-Meier curve of the proportion of patients free of RTEs is shown in Figure 4. Each patient who experienced an RTE for the first time during the trial lowered the percentage of survivors (patients free of RTEs) at the appropriate point on the time axis. As Figure 4 shows, the treated and control groups started to diverge early and continued to diverge during the study, indicating that the benefit of dornase alfa treatment on first occurrence of RTE was sustained throughout the treatment period.

The safety profile of dornase alfa was previously well-described.[14] The already-identified adverse reactions to dornase alfa (voice alteration, pharyngitis, laryngitis, skin rash, chest pain, and conjunctivitis) were closely monitored in PEIT. Of these, only skin rash was found to be more common among relatively healthy CF patients treated with dornase alfa (6%) than with placebo (1%). As expected, there were no deaths during the study, and the frequency of hemoptysis or other serious complications was not different between the groups.

The study was not adequately powered to detect significant differences among subgroups of the population, but because baseline FEV_1 was a significant covariate in the repeated-measures model, a post hoc analysis was performed in which the population was stratified according to baseline FEV_1. As shown in Figure 5, patients with baseline FEV_1 below the median value of 96.4% predicted showed larger benefits with dornase alfa at 96 weeks in terms of percent predicted FEV_1 (4.8 ± 1.8), FEF_{25-75} (10.7 ± 3.2), and MEF (10.6 ± 3.1) (all $P < 0.01$), while benefits in those with baseline FEV_1 above the median were smaller (FEV_1 1.8 ± 1.5, FEF_{25-75} 5.3 ± 3.3, and MEF 5.9 ± 3.0, $P > 0.05$). However, the relative risk of first exacerbation was similar (0.70 with 95% CI 0.41–1.21, and 0.61 with 95% CI 0.33–1.13) in both subgroups, suggesting that relative risk of RTE is reduced by about a third regardless of baseline FEV_1.

DISCUSSION

The results of PEIT are consistent with previous studies,[14,16] and extend evidence of the efficacy of dornase alfa over a 2-year period to a group of patients with almost normal lung function, as evidenced by FVC and

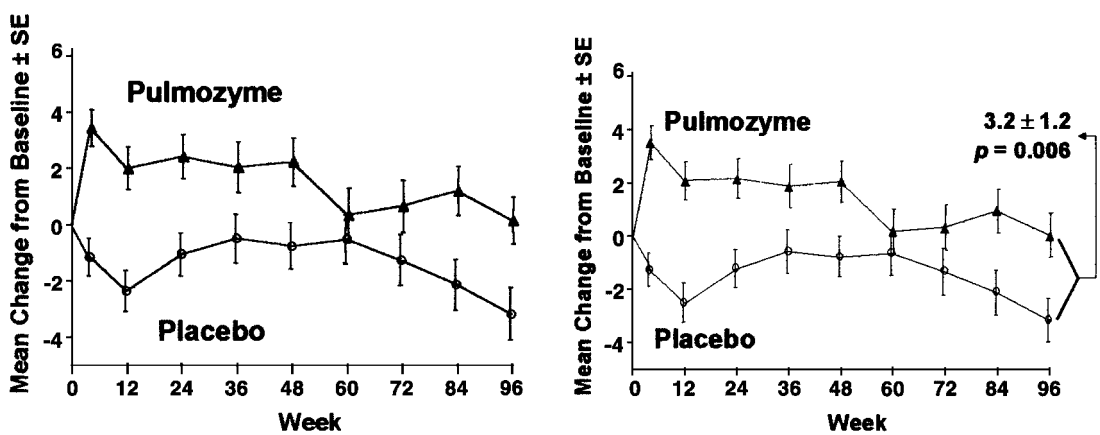

Fig. 2. Mean change from baseline in FEV_1 percent predicted: raw data (left) and according to repeated-measures model (right).[20] Vertical bars represent ± 1 SEM.

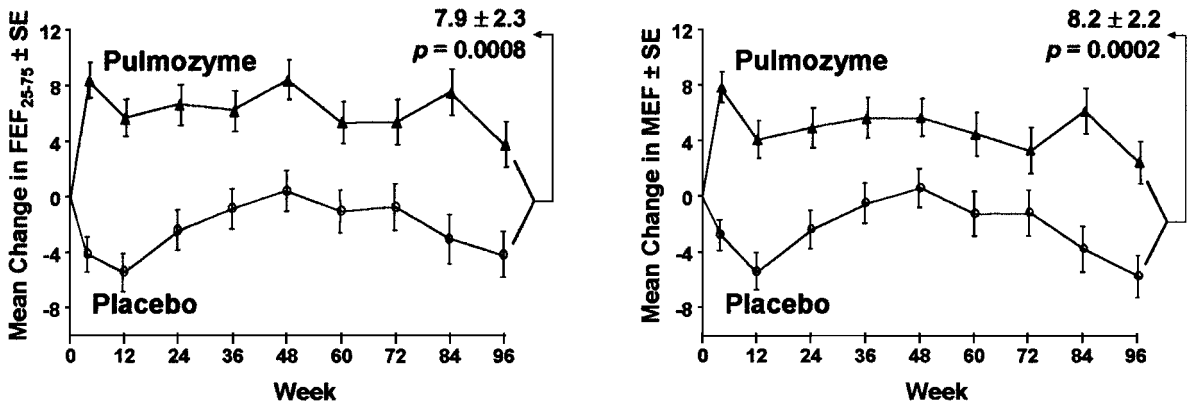

Fig. 3. Mean change from baseline in peripheral flows as calculated by the repeated measures model: FEF_{25-75} percent predicted (left)[20] and MEF percent predicted (right). Vertical bars represent ± 1 SEM.

FEV_1 close to 100% predicted and FEF_{25-75} in the lower normal range.

Elsewhere in this issue, Tiddens presents evidence that even patients with mild lung function abnormalities, such as the subjects of the PEIT study, suffer from considerable architectural and functional impairment of the small pulmonary airways.[2] A principal finding of PEIT was that dornase alfa caused greater improvement in peripheral flows (FEF_{25-75} and MEF) than lung volumes such as FVC or FEV_1 in young patients with early CF lung disease. This is hardly surprising, as lung volumes in these patients, being close to 100% of predicted values, can hardly be improved, and most of the lung damage is expected to be confined to the peripheral airways. A greater improvement in FEF_{25-75} than in FEV_1 was reported previously with dornase alfa in relatively healthy patients,[16] but its importance has not been recognized until now. It indicates that dornase alfa treatment is capable of ameliorating the earliest signs of CF lung disease.

Although only 24% of placebo-treated PEIT patients experienced a respiratory tract exacerbation within the 2-year study period, the impact of these events on the patients' lifestyle and prognosis should not be underestimated. By definition, an RTE required intravenous treatment, and so in many cases resulted in hospitalization. For young, relatively healthy patients, this implies a major disruption in quality of life. This is further highlighted by the finding of a recent study by the US CF Foundation,[22] which concluded that each RTE occurring per patient per year has an impact on 5-year survival that is equivalent to the loss of 12% predicted FEV_1. By reducing the risk of RTEs by one third, dornase alfa can be expected to improve the prognosis and survival of CF patients considerably. Importantly, the lower frequency of RTEs in PEIT patients receiving dornase alfa cannot be attributed to more frequent use of oral or inhaled antibiotics.[20]

Although post hoc and underpowered, the subgroup analysis in which patients were classified according to whether their baseline FEV_1 was above or below the

TABLE 2—Respiratory Tract Exacerbations[20]

	Dornase alfa (N = 237)	Placebo (N = 235)
Number of exacerbations	62	92
No. (%) of patients with ≥ 1 exacerbation	40 (17)	56 (24)
Relative risk (vs. placebo)	0.66	
95% confidence interval	0.44–1.00	
P value	0.048	

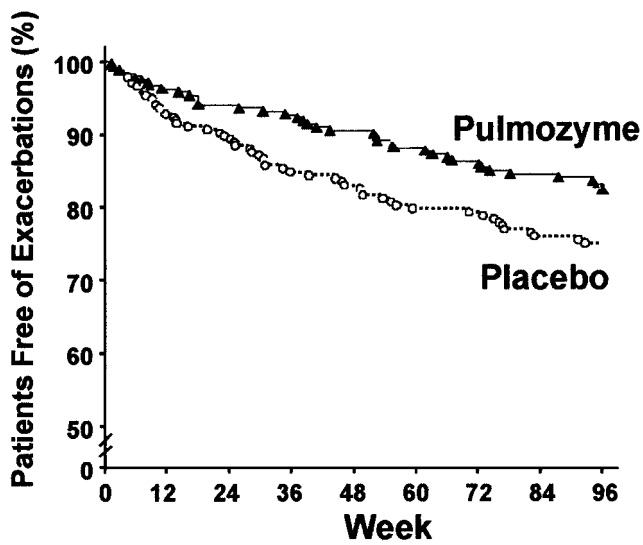

Fig. 4. Kaplan-Meier survival curve of patients free of any respiratory tract exacerbation.[20]

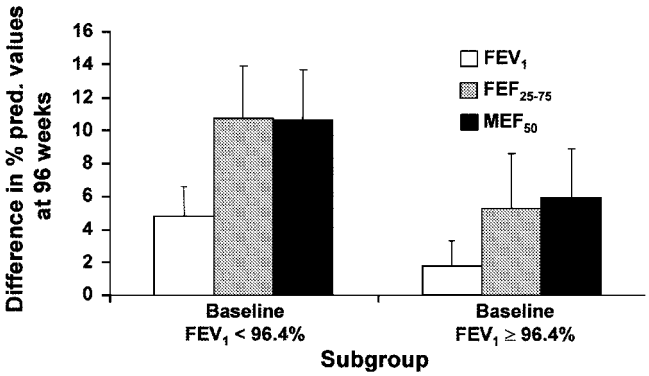

Fig. 5. Spirometric response according to baseline FEV_1 above or below median value.

median value can be justified because baseline FEV_1 was the only significant covariate in the analysis of PFTs. Furthermore, it addresses the important clinical question of whether there is a patient characteristic that is likely to predict the individual's response to dornase alfa. The results of this analysis suggest that the greater the impairment of FEV_1, the more a patient is likely to benefit in terms of PFTs, but that the benefit in terms of reduction in relative risk of RTE is independent of FEV_1. A similar outcome was obtained on subgroup analysis of Fuchs's original efficacy data.[22]

CONCLUSIONS

The results of PEIT confirm the long-term efficacy and safety of dornase alfa, and strongly support early and aggressive therapy for patients with CF.

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REFERENCES

1. Advisory Board for the Epidemiologic Registry of Cystic Fibrosis. ERCF annual report 1998. 2000.
2. Tiddens HAWM. Detecting early structural lung damage in cystic fibrosis. Pediatr Pulmonol 2002;34:228–231.
3. Koch C. Early infection and progression of cystic fibrosis lung disease. Pediatr Pulmonol 2002;34:232–236.
4. Conway S. Evidence-bed medicine in cystic fibrosis: How should practice change? Pediatr Pulmonol 2002;34:242–247.
5. Chernick WS, Barbero GJ. Composition of tracheobronchial secretions in cystic fibrosis of the pancreas and bronchiectasis. Pediatrics 1959;24:739–745.
6. Picot B, Das I, Reid L. Pus, deoxyribonucleic acid, and sputum viscosity. Thorax 1978;33:235–242.
7. Barton AD, Ryder K, Lourenco RV, Dralle W, Weiss SG. Inflammatory reaction and airway damage in cystic fibrosis. J Lab Clin Med 1976;88:423–426.
8. Khan TZ, Wegener JS, Boat T, Martinez J, Accurso FJ, Riches DWH. Early pulmonary inflammation in infants with cystic fibrosis. Am J Respir Crit Care Med 1995;151:1075–1082.
9. Armstrong DS, Grimwood K, Carlin JB, Carzino R, Gutierrez JP, Hull J, Olinsky A, Phelan EM, Robertson CF, Phelan PD. Lower airway inflammation in infants and young children with cystic fibrosis. Am J Respir Crit Care Med 1997;156:1197–1204.
10. Rosenfeld M, Gibson RL, McNamara S, Emerson J, Burns JL, Castile R, Hiatt P, McCoy K, Wilson CB, Inglis A, Smith A, Martin TR, Ramsey BW. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis. Pediatr Pulmonol 2001;32:356–366.
11. Kirchner KK, Wagener JS, Khan TZ, Copenhaver SC, Accurso FJ. Increased DNA levels in bronchoalveolar lavage fluid obtained from infants with cystic fibrosis. Am J Respir Crit Care Med 1996;154:1426–1429.
12. Wagener JS, Rock MJ, McCubbin MM, Hamilton SD, Johnson CA, Ahrens RC. Aerosol delivery and safety of recombinant human deoxyribonuclease in young children with cystic fibrosis: a bronchoscopic study. J Pediatr 1998;133:486–491.
13. Shak S, Capon DJ, Hellmiss R, Marsters SA, Baker CL. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 1990;87:9188–9192.
14. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME. Effect of aerosolised recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994;331:637–642.
15. Geller DE. Aerosolized dornase alfa in cystic fibrosis: is there a role in the management of patients with early obstructive lung disease? Pediatr Pulmonol 1997;24:155–158.
16. Geller DE, Eigen H, Fiel SB, Clark A, Lamarre AP, Johnson CA, Konstan MW. Effect of smaller droplet size of dornase alfa on lung function in mild cystic fibrosis. Pediatr Pulmonol 1998;25:83–87.
17. Hodson ME, Rainisio M, McKenzie S, Harms HK, Koch C, Mastella G, Navarro J, Strandvik B. The European Epidemiological Registry of Cystic Fibrosis (ERCF). Does Pulmozyme make any difference? Neth J Med [Suppl] 1999;54:22–23.
18. Morgan WJ, Stokes D, Konstan MW, Butler S. Risk factors for FEV1 decline in children and adolescents with cystic fibrosis: effect of predicted equations. Am J Respir Crit Care Med 1998; 157(Suppl):A 129.
19. Koch C, McKenzie SG, Kaplowitz H, Hodson ME, Harms HK, Navarro J, Mastella G. International practice patterns by age and severity of lung disease in cystic fibrosis. Data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). Pediatr Pulmonol 1997;24:147–154.
20. Quan JM, Tiddens HAWM, Sy JP, McKenzie SG, Montgomery MD, Robinson PJ, Wohl MEB, Konstan MW. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatr 2001;139:813–820.
21. American Thoracic Society. Standardization of spirometry—1994 update. Am J Respir Crit Care Med 1995;152:1107–1136.
22. Liou TG, Alder FR, FitzSimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153:345–352.