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Dornase Alfa in the Treatment of Cystic Fibrosis in Europe: A Report From the Epidemiologic Registry of Cystic Fibrosis

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Summary. Dornase alfa (Pulmozyme®) treatment for patients with cystic fibrosis (CF) has been shown to improve pulmonary function and reduce exacerbations of infection in a number of placebo-controlled double-blind studies. Data in the Epidemiologic Registry of Cystic Fibrosis (ERCF) in November 1998 were used to assess the long-term effectiveness in routine clinical practice of dornase alfa in terms of pulmonary function and frequency of acute pulmonary exacerbations in CF. At that time, the ERCF contained data on 13,684 CF patients, with a mean observation period of 2.3 years. To be included in the analysis, patients had to have 2 years of data in the Registry in appropriate detail. Overall, untreated patients showed a decline in forced expiratory volume in 1 sec over a 2-year period of −2.3% predicted, but treated patients were stable, showing a change of 0.3% predicted, i.e., a treatment benefit of 2.5%. Compared to untreated patients, there were 25 fewer exacerbations per 100 treated patients per year. The analysis suggested that younger patients were likely to benefit more from treatment. The findings of randomized clinical trials were supported by the data collected in routine clinical practice. **Pediatr Pulmonol. 2003; 36:427–432.** © 2003 Wiley-Liss, Inc.

Key words: dornase alfa; cystic fibrosis; Registry data; lung function.

INTRODUCTION

Cystic fibrosis (CF) is an inherited disease, and the genetic defect leads to abnormalities in the cystic fibrosis transmembrane conductance regulator, which controls chloride and sodium transport. This facilitates bacterial persistence and consequent stimulation of the host's immunological response. The host response leads to an excess of neutrophils in the airways and the production of sputum with a high viscoelasticity. Release of proteases from neutrophils further enhances the inflammatory response. With the median survival of CF patients currently at 31.5 years in the UK,[1] and the major cause of morbidity and mortality being lung disease,[2] new treatments are required for this disease. It is known that disintegrating neutrophils release deoxyribonucleic acid (DNA).[3] Dornase alfa, a recombinant human DNase, reduces the viscoelasticity of extracellular DNA, thus facilitating clearance of airway secretions.

Two short-term, double-blind, controlled studies demonstrated improvements in forced expiratory volume in 1 sec (FEV_1) in patients treated with dornase alfa when compared with controls.[4,5] These studies showed an increase in FEV_1 of between 10–15% in treated

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patients. Longer-term studies showed a more moderate improvement in FEV_1 on the order of 6% from baseline.[6,7] One study also showed a reduction in the risk of pulmonary exacerbations requiring antibiotics. These initial studies were carried out on older patients, but children aged 5–10 years of age have also been shown to benefit, with an improvement in pulmonary function and a reduction in the risk of pulmonary exacerbations that are maintained over 2 years.[8] Studies in patients with severe pulmonary disease ($FEV_1 < 40\%$) confirmed the efficacy in this group of patients.[9,10] These studies showed dornase alfa to be safe and effective in patients with mild, moderate, and severe disease.

The Epidemiologic Registry of Cystic Fibrosis (ERCF), the European database sponsored by F. Hoffmann-La Roche, collected data on the clinical status and treatment of individual patients. The patients were not personally identifiable. The database was administered by quintiles, and enrollment of patients began in January 1994. By November 1998, 13,684 patients from nine countries were enrolled in this database. The data were examined to see if any difference in pulmonary function and exacerbations of infection could be detected when dornase alfa was used in the routine clinical, as opposed to the clinical trial, situation.

METHODS

Data in the ERCF database in November 1998 were downloaded for analysis. The data had previously been cleaned, using >300 computerized checks for context and consistency, and queries had been issued to contributing centers where necessary for clarification.

For analyses of change in pulmonary function, patients had to have a valid pulmonary function test at baseline and at a time interval of 60 days before to 60 days after day 365 and day 730 after baseline. Untreated patients had no dornase alfa during 2 years of observation. Treated patients had treatment recorded at 1 and 2 years after baseline, which was set immediately before they started treatment. Any patient whose start date of dornase alfa therapy was prior to enrollment in the ERCF or not specified was excluded. Gender, height, and age were extracted for all patients.

Results are exploratory only, and must be interpreted with caution because this descriptive study was neither randomized nor controlled. Results are presented as a mean change from baseline in percent of predicted values in treated and untreated patients, and as mean difference between treated and untreated groups in this change, over 1 and 2 years with 95% confidence intervals. Predicted values were calculated according to the patient's age, gender, and current height.[11,12]

For analysis of change in number of pulmonary exacerbations, selected patients had at least 2 years of observation in the ERCF and had either no recorded treatment with dornase alfa during both years, or at least 365 days of treatment following a period of 365 days without treatment. The first year was compared with the second year. Exacerbations were identified by the physician recording either a pulmonary exacerbation or the use of antibiotics for treatment of an exacerbation. To avoid counting the same event more than once, a separate exacerbation was counted only if its date was 30 days or more from the previous exacerbation. Results were presented as mean change in number of exacerbations per year and the mean difference in this value between treated and untreated groups, with 95% confidence intervals.

RESULTS

In total, 2,023 patients were eligible for analysis of FEV_1. Their characteristics are shown in Table 1. The mean (SD) FEV_1 % predicted of patients selected for treatment with dornase alfa was 60.2 (23.1), compared to 79.2 (23.2) for those untreated.

Change in FEV_1 Over 1 and 2 Years

Overall, untreated patients experienced a change in mean FEV_1 % predicted of −1.1 over 1 year and −2.3 over 2 years (Fig. 1). Overall, patients treated with dornase alfa had an FEV_1 higher than baseline after 1 year (by 2.5% predicted), but not after 2 years (0.3% predicted). The difference (95% confidence intervals) between treated and untreated was 3.6 (1.8–5.3)% at 1 year, and 2.5 (0.7–4.4)% at 2 years. The confidence intervals did not overlap zero. Patients of both sexes benefited, and those between 6–<13 years appeared to benefit most from treatment (Fig. 2).

Change in Number of Exacerbations per Year

In total, 4,299 patients were eligible for exacerbation analysis. Their characteristics are shown in Table 2. The

TABLE 1— Baseline Characteristics of Patients in FEV_1 Analysis

Characteristic	Treated	Not treated
N	374.0	1,649.0
Age		
Mean	17.3	14.5
SD	8.5	8.2
FEV_1 (% of predicted)		
Valid	374.0	1,649.0
Mean	60.2	79.2
SD	23.1	23.2
Sex		
Males (%)	51.1	54.8

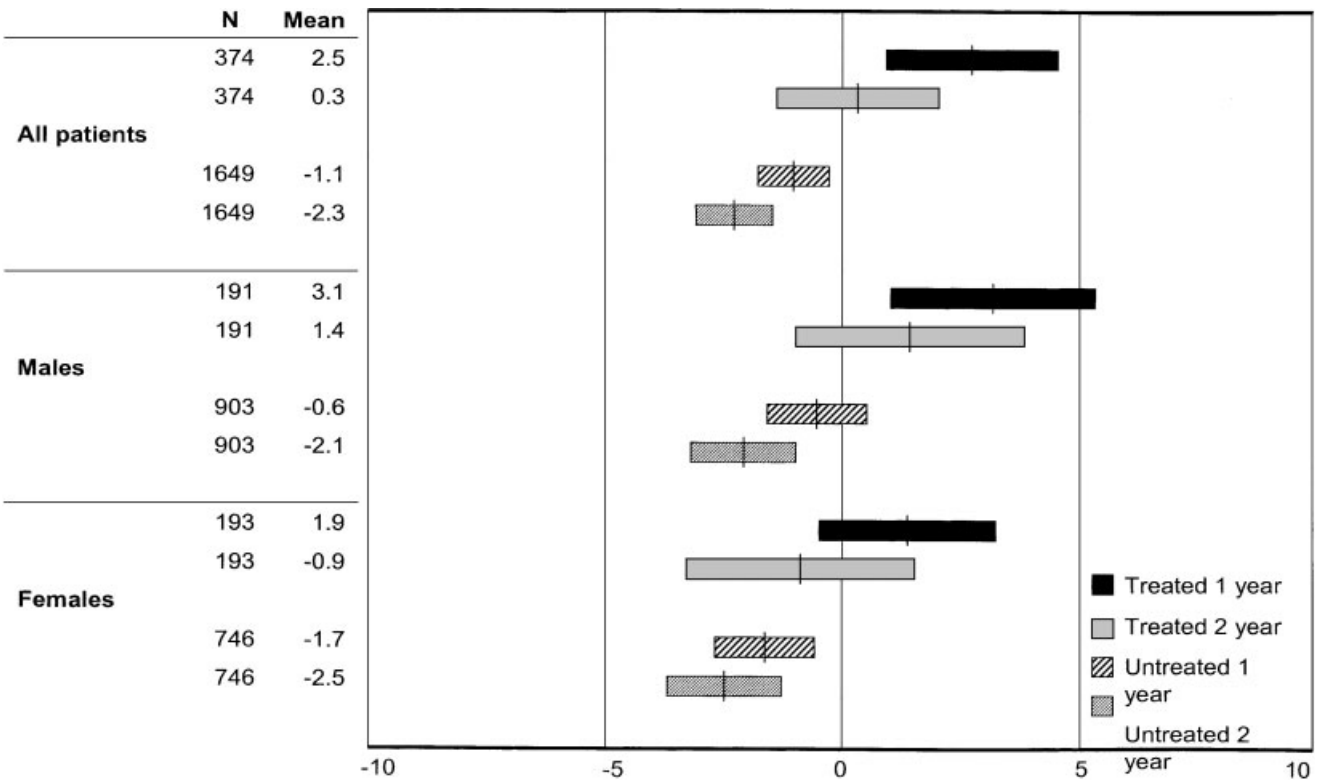

Fig. 1. Change of FEV_1 % from baseline, overall and by gender.

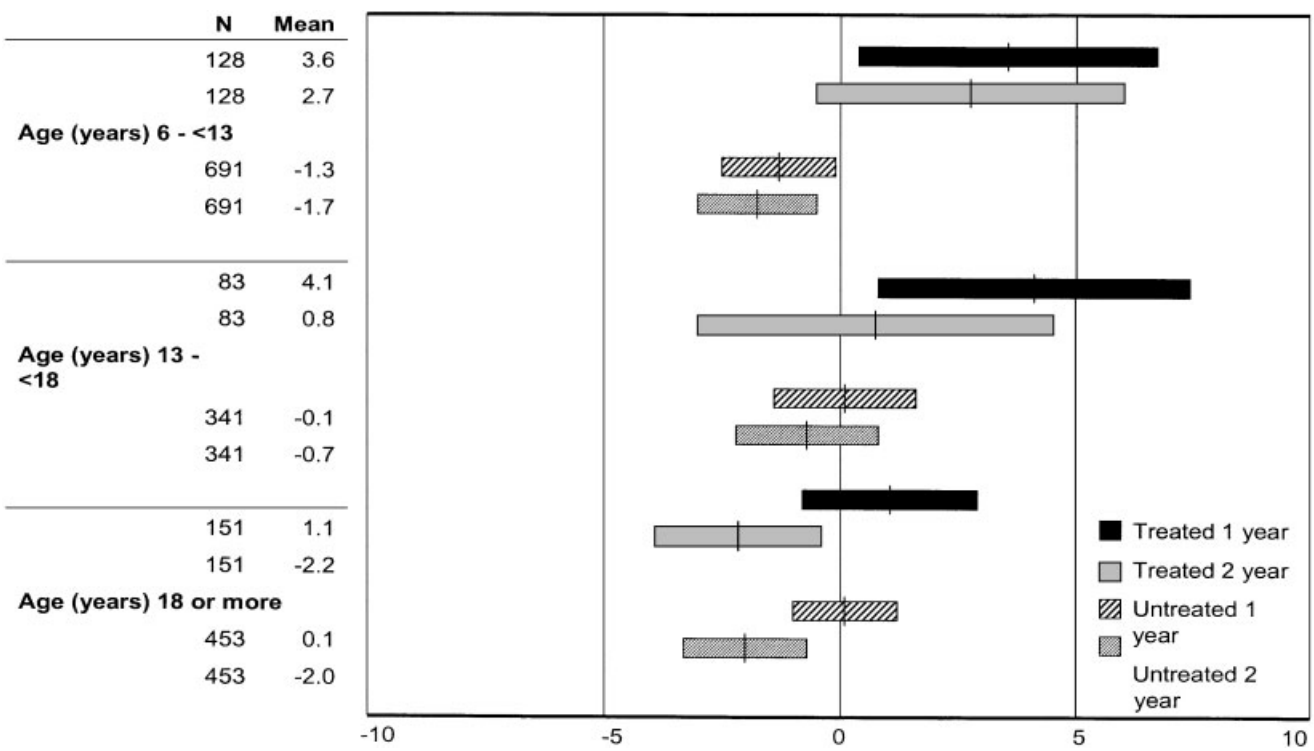

Fig. 2. Change of FEV_1 % from baseline, by age.

TABLE 2— Baseline Characteristics of Patients in Exacerbation Analysis

Characteristic	Treated	Not treated
N	493.0	3,806.0
Age		
Mean	15.4	11.8
SD	8.6	9.0
FEV_1 (% of predicted)		
Valid	400.0	1,922.0
Mean	68.3	80.4
SD	23.0	23.6
Sex		
Males (%)	50.9	54.9

mean FEV_1 (SD) % predicted of patients selected for treatment with dornase alfa was 68.3 (23) compared to 80.4 (23.6) for those untreated. Compared to untreated patients, treated patients had a significant improvement in exacerbation frequency of −0.25, with a 95% confidence interval of −0.12 to −0.39 (Fig. 3). This is equivalent to a reduction of 25 exacerbations per 100 treated patients per year. The confidence intervals did not overlap zero. The difference was found for both males and females. The benefit was most marked in separation of confidence intervals in the younger patients, i.e., 6−<13 years of age.

DISCUSSION

Since the ERCF is not a clinical trial, patients are not randomized to dornase alfa treatment, but rather are treated at the discretion of the participating physician. While the factors prompting dornase alfa prescription are not known, it is clear that treated patients are generally older and sicker in terms of pulmonary function (Tables 1 and 2). By extrapolation, they may also share other characteristics suggestive of a poor prognosis, such as a relatively rapid decline in pulmonary function or frequent exacerbations, before the decision to treat is taken.

In both analyses, the treated patients were older and had a lower baseline FEV_1 than those who were not treated (Tables 1 and 2). However, no attempt was made in this descriptive analysis to account for bias in the assignment of patients to dornase alfa treatment.

The pulmonary function of treated patients was improved at 1 year compared to untreated patients and to baseline. At 2 years, pulmonary function in the treated group had returned to baseline, and the confidence intervals of the treated and untreated patients did not overlap. Younger patients gained the most from treatment. This result is consistent with the general concept that early treatment of cystic fibrosis, before chronic inflammation has led to irreversible lung damage, may be more effective in the long term.[13–16] A similar conclusion was drawn

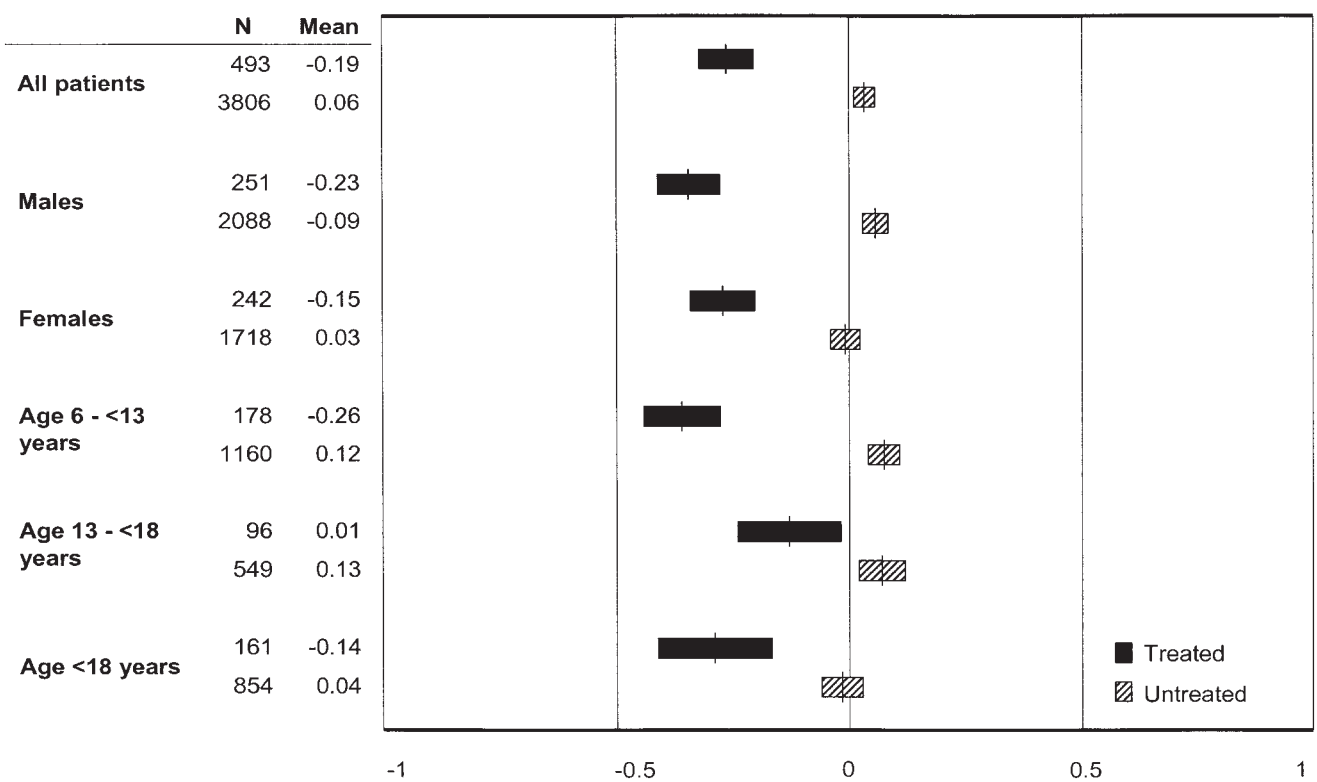

Fig. 3. Change in number of exacerbations from baseline, overall, by gender, and by age.

in a controlled clinical trial of ibuprofen, in which treatment efficacy was observed primarily in patients aged <12 years.[17]

The mean observed change in FEV_1 in untreated patients was −2.2% predicted over 2 years. This value is consistent with the values of −0.9% predicted over 1 year that were previously reported by the ERCF[13] and −1.6% predicted over 1 year reported by the Epidemiologic Study of Cystic Fibrosis (ESCF) in the USA and Canada.[18] Mixed-model analysis of all longitudinal data in the ERCF recently yielded average slopes of −2.7 for severe patients to −1.5 for mild patients % predicted per year.[19] These values are somewhat lower than the average slope of −3.6% predicted per year reported in 43 CF patients treated with placebo in a 4-year clinical trial initiated 10 years ago.[17]

This study does not look at genotype, but other work from the Registry on a larger number of patients showed that pulmonary function did not appear to be genotype-dependent, except for patients with one class 4 mutation, which is a small proportion of all patients.[20] Adherence was not assessed in this study. However, it is an issue for all treatments in patients with CF.[21] This paper presents actual results obtained in a real clinical setting.[21]

The frequency of acute pulmonary exacerbations is considered a risk factor for more rapid decline in pulmonary function. In controlled clinical trials, dornase alfa was shown to reduce the risk of exacerbations requiring intravenous antibiotics by about 30% over a 6-month period.[6] The current analysis confirms that the ERCF can detect a reduction in the number of acute exacerbations during the first year of dornase alfa treatment vs. the previous year without treatment, in contrast to untreated patients who deteriorate slightly during the second year. The magnitude of the difference (25 exacerbations per 100 treated patients per year) is clinically relevant.

Younger patients appear to benefit more from dornase alfa in terms of both reduction of exacerbation frequency and maintenance of pulmonary function. If regression to the mean was an important issue, these younger, fitter patients might have shown less benefit than older, sicker patients. Ultimately, the best way of determining long-term effects of dornase alfa in younger patients is to perform a placebo-controlled clinical trial. The Pulmozyme Early Intervention Trial (PEIT) has just been completed. This studied the effects of dornase alfa on patients 6–10 years old over a 2-year period. Results indicate that dornase alfa improved pulmonary function and reduced the frequency of exacerbation of infection.[8]

Despite an obvious treatment bias in favor of prescribing dornase alfa for older and more severely ill CF patients, the ERCF data seem to confirm in routine clinical practice the findings of the phase III pivotal trial and the PEIT study.[6,8] Dornase alfa provides an overall benefit in pulmonary function at 2 years and reduces the number of exacerbations experienced in the first year of treatment. Younger patients appear to benefit most.

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