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Original article

Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis

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Abstract

Objective:
To investigate adherence to dornase alfa therapy among commercially-insured patients with cystic fibrosis (CF) and to examine the impact of adherence on health and economic outcomes.

Methods:
This retrospective cohort analysis included CF patients with $\geq$1 dornase alfa (Pulmozyme) pharmacy claim between 1 October 2006 and 30 September 2008 and with continuous enrollment in the health insurance plan at least 1 year before and 1 year after their index dornase alfa claim. Adherence was measured with the medication possession ratio (MPR). Multivariate models were used to estimate the relationship between adherence and exacerbations, utilization, and cost.

Results:
Nine hundred and seven patients met the inclusion criteria. The mean age was 19.5 years (SD = 11.5) and 49.1% were female. Overall MPR was 0.59 and by age was 0.66 for patients of 5–12 years, 0.57 for 13–20 years, 0.54 for 21–30 years, and 0.56 for patients $\geq$31 years. Adherence was better in fall and winter than in spring and summer. There was no statistically significant difference in the proportion of patients with inpatient respiratory exacerbations across groups with low (<0.5), moderate (0.5–0.79), and high ($\geq$0.8) adherence (24.5%, 22.3%, and 19.1%, respectively, $p = 0.250$). There was a trend toward higher total charges in more-adherent patients (mean $58,612 in the least-adherent group and mean $69,427 in the most adherent group, $p = 0.107$). In multivariate models, MPR was not significantly associated with the risk of inpatient respiratory exacerbations (hazard ratio = 1.16 for MPR <0.5 vs $\geq$0.8; 95% CI = 0.83–1.61).

Limitations:
Study data were derived from insurance claims; adherence measures were based on prescription fills, not observed medication use.

Conclusion:
Adherence to dornase alfa was generally low, but varied by age and season. Adherence was not found to be significantly associated with respiratory exacerbations or total charges, but was associated with shorter hospital length of stay.

Introduction

Cystic fibrosis (CF) is the most common life-shortening inherited disorder in Caucasians, and mortality is predominately due to pulmonary disease. The use of inhaled and oral antibiotics, hypertonic saline, and mucolytics has been demonstrated to improve outcomes in clinical trials[1]. For most chronic conditions, real-world effectiveness is less than that seen in trials. One likely explanation is that

adherence to therapy for most chronic conditions is as low as 50%. It has been proposed that increasing adherence could have a greater impact on health outcomes than any specific medical treatment[2].

Evidence suggests patients with CF, like those with other chronic conditions, have generally poor adherence to therapy. Estimates for adherence of between 36–80% have been reported in CF, depending on the method used and drug(s) studied. Imperfect adherence to medication therapy has been linked to worse outcomes and higher costs in multiple conditions. Poor adherence contributes to a lack of blood pressure control in more than two-thirds of people with hypertension, can triple the cost of diabetes complications, and decreases quality-of-life, increases utilization, and increases costs in patients with asthma[2].

Dornase alfa (Pulmozyme®, Genentech, Inc., South San Francisco, CA) is a mucolytic agent indicated to reduce the risk of respiratory infections and improve pulmonary function in patients with CF[3]. If adherence to this therapy in a real world setting is low, some of its potential benefits will be missed. Specifically, poor adherence would be expected to increase the risk of respiratory infection and, as a result, increase health service use and cost. Insurance claims are available on a large proportion of the population at a relatively low cost and provide a ready source of secondary data to investigate whether this in fact occurs. In this retrospective study, we used commercial insurance claims to investigate the rate of adherence to dornase alfa therapy among patients with CF. We also examined the impact of adherence on health and economic outcomes. We hypothesized that improved adherence would be associated with lower respiratory exacerbation rates and lower healthcare-related costs.

Patients and methods

Data source

This was a retrospective cohort analysis of health insurance claims. The data source was Thomson Reuters MarketScan database, a HIPAA-compliant administrative claims dataset. The database is derived from adjudicated inpatient medical, outpatient medical, and outpatient prescription drug claims, covering over 30 million individuals with employer-sponsored health insurance in the US. Claims include information on medical procedures, hospitalizations, drugs dispensed, dates of service/prescription, and number of days of medication supplied. Also available are member enrollment and limited patient demographic information. Institutional review board approval was unnecessary as the data do not contain protected health information.

Patients and study period

The analysis included CF patients older than 4 years who were treated with dornase alfa during a 2-year period between 1 September 2006 and 31 August 2008. Dornase alfa was identified using the National Drug Code product identifier. Included patients had at least one claim with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code for CF (277.0), and at least one prescription claim for dornase alfa. The index date was the first dornase alfa fill date in the identification period, provided the patient was continuously enrolled in a health plan for 12 months before and 13 months after that prescription fill. The study was divided into a 12-month pre-index baseline period and a 12-month outcome review period, separated by a 1-month skip period (Figure 1). The data for the study covered the period from 1 September 2005 to 30 September 2009. The 1-month skip period ensured adequate time for the drug to exert its potential clinical effect. Patients were characterized as new users if they did not use dornase alfa in the 12-month pre-index period.

Measures

Adherence to dornase alfa was the primary independent variable in this study. In accordance with expert guidance on studies of adherence and compliance, medication

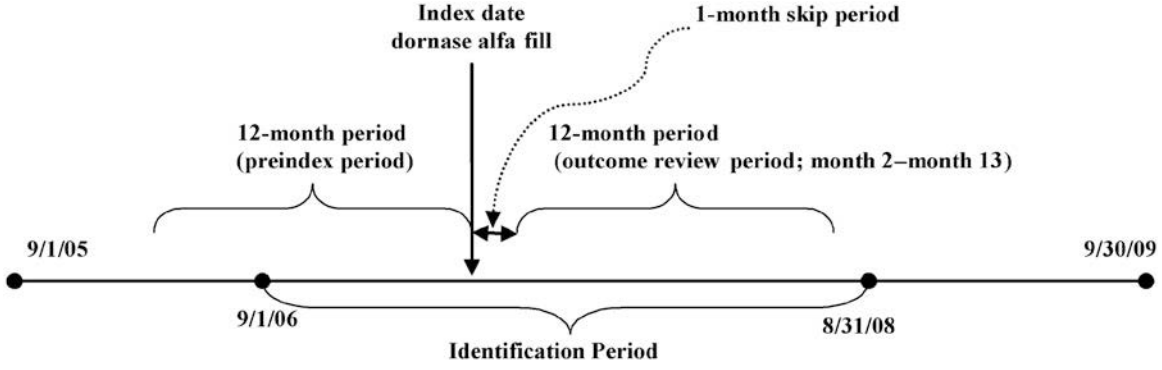


Figure 1. Study timeline for patients with cystic fibrosis who were treated with dornase alfa; 54 × 23 mm (300 × 300 DPI).

adherence was measured with the medication possession ratio (MPR)[4]. MPR, the most common measure of medication adherence in studies using secondary data, is the ratio of days in a fixed period during which medication is available for use over total days in the period. In the claims database, each prescription carries a 'days' supply', indicating the quantity of medication filled. We calculated MPR by summing the days' supply for all dornase alfa prescriptions in the 13-month post-index period and dividing it by total days in the period[4,5].

Using expert clinician (S.Z.N.) opinion, we defined the primary outcome variable, 'respiratory exacerbation', to represent the presence of (1) a medical claim for hemoptysis, pneumothorax, acute asthma, acute respiratory infection, pneumonia, influenza, acute respiratory failure, or bronchospasm; or (2) the presence of a pharmacy claim for oral or intravenous (IV) antibiotics (except oral azithromycin, which is commonly used prophylactically as an anti-inflammatory agent). These exacerbations were subdivided by the site of care reported on the claim (i.e., outpatient, emergency department [ED], or inpatient). Secondary outcomes included total charges and charges for respiratory exacerbations. Only claims meeting criteria 1 or 2 above were considered respiratory exacerbation charges. Descriptive statistics, including mean, standard deviation (SD), and percentage, were reported for all variables.

Control variables included age, gender, region, and physician specialty. 'Usual-care' physician specialty was defined as the specialty seen on the plurality of evaluation and management visits consistent with a validated method[6]. A limitation of claims data is the difficulty in controlling for differing levels of illness between patients. To minimize this problem, we estimated several different control variables related to illness severity using claims from the pre-index year. First, we counted the number of pulmonologist visits and costs in the pre-index year as a proxy for disease severity. Second, we measured the Charlson comorbidity index, a widely reported and validated morbidity measure[7,8]. The Charlson is 0 for patients with no comorbidities; among hospitalized patients a score of 3 or more is associated with >10% chance of dying before discharge[9]. The Charlson index was designed as a predictor of mortality, not health service use, so we estimated the burden of chronic conditions using an additional method that correlates with healthcare spending[10]. This method counts only chronic conditions (unlike the Charlson) so should not be influenced by acute exacerbations. The Charlson has not been validated in a population with CF, so we looked for evidence of comorbidities associated with the disease[11] (diabetes, pancreatic insufficiency, *Pseudomonas aeruginosa* infection, gastroesophageal reflux, chronic sinusitis, malnutrition, osteoporosis, and allergic bronchopulmonary aspergillosis) and for evidence of pre-index respiratory exacerbations. Finally, we measured the use of concomitant CF medications (e.g., inhaled tobramycin, steroids, hypertonic saline) during the pre-index period.

We reported a variety of descriptive statistics. To compare MPR between new and continuing users, across age groups, between genders, and across regions, the *F*-test was used. For comparisons across seasons, a repeated measure analysis was used. We conducted three multivariate models to control for baseline measures. First, in a Cox proportional hazards model we estimated the impact of adherence on the risk of inpatient respiratory exacerbation. We used two generalized linear models (GLM) to estimate the impact of adherence on cost, one model for total healthcare charges and one for respiratory-related charges. All three models included age, gender, region, and season as independent variables. In addition to these four variables, we used forward selection to identify those baseline variables with a statistically significant association ($p < 0.05$) with the outcome. Only those additional variables with such an association were retained in the final models. Both season and MPR over the previous 90 days change over time, so these variables were updated daily throughout the follow-up period. The final independent variables used in the models were adherence, variables selected *a priori*, and those baseline variables found to be significant in forward selection (for Cox: exacerbation charge, any exacerbation, presence of ABPA, reflux, or diabetes; and for GLM: exacerbation charge, use of oral/IV/inhaled ABX, use of inhaled steroids, presence of pseudomonas infection or diabetes, Charlson index, number of dornase alfa claims, and number of pulmonologists visits). The Cox model results are given as the hazard ratio for inpatient exacerbation. GLM results are given as an exponentiated coefficient that provides a ratio of costs between comparison groups. An exponentiated coefficient of 0.8 for a dichotomous variable means, when the variable is present, the cost is 80% of what it would have been if the variable were absent. Cost models used MPR as a categorical variable. Several sensitivity analyses were conducted using continuous measures of MPR. Sensitivity analyses produced results that were similar to the main model; only the main analysis is presented. All data transformations and statistical analyses were performed using SAS© version 9.2 (SAS Institute, Cary, NC).

Results

We identified 2493 dornase alfa users in the period from 1 September 2006 to 31 August 2008: 1317 did not meet the continuous enrollment criteria, 182 had no CF diagnosis in the 12 months before or 13 months after the index dornase alfa fill, and 87 were ≤4 years old, leaving 907 patients in our analysis cohort. Most (73.8%) of these 907 patients were ongoing users of dornase alfa, whereas 26.2% were

Table 1. Demographics and selected baseline characteristics of cystic fibrosis patients treated with dornase alfa.

Variable	All ($n = 907$)
New dornase alfa user (no fills in 12 mo), *n* (%)	238 (26.2)
Age, mean (SD), years	19.5 (11.5)
Age group, no. (%), years	
5–12	274 (30.2)
13–20	337 (37.2)
21–30	140 (15.4)
31+	156 (17.2)
Female, *n* (%)	445 (49.1)
Usual-care physician specialty, *n* (%)	
Pulmonologist	327 (36.1)
Primary care	266 (29.3)
Gastroenterology	27 (3.0)
Otolaryngology	23 (2.5)
Other[a]	133 (14.7)
Unknown[b]	131 (14.4)
Annual pulmonologist visits, mean (SD) [median]	5.3 (9.2) [3]
Charlson comorbidity index, mean (SD) [median]	1.2 (1.5) [1]
No. of chronic conditions[c], mean (SD) [median]	2.3 (1.3) [2]
Comorbidities associated with CF[d], *n* (%)	
Diabetes	154 (17.0)
Pancreatic insufficiency	734 (80.9)
Pseudomonas infection	705 (77.7)
Gastroesophageal reflux	65 (7.2)
Chronic sinusitis	215 (23.7)
Malnutrition or failure to thrive	65 (7.2)
Osteoporosis	16 (1.8)
Allergic bronchopulmonary aspergillosis	16 (1.8)
Any use of inhaled antibiotics, *n* (%)	527 (58.1)
No. of fills of oral or IV antibiotics, mean (SD) [median]	3.8 (3.6) [3]
Any use of inhaled steroids (including steroid combination), *n* (%)	486 (53.6)
Any use of hypertonic saline, *n* (%)	187 (20.6)

[a]Individual specialties making up less than 2% of the total.
[b]No data on specialty or no qualifying visits.
[c]A condition expected to last ≥12 months and resulting in functional limitations and/or the need for ongoing medical care. Identified using a validated list of ICD-9-CM codes[6].
[d]Derived from literature and identified using a published list of ICD-9-CM codes[7].
CF, cystic fibrosis; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; IV, intravenous; SD, standard deviation.

new users. Mean (SD) age was 19.5 (11.5) years, evenly divided by gender. Pulmonologists and primary care physicians were the usual-care physicians for most patients (36.1% and 29.3% of patients, respectively). The annual mean number of pulmonologists visits was 5.3 (median = 3, SD = 9.2) (Table 1).

At baseline, patients had a mean of 2.3 chronic conditions and a median Charlson score of 1. Pancreatic insufficiency and chronic pulmonary pseudomonas infection were the most common comorbidities seen, affecting 80.9% and 77.7% of patients, respectively. Chronic sinusitis was diagnosed in 23.7% of patients and diabetes in 17%. Malnutrition or failure to thrive affected 7.2%, and 1.8% had allergic bronchopulmonary aspergillosis. At baseline, 58.1% of patients used inhaled antibiotics, 53.6% used inhaled steroids (either alone or in combination with bronchodilators), and 20.6% used hypertonic saline (Table 1).

Mean adherence to dornase alfa, as measured by the MPR, was 0.59 (SD = 0.30, median = 0.60) over the 13-month post-index period. The MPR among patients who did not use dornase alfa for at least 12 months before the index date was 0.39, compared with 0.66 among patients who had previously used the drug ($p < 0.001$). Adherence also varied with age (the MPR for patients 5–12 years old was 0.66, for those 13–20 years old was 0.57, for those 21–30 years old was 0.54, and for those ≥31 years old was 0.56) and by season (the MPR was 0.61 in fall and winter, 0.59 in spring, and 0.56 in summer) with $p < 0.001$ for both age and season (Table 2). Mean adherence in the least adherent group was 0.28, compared to 0.65 in the middle and 0.93 in the most adherent groups.

To test the association between adherence and outcomes, patients were grouped into low (<0.5), moderate (0.5–0.79), and high (≥0.8) adherence ranges using MPR values. There was no statistically significant difference in the proportion of patients with respiratory exacerbations requiring inpatient care across these three groups (24.5%, 22.3%, and 19.1%, respectively, $p = 0.250$), although, among patients with inpatient exacerbations, there was a statistically significant difference in hospital length of stay, with a mean (SD) length of stay of 17.3 (19.1) days in patients with the lowest MPR (<0.5) and 10.8 (10.0) days in those with the highest MPR (≥0.80) ($p = 0.038$). There was no statistically significant difference between groups in the proportion with ED visits for respiratory exacerbations or the number of outpatient visits. The least adherent group had the fewest fills of oral or IV antibiotics (mean = 3.9, SD = 3.6), and the most adherent group had the highest number of antibiotic fills (mean = 5.1, SD = 4.6; $p < 0.001$) (Table 3).

There was a trend toward higher total healthcare charges in more adherent patients (mean $58,612 in the least adherent group, $67,565 in the intermediate group, and $69,427 in the most adherent group; $p = 0.107$). There was a statistically significant difference in respiratory exacerbation-related charges in the opposite direction, with significantly higher mean charges in the least adherent group ($17,163) compared with the intermediate ($13,408) and the most adherent group ($9264) ($p = 0.048$) (Table 3).

In the Cox regression, the MPR over the previous 90 days was not significantly associated with the risk of respiratory exacerbation requiring inpatient admission (hazard ratio = 1.16 for MPR <0.5 vs ≥0.8; 95% CI = 0.83–1.61) (Figure 2A). In the generalized linear model examining total healthcare costs, lower adherence was a statistically significant predictor of lower cost, with a cost ratio of 0.67 for low vs high adherence (95% CI = 0.60–0.75) and 0.88 for moderate vs high adherence (95% CI = 0.79–0.99) (Figure 2B). In the generalized

Table 2. Dornase alfa adherence as measured by medication possession ratio in the post-index period.

	No. of patients	Mean	(SD)	[Median]	*p*-value[a]
All	907	0.59	(0.30)	[0.60]	
New or continuing user[b]					<0.001
New	238	0.39	(0.26)	[0.32]	
Continuing	669	0.66	(0.28)	[0.70]	
Patient age, years					<0.001
5–12	274	0.66	(0.29)	[0.71]	
13–20	337	0.57	(0.29)	[0.55]	
21–30	140	0.54	(0.30)	[0.52]	
31+	156	0.56	(0.31)	[0.58]	
Gender					0.883
Male	462	0.59	(0.30)	[0.59]	
Female	445	0.59	(0.30)	[0.61]	
Region					0.285
North Central	269	0.60	(0.30)	[0.65]	
Northeast	113	0.55	(0.31)	[0.58]	
South	383	0.58	(0.30)	[0.57]	
West	142	0.62	(0.28)	[0.61]	
Season[c]					<0.001
Spring	907	0.59	(0.36)	[0.65]	
Summer	907	0.56	(0.37)	[0.65]	
Fall	907	0.61	(0.35)	[0.68]	
Winter	907	0.61	(0.34)	[0.67]	

[a]*F*-test was used for comparisons between new and continuing users, across age groups, between genders, and across regions. Repeated measure analysis was used for comparison across seasons.
[b]New users had no fills of dornase alfa for ≥12 months, continuing users had at least one fill.
[c]Medication possession ratio for season calculated using the 3 months of that season alone rather than the entire post-index period.
SD, standard deviation.

linear model of exacerbation-related costs, adherence was not a statistically significant predictor. Sensitivity analyses for the cost models with MPR as a continuous variable had similar results.

Discussion

We used healthcare claims data to study a large group of commercially insured patients with CF, and found variable adherence to dornase alfa. About 33% of patients were highly adherent (MPR = 0.8–1.0), but 42% filled less than half their prescriptions (MPR < 0.5). Younger patients were generally more adherent than older ones, with an MPR of 0.66 for ages 5–12, dropping to 0.57 for ages 13–20, and 0.54 for ages 21–30, before rising slightly to 0.56 in those older than 30. Continuing users had greater adherence than new users. Adherence was better in the fall and winter seasons (MPR = 0.61) than in the spring (MPR = 0.59) and summer (MPR = 0.56). These findings may be attributed to a variety of factors. Greater parental oversight of treatments might improve adherence in younger children compared with adolescents. Continuing users represent a group in which some of those patients likely to discontinue have already done so. Patients may have fewer respiratory infections in spring and summer. In addition, school-aged children may be less adherent when they are out of school, traveling, or away from their usual routine. To our knowledge, this is the largest study to examine adherence to dornase alfa outside of clinical trials. Our overall estimate of adherence of 0.59 is consistent with the MPR of ~0.70 estimated at a single center using pharmacy data[12]. Electronic monitoring of nebulizers has produced substantially lower estimates (median of 36% of doses taken appropriately)[13].

In our analysis, improved adherence was associated with shorter hospital stays among those admitted with respiratory exacerbations, but was not associated with lower utilization of healthcare services or lower cost. This is in contrast to a recent study at a single center that found an association between a composite measure of medication adherence to four drugs and exacerbations (although the prior study found no significant relationship of outcomes to adherence to any of the specific drugs)[12]. There are several differences between that study and ours that may explain the disparate results. The prior study measured adherence using a composite measure for four CF medications, rather than for a single drug. High compliance with multiple therapies, rather than a specific one, may be necessary to reduce exacerbations. Second, although we attempted to control for illness severity, our ability to do so was limited as the data used did not include FEV_1 (forced expiratory volume in 1 s), recognized as the single best measure of severity[14]. Eakin *et al.*[12] found that baseline FEV_1 was a more powerful predictor of

Table 3. Utilization and healthcare charges in the outcome period, stratified by dornase alfa adherence, in patients with cystic fibrosis.

Variable	All ($n=907$)	MPR			*p*-value
		<0.5 ($n=380$; 41.9%)	0.5–<0.8 ($n=229$; 25.2%)	0.8–1.0 ($n=298$; 32.9%)	
Any inpatient respiratory exacerbation, *n* (%)	201 (22.2)	93 (24.5)	51 (22.3)	57 (19.1)	0.250
LOS[a], mean (SD) [median]	14.3 (16.2)[9]	17.3 (19.1)[11]	12.6 (15.2)[8]	10.8 (10.0)[7]	0.038
Any ED visit for respiratory exacerbation, *n* (%)	37 (4.1)	19 (5.0)	6 (2.6)	12 (4.0)	0.355
No. of outpatient visits for respiratory exacerbations, mean (SD)	1.2 (3.1)	1.3 (3.7)	1.3 (2.9)	1.2 (2.4)	0.880
No. of fills of oral or IV antibiotics, mean (SD) [median]	4.4 (4.1)[3]	3.9 (3.6)[3]	4.4 (4.2)[3]	5.1 (4.6)[4]	<0.001
Total healthcare charges, $ mean (SD) [median]	64,426 (71,019) [44,878]	58,612 (81,959) [32,765]	67,565 (68,380) [44,492]	69,427 (56,110) [55,524]	0.107
Total respiratory exacerbation–related charges[b], $ mean (SD) [median]	13,620 (41,484) [426]	17,163 (48,469) [374]	13,408 (41,265) [399]	9264 (30,159) [472]	0.048

[a]Among 201 patients with at least one respiratory exacerbation requiring inpatient care.
[b]Respiratory exacerbation related were charges identified for (1) medical claims for hemoptysis, pneumothorax, acute asthma, acute respiratory infection, pneumonia, influenza, acute respiratory failure, or bronchospasm; and (2) pharmacy claim for oral or IV antibiotics (except oral azithromycin).
LOS, hospital length of stay; ED, emergency department, MPR, medication possession ratio; SD, standard deviation.

exacerbation than was adherence. Finally, Eakin *et al.* defined an exacerbation to include only IV antibiotics used to treat a pulmonary exacerbation, whereas our definition included both IV and oral antibiotics (except oral azithromycin), as well as claims for hemoptysis, pneumothorax, acute asthma, acute respiratory infection, pneumonia, influenza, acute respiratory failure, or bronchospasm. Our definition was designed to capture the clinical spectrum of events viewed as exacerbations by clinicians, and was based on literature and clinical experience[15].

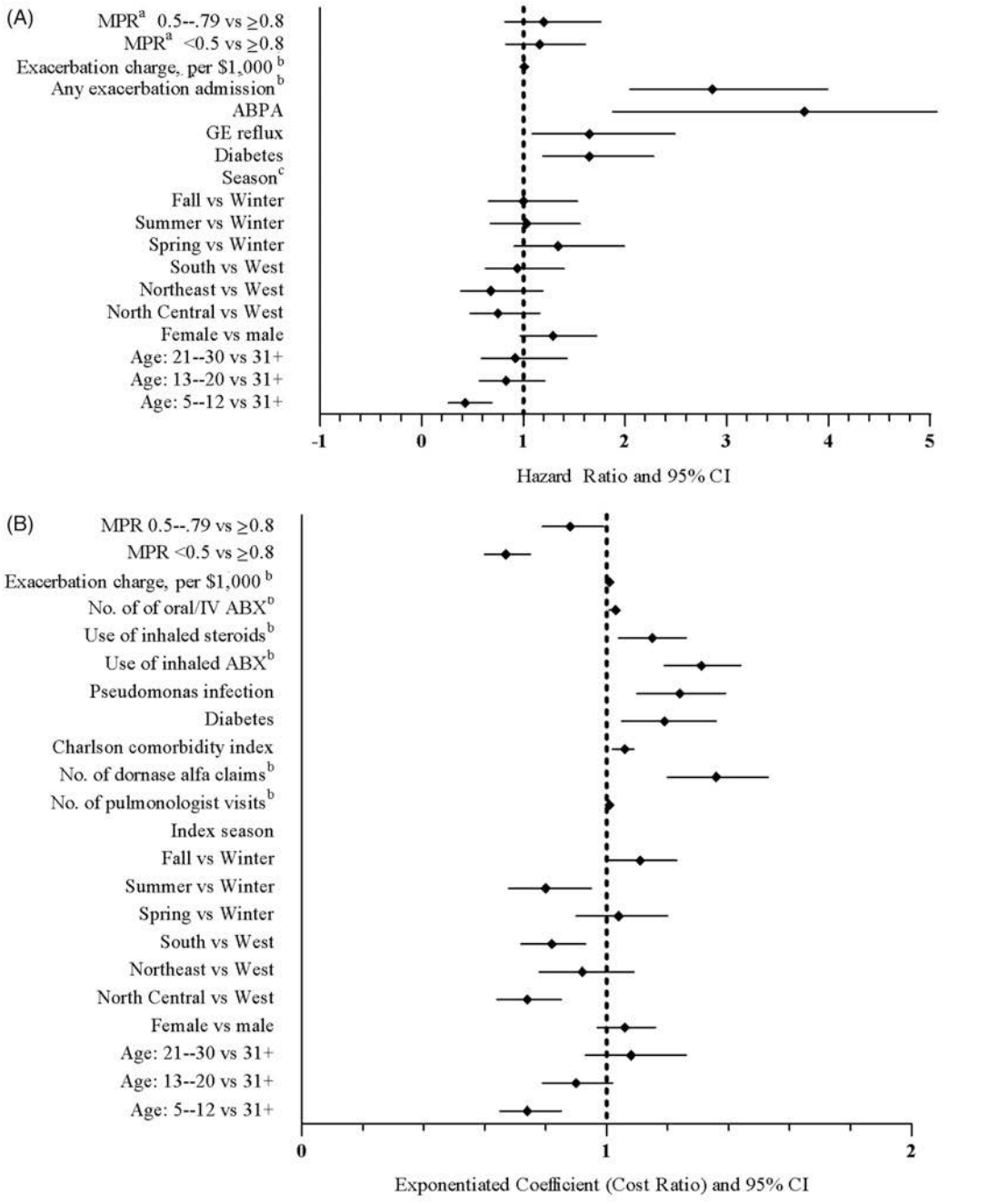
In our study, mean length of stay for inpatient respiratory exacerbations was significantly shorter among the most adherent compared with the least adherent patients. Respiratory exacerbation related costs were also lower in the most adherent patients. Dornase alfa has a wholesale acquisition price of ~$24,000/year[16], and therefore an increase in MPR from 0.28 (the least adherent group) to 0.93 (the most) would be expected to add $15,600 in medication charges alone. The observed difference in total charges between those groups was actually $9000, supporting the theory that greater use of dornase alfa reduces medical costs, albeit not enough to offset the greater medication cost.

Higher costs among patients with higher adherence may also result from confounding by the level of illness. That is, sicker patients may have been both more adherent to therapy and more costly, but the cost was not necessarily a result of the adherence. Although there was no statistically significant difference in the mean Charlson comorbidity index between groups, 87.9% of patients with an MPR over 0.80 had pancreatic insufficiency compared with 77.4% of those with an MPR under 0.50 ($p<0.001$).

How might our results be used? The Cystic Fibrosis Foundation has a list of seven goals for quality improvement, one of which states that 'all people with CF will receive appropriate therapies for maintaining lung function and reducing acute infection'. The Foundation's guidelines strongly recommend dornase alfa for patients with moderate-to-severe lung disease and also recommend dornase alfa for those who are asymptomatic or have mild lung disease[1], yet two-thirds of patients have less than optimal adherence to this treatment. These patients may derive substantial benefits from increased compliance with their treatment regimen.

The results of this study could inform ongoing quality improvement and educational efforts directed to CF patients and their families. These efforts could be intensified in the spring and summer to coincide with the decrease in adherence. A goal of at least 80% adherence to recommended therapies could be incorporated into quality improvement plans.

The current study involved a large sample of patients rather than a single institution or geographic region. The database was representative of the CF population in the US, with a mean age of just under 20, an even split



ABPA, allergic bronchopulmonary aspergillosis; ABX, antibiotics; GE, gastroesophageal; IV, Intravenous; MPR medication possession ratio.

[a]MPR over the previous 90 days (updated at each follow-up day)

[b]Baseline utlization/costs

[c]Current season (updated at each follow-up day)

Figure 2. Forest plots of multivariate model results for patients with cystic fibrosis who were treated with dornase alfa. (A) Cox regression: risk of inpatient respiratory exacerbation. (B) Generalized linear model: all cause healthcare costs.

between males and females, and wide geographic diversity. The proportion of co-morbid illnesses in our CF patient population was similar to that seen in a US registry of more than 26,000 CF patients: in our analysis, 81% had pancreatic insufficiency, compared with 86% in the registry; 78% had chronic pulmonary pseudomonas infection compared with 61% in the registry; and 24% had chronic sinusitis compared with 27% in the registry[17].

Total annual healthcare charges averaged $64,426 in our study. In a 2003 review of cost literature, Krauth *et al.*[18] identified direct cost estimates for patients with CF between $6200–$43,100 annually. In 2009, Ouyang *et al.*[11] used claims data from 2006 to estimate an average annual expenditure of $48,098. Comparisons with present estimates are difficult, as the data used by Ouyang *et al.* reported payer and patient payments, whereas our database used charges. Charges are an imperfect proxy for costs but were the only measure available to us in this study database.

Our study had other limitations. All the measures of adherence we studied were derived from prescription fill data, not from actual use, so they may over-estimate adherence. The data used for this study were developed to pay claims, not for research, and miscoding may affect the interpretation of our findings. We did not have access to data on demographics, such as socioeconomic status, which may be associated with CF outcomes[19]. We could not control for illness severity as measured by pulmonary function. We did use a variety of measures (including Charlson comorbidity index, number of pulmonology visits, presence of specific respiratory comorbidities, and use of CF medications) to control for severity, but these measures have not been independently validated in this population. Finally, the data for this study were from 2005–2009, and practices may have changed since that time. In particular, as a result of more recent recommendations[1] antibiotic use may have increased, inhaled corticosteroid use declined, and hypertonic saline increased since the study period. As a result of these limitations, a retrospective study such as this one may best be used to describe a population and suggest hypotheses to be tested in prospective studies.

Conclusions

We found generally low adherence to dornase alfa, a therapy that has been shown to decrease respiratory exacerbations in patients with CF. Improving adherence to therapy for a chronic condition with a high treatment burden is a complex challenge, because many medications for CF are time-consuming and require nebulization. Future studies should address the development and evaluation of programs that may improve adherence to therapies in patients with CF.

Transparency

Declaration of funding
The work described in this manuscript was funded by Genentech, Inc. The sponsor did not alter or influence the results of the study, which was conducted using clearly delineated analytic methods.

Declaration of financial/other relationships
MB and EC are employees of Partnership for Health Analytic Research, which was paid by Genentech to conduct the research described in this manuscript. SN served as a member of a Genentech advisory board in 2011. She did not receive any compensation for work on this study or manuscript. KV and WC are employees of Genentech.

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References

1. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic Fibrosis Foundation, Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines. Am J Respir Crit Care Med 2007;176:957–69
2. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003
3. Pulmozyme®. (dornase alfa) [prescribing information]. South San Francisco, CA: Genentech, Inc., 2010
4. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44–7
5. Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10:3–12
6. O'Malley AS, Pham HH, Schrag D, et al. Potentially avoidable hospitalizations for COPD and pneumonia: the role of physician and practice characteristics. Med Care 2007;45:562–70
7. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83
8. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9
9. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676–82
10. Hwang W, Weller W, Ireys H, et al. Out-of-pocket medical spending for care of chronic conditions. Health Aff (Millwood) 2001;20:267–78
11. Ouyang L, Grosse SD, Amendah DD, et al. Healthcare expenditures for privately insured people with cystic fibrosis. Pediatr Pulmonol 2009;44:989–96
12. Eakin MN, Bilderback A, Boyle MP, et al. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. J Cyst Fibros 2011;10:258–64
13. Daniels T, Goodacre L, Sutton C, et al. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. Chest 2011;140:425–32
14. Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care: consensus conference report. Chest 2004;125(Suppl 1):1S–39S
15. Rosenfeld M, Emerson J, Williams-Warren J, et al. Defining a pulmonary exacerbation in cystic fibrosis. J Pediatr 2001;139:359–65
16. PriceRx, Wolters Kluwer Health. http://www.medispan.com/drug-pricing-analysis-pricerx.aspx. Accessed November 10, 2011
17. Cystic Fibrosis Foundation. Patient Registry. 2010 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation, 2011
18. Krauth C, Jalilvand N, Welte T, et al. Cystic fibrosis: cost of illness and considerations for the economic evaluation of potential therapies. Pharmacoeconomics 2003;21:1001–24
19. Schechter MS, Shelton BJ, Margolis PA, et al. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. Am J Respir Crit Care Med 2001;163:1331–7

