Longitudinal association between medication adherence and lung health in people with cystic fibrosis

Michelle N. Eakin a, Andrew Bilderback a, Michael P. Boyle a, Peter J. Mogayzel b, Kristin A. Riekert a,*

a Division of Pulmonary and Critical Care Medicine, Johns Hopkins School of Medicine, USA
b Department of Pediatrics, Johns Hopkins School of Medicine, USA

Received 22 December 2010; received in revised form 4 March 2011; accepted 5 March 2011
Available online 31 March 2011

Abstract

Background: This study examined the relationship of medication adherence to frequency of pulmonary exacerbation and rate of decline in FEV1% predicted (FEV1). Methods: 95 CF patients aged 6 years or older and prescribed a pulmonary medication, were enrolled in a longitudinal retrospective review of medication adherence and health outcomes (the occurrence and frequency of intravenous (IV) antibiotic treatments and FEV1) over 12-months. Pharmacy refill records were used to calculate a medication possession ratio (MPR). Results: Composite MPR predicted the occurrence of at least one pulmonary exacerbation requiring a course of IV antibiotics (IRR=2.34, p=0.05), but not the frequency of exacerbations, after controlling for gender, baseline FEV1, and regimen complexity. Composite MPR predicted baseline FEV1 (estimate=29.81, p=.007), but not decline in FEV1.

Conclusions: These results demonstrate a significant relation between medication adherence and IV antibiotics in CF patients, highlighting the importance of addressing adherence during clinic visits to improve health outcomes.

© 2011 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Adherence; Cystic fibrosis; Health outcomes; Treatment; Pulmonary exacerbation

1. Introduction

Chronic use of inhaled and oral therapies is the cornerstone of maintaining lung health for cystic fibrosis (CF) patients [1]. While medications used chronically by CF patients are effective relative to placebo in the context of clinical trials, there are little data about the relationship between level of adherence to a regimen and health outcomes in a real-world setting. This knowledge is critical because a substantial body of literature demonstrates that adherence to medications is poor among people with CF. Objective data, including pharmacy refill history and electronic medication monitors, show that levels of medication adherence range from 67% for oral antibiotics to 31–53% for inhaled antibiotics, 53–79% for mucolytic agents, and 41–72% for hypertonic saline [2–7]. Adding to the challenge of accurately assessing adherence is that people with CF are prescribed treatment regimens of varying complexity, suggesting a need for a simple measure of global adherence to pulmonary medications for use in clinical care.

Adherence to medications has been shown to be related health outcomes in other illness, such as asthma. Adherence is related to greater asthma morbidity, including increased symptoms and healthcare utilization [8] functional impairment [9] and more

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in the first second; HLM, hierarchical linear model; IRR, incidence rate ratio; IQR, interquartile range; MPR, medication possession ratio; PFT, pulmonary function test; SD, standard deviation.
☆ Funding sources: NHLBI Grants R01 HL087997 and K23 HL075344.
* Corresponding author at: Johns Hopkins University, Division of Pulmonary and Critical Care Medicine, 5501 Hopkins Bayview Circle, 4B.74, Baltimore, MD 21224, USA.
E-mail addresses: meakin1@jhmi.edu (M.N. Eakin), abilder1@jhmi.edu (A. Bilderback), mboyle@jhmi.edu (M.P. Boyle), pmogayze@jhmi.edu (P.J. Mogayzel), kriekert@jhmi.edu (K.A. Riekert).

1569-1993/$ - see front matter © 2011 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jcf.2011.03.005
frequent oral steroid bursts [10]. To our knowledge, no study has specifically examined the relationship between medication adherence and health outcomes in CF. Two small studies examined the relationship using archival records but neither found a significant correlation. One study found that adults rated as nonadherent with unnamed medications tended to be hospitalized more often (p=.08) [11], while the other found a trend between adherence to mucolytic agents and lung function (p=.10) [12]. Thus a key research area is to determine whether nonadherence is associated with health outcomes and, if so, what level of adherence to which drug is necessary to confer benefit.

Therefore, the purpose of this study was to examine the relationship of medication adherence to health outcomes, specifically the frequency of intravenous (IV) antibiotics to treat pulmonary exacerbations and change in FEV1% predicted over a 12-month period. This study also examined the validity of a composite adherence score that combined adherence data into a single score for the four medications of interest. We hypothesized that low medication adherence would be associated with more frequent courses of IV therapy and lower baseline lung function. Furthermore, we hypothesized that patients with the highest adherence would have sustained improvement in lung function. Some of the results of these studies have been reported previously as abstracts [13,14].

2. Methods

Patients 6 years or older with CF were eligible if they had been seen at the clinic for at least 18 months, and were prescribed at least one of the following for a minimum of 12 months: dornase alfa, inhaled tobramycin, azithromycin, or hypertonic saline. These drugs were selected because of the strong evidence of their efficacy in improving lung health [1]. Furthermore, these medications are often prescribed for chronic use, with a regular regimen prescribed for each drug (i.e., not used as needed). This protocol was approved by the Johns Hopkins Medicine Institutional Review Board.

2.1. Procedures

This study was a longitudinal retrospective review of medication adherence over the previous year and health outcomes over 18 months. Participants provided the name and contact information for all pharmacies they used to obtain CF medications on a scale of 0–4) was included as another predictor and the two outcomes. Only covariates that significantly predicted each outcome variable (lung function and exacerbations, zero-inflated Poisson regression models were included in a final multivariate model. Because of the high proportion of participants having no exacerbations, zero-inflated Poisson regression models were conducted to predict the occurrence and frequency of pulmonary exacerbations in clinical trials [16]. The use of IV antibiotics was selected to define an exacerbation in the study as it has been shown to be predictive of mortality [17] and has been used in several recently published outcome studies [18,19]. Thus, while it is not an ideal measure, it is commonly used and predictive of poor outcomes. Baseline FEV1% predicted was determined by selecting the highest FEV1 in the 6 months prior to the study period examined.

2.2. Measures

Patient pharmacy refill records were used to calculate a medication possession ratio (MPR), defined as the sum of all days of medication supply received, divided by the number of days the medication was prescribed for chronic use during the study period [20]. The number of days in the hospital was removed from the denominator to account for days participants did not use their home supply of medications. MPRs were calculated for each of the targeted medications individually, with values truncated to 100%. The MPRs of each medication were averaged across all medications to obtain the Composite MPR. If an individual was prescribed only one drug, then the Composite MPR would be equal to his or her MPR for that individual drug. The MPR calculations were adjusted for medication cycled every-other month (e.g., inhaled tobramycin), such that a 28 or 30 day supply but was recorded as a 60 day supply.

The primary outcome variable was the number of courses of IV antibiotics to treat a pulmonary exacerbation in the 12 months prior to the consent date, as this period was concurrent with the pharmacy records used to calculate MPR. Lung function, as measured by FEV1% predicted [21], was a secondary outcome. Pulmonary function tests (PFTs) conducted 14 days before and after a course of IV antibiotics were removed from these models.

2.3. Statistical analyses

Given the high number of potential covariates and small sample size, we examined the bivariate relation between each predictor and the two outcomes. Only covariates that significantly predicted each outcome variable (lung function and pulmonary exacerbation) were included in a final multivariate model. Because of the high proportion of participants having no exacerbations, zero-inflated Poisson regression models were conducted to predict the occurrence and frequency of
pulmonary exacerbations in the previous year from the Composite MPR. We used a random effects model with restricted maximum likelihood to predict both the intercept (baseline FEV$_1$% predicted) and slope (change in FEV$_1$% predicted) over 12 months. This model is suitable for longitudinal data analyses because it produces serial correlations among measurements performed on several occasions. Analysis and data management were performed using SAS v 9.2 (SAS Institute, Cary, NC). Follow-up analyses were completed with each individual drug MPR as the predictor to examine the relation between adherence to individual drugs and health outcomes.

3. Results

3.1. Participants

A total of 107 people with CF consented to join the study. We received complete refill records for 101 (94%) participants and six participants did not have baseline lung function results because they had no clinic visits during the 6-month baseline period, resulting in a final sample of 95 participants (Table 1). Those excluded from the analyses did not differ from those included on baseline demographics.

3.2. Prescribed regimen and overall adherence

Almost all participants were prescribed dornase alfa (95%); 80% were prescribed azithromycin, 68% inhaled tobramycin, and 26% hypertonic saline. The most common regimen was azithromycin, dornase alfa, and inhaled tobramycin (37%). The median MPR for each medication ranged from 49% (Interquartile Range (IQR)=0%–85%) for hypertonic saline to 76% (IQR=49%–90%) for azithromycin (Fig. 1).

There were no statistically significant differences in MPRs among the different medications. The median Composite MPR was 63% (IQR=39%–80%: Range 0%–100%). The MPR for each individual drug was significantly correlated with the Composite MPR, ranging from Spearman’s rho=.52 for hypertonic saline to Spearman’s rho=.80 for dornase alfa (all p values <.01). However, the Composite MPR was not correlated with regimen complexity (number of medications prescribed; Spearman’s rho=−.07, p=.53). There were no statistically significant age differences in medication adherence (p<.14 see Fig. 2).

3.3. Association between adherence and health outcomes

3.3.1. Pulmonary exacerbations

During the 12-month observation period, 40% of the participants (n=38) had at least one course of IV antibiotics to treat a pulmonary exacerbation (Table 1). Bivariate analyses indicated that gender, regimen complexity, baseline FEV$_1$% predicted, and Composite MPR were the only variables that...
significantly predicted pulmonary exacerbations treated with IV antibiotics and were included in the final model. Table 2 presents the results of the zero-inflated Poisson regression, which had a good fit to the distribution of pulmonary exacerbations (Vuong test z=2.97, p=0.002). Female gender and lower Composite MPR significantly predicted having one or more courses of IV antibiotics to treat a pulmonary exacerbation during the year (Fig. 3). In contrast, lower baseline FEV1% predicted and female gender were the only variables associated with the frequency of exacerbations. When analyses with the MPR of each individual drug were repeated, a trend was evident for an association between lower azithromycin MPR and having a pulmonary exacerbation (IRR=2.23, p=0.07). No other individual drug MPR was associated with the occurrence or frequency of a pulmonary exacerbation.

### 3.3.2. Lung function

Because of our inclusion criteria, all participants had to have at least 2 clinic visits in the 18 months observation period. The number of PFT’s per participant during the observation period ranged from 3 to 15, after removing PFTs during courses of IV antibiotics. Bivariate analyses indicated that regimen complexity, BMI, and Composite MPR were the only variables that significantly predicted lung function and were included in the model. Slope of FEV1 was modeled with a linear, as well as a quadratic, function. A comparison of the model fit statistics demonstrated that the model without the quadratic term for time had an AIC index = 5069.2 and the model with the quadratic term had an AIC index = 5046.6, indicating a better model fit with the quadratic term. Furthermore, the difference in chi-square model fit statistic was 10.41, P<0.01, indicating a better model fit with the quadratic term. The Composite MPR was a significant predictor of the fixed effect of the intercept (i.e., baseline FEV1% predicted) and accounted for an additional 11% of the variance in the intercept (Table 3). However, the Composite MPR was not a significant predictor of change in slope (estimate =0.26, p=0.49) and did not account for any additional variance in the slope of FEV1% predicted. We categorized adherence into three groups – MPR=80–100%, MPR=50–80%, and MPR<50% – to request least squared means at quarter 1 and quarter 4. Fig. 4 shows that participants who had a Composite MPR of ≥80% had a mean FEV1% predicted that increased 0.53%. In contrast, those with a Composite MPR of 50–80% and <50% experienced a decline of 2.22% and 0.39% in their lung function, respectively; however, the group differences in slope are not statistically significant. These models were repeated using MPR for each individual drug; the dornase alfa MPR (estimate=28.11,

### Table 2

Zero-Inflated Poisson regression predicting pulmonary exacerbations over 12-months (N=95).

<table>
<thead>
<tr>
<th>Variable</th>
<th>IRR*</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dichotomous outcome (occurrence)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.30</td>
<td>0.621</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline FEV1% predicted</td>
<td>0.03</td>
<td>0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Regimen complexity</td>
<td>−0.51</td>
<td>0.35</td>
<td>0.15</td>
</tr>
<tr>
<td>Composite MPR</td>
<td>2.34</td>
<td>1.18</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Continuous outcome (frequency)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.75</td>
<td>0.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline FEV1% predicted</td>
<td>0.98</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regimen complexity</td>
<td>1.13</td>
<td>0.15</td>
<td>0.33</td>
</tr>
<tr>
<td>Composite MPR</td>
<td>1.23</td>
<td>0.49</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*IRR=incidence rate ratio.

### Table 3

Mixed effect modeling estimates of FEV1% predicted over 12-months (N=95).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>−1.93</td>
<td>0.62</td>
<td>0.003</td>
</tr>
<tr>
<td>Regimen complexity</td>
<td>−9.19</td>
<td>2.34</td>
<td>0.002</td>
</tr>
<tr>
<td>Linear slope of FEV1%</td>
<td>0.97</td>
<td>0.34</td>
<td>0.005</td>
</tr>
<tr>
<td>Quadratic slope of FEV1%</td>
<td>−0.08</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>Composite MPR</td>
<td>29.81</td>
<td>8.48</td>
<td>0.007</td>
</tr>
<tr>
<td>Slope of FEV1%*Composite MPR</td>
<td>0.26</td>
<td>0.37</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Fig. 3. Pulmonary Exacerbations by Composite MPR (Probability of number of pulmonary exacerbations by Composite MPR while controlling for gender, regimen complexity and baseline lung function).

Fig. 4. Lung function over time by adherence category after controlling for regimen complexity and BMI.
studies that have demonstrated that dornase alfa and inhaled tobramycin MPR (estimate = 20.03, p = 0.03) were the only drugs that predicted baseline FEV1, respectively, accounting for an additional 9% and 7% of the variance in the intercept. No individual drug MPR predicted change in FEV1% predicted slope.

4. Discussion

In this retrospective longitudinal study, we examined the relation between medication adherence and health outcomes for people with CF. Consistent with other studies using objective measures, participants on average demonstrated poor adherence to all pulmonary medications, with high variability across participants, regardless of the medication or delivery method. This is the first study to demonstrate an association between medication adherence and the occurrence of a course of IV antibiotics to treat pulmonary exacerbations. Medication adherence was also associated with baseline FEV1 predicted although it did not predict change in lung function over 12-months. The lack of findings on the rate of decline in lung function is not surprising since the most commonly used therapist have not been shown to reduce the rate of FEV1 but rather to maintain lung function compared to placebo [23, 24]. Furthermore, the use of FEV1 decline as an endpoint is difficult due to the individual variability in FEV1, which would require long study durations and large sample sizes [23]. While not statistically significant, it is interesting that lung function was maintained in those patients with adherence > 80%, while those with < 80% adherence experienced a loss in lung function. This observation merits further study.

Adherence to one medication was highly correlated with adherence to the other medications, and all of the medications evaluated in this study have been shown individually to improve CF outcomes in randomized trials. Unfortunately, no comparative effectiveness trials have been conducted to demonstrate whether one medication is more effective than another, or if there is a cumulative or synergistic effect of using multiple medications. When there is no clear primary outcome, a composite variable can address the issue of multiplicity without having to adjust for type I error [25]. Therefore, a composite adherence score, rather than evaluation by a single drug, may best reflect the cumulative impact of the drug regimen on the participant’s health. Indeed, we found that the Composite MPR was as good or better a predictor of requiring at least one course of IV antibiotics and lung function than any individual drug MPR. We did, however, identify the following differences among individual drugs: dornase alfa and inhaled tobramycin adherence were positively associated with higher baseline FEV1%, predicted, and there was a trend for an association of azithromycin nonadherence with having a pulmonary exacerbation. These findings are similar to other studies that have demonstrated that dornase alfa and inhaled tobramycin sustain improvement in FEV1 compared to placebo [26–29]. However, results are mixed regarding the efficacy of these medications on pulmonary exacerbations, with some studies reporting a statistically significant association [16, 26, 29], and other studies reporting no association [27, 30].

Previous studies have demonstrated that azithromycin is associated with fewer pulmonary exacerbations regardless of improvement in FEV1, similar to our findings [1, 31, 32]. It should be noted that the absence of correlation between health outcomes and MPRs for each individual drug may be due to small sample size and thus a lack of power to detect differences; this warrants further evaluation before drawing a conclusion about the relative value of adhering to each medication. These results suggest that medication adherence is an important prognostic indicator for the likelihood of having a pulmonary exacerbation. This highlights the need for physicians to incorporate assessment of medication adherence to more accurately predict the likelihood of a pulmonary exacerbation and promote more aggressive intervention, in addition to routinely monitoring current lung function and pulmonary symptoms. Physicians have long been encouraged to assess adherence to medications during each clinic visit; however, most rely on clinical judgment or patient self-report to rate a patient’s level of medication adherence. Both methods of adherence assessment regardless of treatment team role (e.g., physician, nurse or respiratory therapist) have been shown to be inaccurate for identifying patients who are nonadherent [33–36]. This study relied on prescription refills as objective data from which to calculate adherence. As the use of e-prescribing and electronic medical records increases, refill-derived adherence scores could be calculated automatically and inserted into the patient record offering a cost-effective strategy for obtaining this clinically useful information. Beyond assessing adherence, counseling nonadherent patients is frequently cited as a major source of frustration for healthcare providers [37]. One potential strategy for improving medication adherence is to discuss with patients the association between medication adherence and health outcomes and tailor this message to the patient’s current level of adherence. Qualitative interviews with adult CF patients indicate that patients are more likely to take a medication if they know it is working for them or others [38]. According to social learning theory, provision of health feedback using clinical outcome data increases patients’ outcome expectations for the targeted health behavior, which may lead to an increased likelihood that they will change [39]. Furthermore, interventions such as problem-solving may be helpful for CF care teams to use with their patients to identify and collaborate on potential solutions for barriers to medication adherence [40].

Individuals with CF already experience significant treatment burden due to the length of time required to complete their treatments. A greater understanding of the dose–response relationship for each drug will provide valuable information to clinical care teams about expected response to treatment, the decision to initiate new medications, and the need for supportive counseling about the level of adherence required for the patient to see treatment benefit. Therefore, it is important for clinical outcomes research to begin including objectively measured adherence as a covariate when evaluating the efficacy of new and existing medications over time to better understand how the benefits (and risks) of a medication are influenced by treatment adherence.
This study has several limitations. This study was a retrospective review of the association between medication adherence and health outcomes over a one-year period, thus limiting our ability to see longitudinal change in health outcomes. Pharmacy refill records provide overall estimates of the maximum possible adherence, but they do not confirm ingestion or appropriate patterns of use and cannot account for stockpiling medicine [41]. In CF it is not possible to obtain a measure of actual medication usage because electronic monitoring devices are not available for most nebulizers. However, as noted above, refill data are a cost-effective strategy for obtaining objective data and are more accurate than self-report [42]. There are many predictors of CF outcomes that were not included in this analysis. Because of our sample size, we limited our predictor variables to include only variables associated with the health outcomes at the bivariate level. Some previously identified associations, such as median household income by zip code [43], were not found in our study. However, these variables may not have been sensitive for use in a single site study where most participants come from a homogeneous geographic area. We did not include oral antibiotics in our definition of a pulmonary exacerbation because often we could not discern the reasons for prescribing (e.g., exacerbation versus sinus infection); this may have resulted in underestimating the frequency of mild exacerbations. Finally, physician perceptions of patient adherence may affect their decision to treat with IV antibiotics. Because 1) physicians did not have access to the pharmacy records, and 2) studies have shown physicians are inaccurate in identifying nonadherence [33,35,36], we do not feel that this explains the association between adherence and exacerbations. Given the above caveats, and the short duration of follow-up, it is remarkable that we found a relationship between nonadherence and the occurrence of pulmonary exacerbations. These results highlight the need for future research with larger sample sizes from a diverse population of individuals with CF and for a longer period of time to determine if the association between medication adherence and health outcomes persists after controlling for other predictors, and to tease out the relationship between illness severity, regimen complexity, and adherence.

The results from this study demonstrate for the first time that poor CF medication adherence is a significant predictor of having a pulmonary exacerbation during a concurrent 12-month period and baseline lung function. This result highlights the importance of both medication adherence in the treatment of CF and of physicians assessing adherence during clinic visits to promote appropriate interventions to improve adherence and subsequent health outcomes.

Acknowledgments

Dr. Eakin contributed to the study design, analysis, and writing of the manuscript.
Mr. Bilderback contributed to the study design and data analysis.
Dr. Boyle contributed to the planning and design of the study, and revising and approving the final manuscript.

Dr. Mogayzel contributed to the planning and design of the study and revising and approving the final manuscript.
Dr. Riekert contributed to the planning and study design, data collection, analysis, and writing and editing of the manuscript.

References


