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Original Article

Electronic monitoring reveals highly variable adherence patterns in patients prescribed ivacaftor☆,☆☆,★

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Abstract

Background: Previous studies of CF treatments have shown suboptimal adherence, though little has been reported regarding adherence patterns to ivacaftor. Electronic monitoring (EM) of adherence is considered a gold standard of measurement.
Methods: Adherence rates by EM were prospectively obtained and patterns over time were analyzed. EM-derived adherence rates were compared to pharmacy refill history and self-report.
Results: 12 subjects (age 6–48 years; *CFTR-G551D* mutation) previously prescribed ivacaftor were monitored for a mean of 118 days. Overall adherence by EM was 61%(SD = 28%) and decreased over time. Median duration between doses was 16.9 hours (IQR 13.9–24.1 hours) and increased over time. There was no correlation between EM-derived adherence and either refill history (84%, r = 0.26, p = 0.42) or self-report (100%, r = 0.40, p = 0.22).
Conclusions: Despite the promising nature of ivacaftor, our data suggest adherence rates are suboptimal and comparable to other prescribed CF therapies, and more commonly used assessments of adherence may be unreliable.

Keywords: Adherence; Potentiator; Pediatric

1. Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic disease among Caucasians with an incidence of one per 3500 births in the United States [1]. Early treatment efforts exclusively targeted disease symptoms in an attempt to slow its progression, and with advancements in available therapies, the median age of survival has increased to 37 years. However, these same advancements also contribute to the complexity of managing a time-consuming and often burdensome treatment regimen. Moreover, treatment burden is likely to increase throughout a patient's lifetime, as patients develop comorbidities such as CF-related diabetes mellitus and complex bacterial infections as their illness progresses. There is now a therapy available to directly target the underlying cause of CF, namely,

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; EM, electronic monitoring; FEV1PP, forced expiratory volume in 1 second percent predicted; MEMS, Medication Events Monitoring System; MPR, medication possession ratio; SD, standard deviation.

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the cystic fibrosis transmembrane conductance regulator (*CFTR*) protein. *CFTR*, when not synthesized correctly or in enough quantity, is responsible for the buildup of abnormally thick and sticky mucus in the lungs, pancreatic insufficiency, and other disease manifestations. This results in a progressive lung disease caused by recurrent respiratory infections and is the leading cause of death in CF [2].

In 2012, the US Food and Drug Administration approved ivacaftor, the first *CFTR* potentiator therapy for patients with CF ages 6 years and older who have a *CFTR-G551D* mutation. This genotype-specific therapy has subsequently been expanded to include patients with a number of additional *CFTR* mutations that result from gating and conduction defects. Ivacaftor represents a fundamental shift in CF treatment, targeting the cause of disease rather than its downstream manifestations. Initial findings have been promising, with sustainable improvement in *CFTR* function, lung function, quality of life, and nutritional status [3–5]. With ongoing research using a similar genotype-targeted approach, there is a real potential to restore function to the most common *CFTR* mutations in CF [6].

In light of these recent advancements, adherence to prescribed regimens remains a serious concern. Consistent with suboptimal adherence rates reported in other chronic illness literature, studies in CF have found adherence rates ranging from 22% to 90% across treatment components and methods of adherence measurement [7–9]. Multiple studies have shown that higher adherence has been associated with fewer and shorter hospitalizations and less pulmonary exacerbations [10–12]. Notably, the landmark study [3] by Ramsey and colleagues reported adherence rates of 89–91% for ivacaftor, with estimates based primarily on patient report and pill counts. While adherence rates are often high in clinical trials, frequently, this fails to fully translate into clinical practice.

While initial findings support the efficacy of ivacaftor, there have been few systematic studies of adherence rates and associated factors for this new class of medication. A screening of early pharmacy refill data at our center (Source: Vertex Pharmaceuticals) and anecdotal clinical experience suggests non-adherence may be a factor associated with poor clinical response to therapy. Our prospective, observational study had two primary aims: 1) to document adherence rates and patterns objectively for ivacaftor by utilizing electronic monitoring; 2) to compare the gold standard of electronic monitoring with self-report and pharmacy refill data, modalities that are more commonly used in clinics. We hypothesized that despite the benefit and simplicity of this intervention, adherence rates would be similar to those of standard CF therapies. We also hypothesized that a significant difference in adherence rates by measurement method would be observed, such that rates of self-reported adherence would be higher compared to those obtained from electronic monitoring or pharmacy refill data.

2. Methods and materials

2.1. Sample selection and procedure

Patients were recruited from two accredited CF centers, one pediatric (250 total patients) and one adult (140 total patients). Patients included in the study met the following criteria: confirmed diagnosis of CF with the *CFTR-G551D* mutation (the only approved mutation at the time of the study), ages 6 years and older, and had been prescribed ivacaftor for at least 1 month. Patients were excluded if there was a provider-initiated reason for them not to take their ivacaftor or if there was a developmental disability that prevented them from effectively monitoring their adherence or completing surveys.

Eligible patients were approached by trained research staff during routine CF clinic visits. Patients who provided written consent to participate in the study were given an electronic monitoring (EM) device and instructed to use the device to dispense their ivacaftor for the duration of the study. Self-report measures of medication adherence were completed at time of enrollment and 3–4 months later during a routine CF clinic visit. Data from the EM device were downloaded, and patients received feedback on their adherence data. Patients who demonstrated non-adherence and expressed interest were referred for outpatient adherence promotion intervention. Medical chart review was conducted to extract patient demographic information (e.g., age, gender, duration of prescribed ivacaftor), forced expiratory volume in 1 second as a percent predicted (FEV1PP) for age and height, and body mass index (BMI). This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center (2013-5341) and the University of Cincinnati Medical Center (2013-5341).

2.2. Primary adherence measure—electronic monitors

The Medication Event Monitoring System (MEMS®; AARDEX Ltd. Zug, Switzerland), which has been used extensively in research studies in both adult and pediatric samples [13–15], was used to objectively monitor adherence. MEMS® mimics a traditional pill bottle in both appearance and utility and tracks the date and time of each bottle opening. Graphic feedback is provided in the form of calendars and time plots at each data download. The number of bottle openings per day is indicated in the calendar feedback, while the frequency of time points for bottle openings is indicated in time plots.

EM data were used to calculate overall adherence rates, weekly adherence rates, and mean duration between doses. For each patient, the overall adherence rate was defined as $\frac{\text{Total doses taken}}{\text{Total days monitored} \times 2 \text{ doses per day}}$, and the weekly adherence rate was defined as $\frac{\text{Total doses taken every 7 days}}{7 \text{ days} \times 2 \text{ doses per day}}$. The weeks were counted from the first recorded date by the MEMS®. If the last week contained only 1 day, it was excluded from the analysis of weekly adherence. Appropriate adjustments were applied for half days when counting the doses that should have been taken in the denominator of the formula.

Duration between doses was also obtained. For each patient, the mean over the total monitoring period was defined as the overall mean duration between doses. The mean of every 7 days was defined as the weekly mean duration between doses. Many subjects took "drug holidays" for several days at a time, resulting in prolonged intervals between doses. Intervals between doses greater than 72 hours were truncated at 72 hours (both overall and weekly).