JPPT | Single Center Retrospective Study

Effect of Elexacaftor/Tezacaftor/Ivacaftor on *Pseudomonas aeruginosa* Acquisition and Chronic Infection at a Single Pediatric Cystic Fibrosis Care Center

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OBJECTIVES As cystic fibrosis (CF) lung disease progresses, the airways become infected with opportunistic pathogens, such as *Pseudomonas aeruginosa* (PA). In October 2019, the US Food and Drug Administration approved elexacaftor/tezacaftor/ivacaftor (ETI), a highly effective modulator therapy (HEMT), for individuals 12 years and older with 1 copy of the F508del cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation. ETI increases the amount of and function of CFTR in the respiratory epithelium, improving mucociliary clearance and reducing static airway mucus, a major trigger for chronic infection and inflammation.

METHODS A retrospective analysis of inhaled tobramycin (iTOB) prescriptions between January 1, 2016, and December 31, 2021, was performed. This captured data before and after ETI approval at Children's Mercy Kansas City (CMKC). The number of individuals with new PA acquisition and individuals considered chronically infected was analyzed.

RESULTS The number of eradication prescriptions declined in 2020 and 2021, with 15 (7%) and 12 (5%) individuals prescribed therapy for those years, respectively. A similar pattern was observed for prescriptions for chronic infection. A reduction was seen in 2020 and 2021, with 28 (13%) and 20 (9%) individuals prescribed therapy for the respective years.

CONCLUSIONS The CMKC experienced a decrease in the number of courses of iTOB prescribed during the last 6 years. The reasons for this are likely multifactorial and may include the implementation of standardized PA surveillance and eradication protocols, the effect of HEMT on mucociliary clearance and airway microbiology, and the poorly understood effects of the SARS-CoV-2 pandemic on the epidemiology of respiratory infections.

ABBREVIATIONS BAL, bronchoalveolar lavage; CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator; CMKC, Children's Mercy Kansas City; ES, expectorated sputum; ETI, elexacaftor/tezacaftor/ivacaftor; FDA, US Food and Drug Administration; HEMT, highly effective modulator therapy; iTOB, inhaled tobramycin; OPS, oropharyngeal swab; PA, *Pseudomonas aeruginosa;* PwCF, people with cystic fibrosis

KEYWORDS cystic fibrosis; *Pseudomonas*; tobramycin

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. This gene codes for the CFTR protein, a complex protein found in the epithelial surfaces of most organs, which functions inherently as an ion channel and controls the function of other ion channels. Mutations in *CFTR* can result in completely absent or significantly reduced amounts of CFTR protein present in epithelial surfaces, significantly reduced CFTR function, or both. These deficits lead to altered ion transport and resultant abnormal hydration of the luminal contents of several organ systems.[1] In the airways, abnormal ion transport leads to airway surface liquid depletion, promoting a cycle of inflammation, obstruction, and infection by opportunistic pathogens. Infection is typically transient or intermittent in the early stages of disease. As CF lung disease progresses, the airways become chronically infected with organisms, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* (PA), and atypical pathogens, including *Stenotrophomonas maltophilia*, *Achromobacter* sp, and *Burkholderia cepacia* complex. Chronic infection by PA is associated with lung function decline, increased treatment burden, and increased mortality. The Cystic Fibrosis Foundation (CFF) recommends

routine surveillance to identify initial PA acquisition and early antibiotic therapy to eradicate transient infection, thus preventing chronic infection.[2] The CFF also recommends long-term suppressive therapy for people with CF (PwCF) who have chronic PA airway infection. According to the 2019 CFF Patient Registry Report, approximately 45% of individuals with CF had a respiratory culture positive for PA; among those, 30% of individuals were considered chronically infected.[3]

Chronic airway obstruction, infection, and inflammation leads to mucus hypersecretion, dysfunctional mucociliary clearance, and airway damage. CFTR modulator therapy increases the amount of functional CFTR protein in the airways, thus improving mucociliary clearance and reducing static airway mucus. It is thought that CFTR modulator therapy, by decreasing airway mucus and disrupting the cycle of obstruction, infection, and inflammation, may lead to reduced burden of typical CF airway bacteria, including PA.[4]

On October 21, 2019, the US Food and Drug Administration (FDA) approved elexacaftor/tezacaftor/ivacaftor (ETI), a highly effective CFTR modulator, for PwCF 12 years and older with 1 copy of the *CFTR* mutation, F508del.[5,6] ETI contains 2 corrector molecules (elexacaftor and tezacaftor) and 1 potentiator (ivacaftor). The combined effect of ETI is increased quantity and function of CFTR at the cell surface and increased chloride transport. In December 2020, the FDA announced that 177 rare mutations had been added, based on *in vitro* response, to ETI labeling. In June 2021, the FDA expanded ETI approval to patients as young as 6 years.[7] It is estimated that ETI and other highly effective modulator therapies (HEMTs) will eventually be available to 90% of PwCF.[8]

Clinical care and quality improvement teams routinely monitor new PA acquisition and chronic PA infection rates among individuals treated at our CF Care Center. Prescribing patterns for eradication courses of inhaled antibiotics (generally inhaled tobramycin [iTOB]) and chronic, every-other-month, suppressive antibiotic therapy are also tracked. A marked reduction in inhaled antibiotic prescriptions was noted in 2021. This corresponded to the FDA approval of ETI in late 2019. These observations led to a formal retrospective chart review of culture results and prescribing patterns between 2016 and 2021 to determine the effect of ETI on PA acquisition and chronic infection rates at Children's Mercy Kansas City (CMKC). During the study period, CMKC provided care for 225 to 253 PwCF ages 0 to 21 years. In 2021, 91% of the PwCF receiving care at CMKC were eligible, based on FDA labeling, for any of the 4 available CFTR modulators. Of those patients, 84% were prescribed a CFTR modulator.

Materials and Methods

A retrospective analysis of outpatient iTOB prescriptions written between January 1, 2016, and December 31, 2021, was performed. An electronic medical record query was used to identify all iTOB prescriptions written for the study period. Prescriptions written for individuals with a diagnosis other than CF were excluded.

Respiratory cultures are typically obtained at all clinic encounters even when individuals are not chronically infected with PA (based on the Leeds criteria; PA recovered in ≥50% of airway cultures in the previous 12 months).[9] Specimens are obtained from expectorated sputum, when available, or from oropharyngeal swabs from individuals not able to expectorate. All culture results from the study period were included in analyses.

The number of PwCF considered chronically infected with PA was determined by identifying individuals receiving chronic, every-other-month iTOB prescriptions and confirmed by respiratory cultures indicating chronic infection.

The number of PwCF with new PA acquisition was determined by identifying electronic prescriptions for iTOB eradication courses. An eradication course was defined as the first lifetime prescription for iTOB or a new prescription for iTOB submitted at least 1 year after previous successful eradication confirmed by negative respiratory cultures. The eradication protocol at CMKC includes a 28-day course of 300 mg of iTOB twice daily. To determine the PwCF at risk for new PA acquisition, the number of PwCF considered chronically infected with PA was subtracted from the total number of individuals with CF followed at CMKC for the respective year.

Descriptive statistical analyses included median, range, and percentages. Additional analysis included χ^2 tests for categoric data. All tests of significance were 2-tailed, and p values of ≤0.05 were considered statistically significant. Statistical analysis compared 2016 as baseline percentages to 2020 and 2021 based on ETI FDA approval date for both indications of either new PA acquisition or chronic infection.

Results

Inhaled tobramycin was prescribed for chronic PA infection to 57 of 253 individuals (25%) receiving care at CMKC in 2016. A reduction was seen in 2020 and 2021, with 28 of 225 (12%; p = 0.0407) and 20 of 242 (8%; p = 0.0034) individuals prescribed chronic therapy for the respective years (Table 1). A similar pattern was observed for eradication course prescriptions. Eradication courses were prescribed to 34 of 196 individuals (17.3%) at risk for new PA acquisition at CMKC in 2016. The number of eradication prescriptions declined in 2020 and 2021, with 15 of 197 (7.6%; p = 0.0543) and 12 of 222 (5.4%; p = 0.0067) individuals prescribed eradication therapy during those years, respectively (Table 2). The median ages of the PwCF prescribed iTOB each year are presented in Tables 1 and 2.

Table 1. The Number of Individuals Prescribed Inhaled Tobramycin (iTOB) for Chronic Infection per Year and the Median Age

Year	Total Number of PwCF Followed at CMKC	Number of PwCF Prescribed iTOB for Chronic Infection, n (%)	Age, Median (Range), yr
2016	253	57 (22.5)	12 (0–19)
2017	244	51 (20.9)	12 (1–19)
2018	236	39 (16.5)	12 (4–19)
2019	242	48 (19.8)	13 (0–19)
2020	225	28 (12.4)*	12.5 (4–19)
2021	242	20 (8.3)†	13 (5–18)

CMKC, Children's Mercy Kansas City; PwCF, people with cystic fibrosis

* p = 0.0407.
† p = 0.0034.

Discussion

CFTR modulator therapy was introduced into CF care regimens in 2012 when ivacaftor was approved for use among individuals 12 years and older with a single G551D CFTR mutation. A decrease in chronic PA infection was reported in several studies among individuals prescribed ivacaftor therapy with one G551D mutation. Rowe and colleagues[10] evaluated ivacaftor in the clinical setting and described a significant improvement in PA burden in their longitudinal cohort study. The percent of individuals with at least 1 respiratory culture positive for PA was reduced by 18.8% in the 6-month period after ivacaftor initiation.[10] Similarly, Heltshe and colleagues[11] described a 29% reduction in PA culture positivity in the 6-month period after ivacaftor initiation.

Since ivacaftor's approval, the number of CFTR modulator treatments available, indicated mutations, and labeled age range have increased during the past decade, resulting in a higher proportion of PwCF eligible for treatment. However, at this time, there are limited data available on rates of PA infection for individuals prescribed other modulators, such as lumacaftor-ivacaftor, tezacaftor-ivacaftor, or ETI.

Subsequent postmarketing observations of ETI using CFF registry data demonstrate a decrease in PA culture positivity rate. Nationally, PA positivity rates have declined over time, likely due to the CFF Pulmonary Guideline regarding surveillance and eradication of PA published in 2014.[2] During 2015 to 2019, the median PA culture positivity rate according to the 2021 CFF patient registry report was approximately 30%.[12] Additional notable declines were seen in 2020 and 2021 with median positive rates of 20.7% and 17.6% for each year, respectively. The trends seen at CMKC are consistent with the national observations and will be interesting to compare to the results of the PROMISE study (NCT04038047), which is a prospective observational study following patients for 2 years after ETI initiation. A key outcome in the PROMISE study is assessment of changes in airway microbiology after ETI initiation.

A confounding factor potentially affecting these observations is the effect of the SARS-CoV-2 pandemic on the traditional CF care model. The CFF recommends 4 visits and obtaining 4 respiratory cultures per year.[13]

Table 2. The Number of Individuals Prescribed Inhaled Tobramycin (iTOB) for *Pseudomonas aeruginosa* (PA) Eradication per Year and the Median Age

Year	Total Number of PwCF at Risk for New PA Acquisition	Number of PwCF Prescribed iTOB Eradication Courses, n (%)	Number of PwCF Prescribed iTOB Eradication and HEMT*	Age, Median (Range), yr
2016	196	34 (17.3)	2 (1.0)	8 (0–18)
2017	193	35 (18.1)	2 (1.0)	10 (1–19)
2018	197	23 (11.7)	3 (1.5)	9 (0–18)
2019	194	32 (16.5)	1 (0.52)	12 (0–18)
2020	197	15 (7.6)†	8 (4.1)	14 (0–18)
2021	222	12 (5.4)‡	6 (2.7)	5.5 (2–19)

HEMT, highly effective modulator therapy; PwCF, people with CF

* HEMT includes ivacaftor and elexacaftor/tezacaftor/ivacaftor.
† p = 0.0543.
‡ p = 0.0067.

Clinic closures and implementation of telemedicine limited in-person patient visits during early 2020 at CMKC. Despite limited in-person visits, the average number of respiratory cultures per individual at CMKC was 3.5 and 3.8 in 2020 and 2021, which is consistent with previous years and likely secondary to the implementation of a drive-through respiratory specimen collection process and return to in-person visits in late 2020. Therefore, the decreased number of iTOB courses cannot be attributed to a decreased frequency of respiratory cultures. School closures and social distancing may have also affected the prevalence of new PA acquisition and chronic infection. There are several published epidemiology studies indicating that the incidence of respiratory viral infections significantly decreased during the pandemic, with authors concluding these decreases were most likely attributable to social distancing and the widespread use of face masks.[14–16] Other data suggest that viral infections alter bacterial flora and inflammation in CF airways, leading to positive correlation between the frequency of viral infections and the prevalence of common CF respiratory pathogens.[17] The decreased frequency of respiratory viral infections during the pandemic with a resultant decrease in CF pathogens provides a plausible explanation for the observation that there was a decrease in the incidence of new PA infection among PwCF during this time.

Another potential confounder during the study is that the source of the culture; oropharyngeal swab (OPS) versus expectorated sputum (ES) was not reported. Although cultures obtained from bronchoalveolar lavage (BAL) are considered the "gold standard" for identifying lower respiratory tract infection among PwCF, OPS and ES do have high positive predictive value for PA compared with BAL.[18,19] Hence, ES is deemed an acceptable surrogate that reliably reflects PA lower respiratory tract infection. ETI use is associated with improved lung function and decreased sputum production, leading to decreasing prevalence of ES specimens and resultant increasing dependence on OPS cultures. If OPS cultures are less sensitive than ES cultures, our data may underestimate the true incidence of new PA acquisition and chronic PA infection, leading to fewer antimicrobial courses. There are, however, robust data indicating that negative OPS cultures are highly correlated with negative BAL cultures for PA, and that lower respiratory tract infection is unlikely with negative OPS.[20,21] Thus, this issue is unlikely to affect the results of the study.

Because this was a retrospective review, the number of PwCF followed at CMKC per year does not specifically reflect the number of new PwCF receiving care (new diagnosis or transfer of care from a different CF center) or the PwCF leaving CMKC (lost to follow-up, transitioned to adult care, or deceased). In aggregate, new and leaving patients are included in the data analysis and represented in Tables 1 and 2. Additionally, the number of PwCF prescribed a specific CFTR modulator was not captured for each year because this number changed continuously based on changes in FDA labeling. Overall, these data would likely not significantly affect the trends identified.

Conclusion

The CMKC has observed a decline in the number of iTOB prescriptions for eradication and chronic PA infection during the past 6 years. This is likely multifactorial and includes 1) standardized PA surveillance and eradication protocols; 2) the effect of HEMT on airway microbiology; and 3) poorly understood effects of the SARS-CoV-2 pandemic. The incorporation of PA eradications protocols into clinical practice led to a steady decline in PA over the years, but a notable decline was seen in 2020 and 2021.

Article Information

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