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ORIGINAL ARTICLE

Adherence to cystic fibrosis transmembrane conductance regulator (CFTR) modulators: analysis of a national specialty pharmacy database

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ABSTRACT

Background: There have been significant advances in Cystic Fibrosis (CF) treatment, with the introduction of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators. Adherence is an important goal for CF management, as nonadherence is linked to poor health outcomes.

Objective: To calculate the medication adherence in patients taking CFTR modulators using a national specialty pharmacy database.

Methods: This retrospective observational cohort study utilized de-identified specialty pharmacy data from September 2017 to August 2018 to assess medication adherence for three CFTR modulators: ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor & ivacaftor. The primary outcome was proportion of days covered (PDC) for each medication, with mean PDC values compared across age groups and insurance characteristics. All analyses were performed using the SAS 9.4 University Edition (SAS Institute, Cary, NC).

Results: A total of 2,548 patients were analyzed, including 1,289 (50.59%) patients on lumacaftor/ivacaftor, 784 (30.77%) on ivacaftor, and 475 (18.64%) on tezacaftor/ivacaftor & ivacaftor. The mean PDC value for all CFTR modulators was above 0.80. Tezacaftor/ivacaftor & ivacaftor had the highest overall PDC of 0.92, while PDC values for both lumacaftor/ivacaftor and ivacaftor were 0.84. Children/adolescents on lumacaftor/ivacaftor ($p = 0.0001$) and tezacaftor/ivacaftor & ivacaftor ($p = 0.001$) had significantly higher mean PDC values compared to adults but not for ivacaftor ($p = 0.3744$). No statistical differences were seen in PDC across insurance characteristics.

Conclusion: To the best of our knowledge, this is the first study to assess the adherence of three CFTR modulators using a large nationwide specialty database. With high acquisition costs of CFTR modulator therapies, there is a need to improve rates of adherence in patients with CF.

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Introduction

Cystic fibrosis (CF) is a progressive, autosomal recessive genetic disorder. It manifests in multiple organs and systems including the respiratory, digestive, and reproductive system[1]. For most patients, morbidity and premature mortality are associated with chronic airway infection, progressive loss of lung function, and development of potentially fatal lung disease[2]. Some other complications associated with CF include pancreatic insufficiency, intestinal malabsorption, diabetes, and pain or discomfort[3]. The primary cause of CF is mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. This gene encodes the CFTR protein, which is mainly responsible for regulating sodium and chloride transport across epithelial cell membranes. The absence or inadequate functioning of CFTR protein results in thick mucus buildup leading to blockage of airways, respiratory difficulties, and subsequently affecting multiple systems and organs[4]. More than 2000 *CFTR* gene variants have been identified so far and over 350 mutations have been classified as disease causing, with F508del being the most predominant mutation seen in over 70% of CF cases[5–7].

In the US, the prevalence of CF is around 30,000[8], with an estimated 7–10 million individuals classified as CF carriers[9]. Although CF is considered a rare condition, it's economic impact is substantial with the annual cost of CF care per person estimated around 48,000 (2006 US dollars), over 20-times higher than that for someone without CF[10]. In 2010, newborn screening to diagnose CF was implemented across all 50 states in the US. This has resulted in diagnosing over 75% of the children with CF by the age of 2 years. The median age of survival has also increased from 34 years during 1991–1995[11] to 47.4 years in 2018[8]. The improvement in clinical outcomes and survival in CF can be attributed to earlier diagnosis, and active disease management[12].

The CFTR modulators target specific defects in CFTR protein function caused by gene mutation and are designed to correct the malfunctioning protein by improving production,

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intracellular processing, and/or function of the defective CFTR protein[4]. Currently, four CFTR modulators are approved for the treatment of CF. These include ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor & ivacaftor (Symdeko), and elexacaftor/tezacaftor/ivacaftor & ivacaftor (Trikafta)[13,14]. Ivacaftor is classified as a potentiator drug which improves the opening of the CFTR channel, while lumacaftor, tezacaftor, and elexacaftor are classified as corrector drugs which help in improving the CFTR protein folding so it can reach the cell surface[12]. Because different mutations cause different defects in the CFTR protein, these therapies are effective in individuals with specific mutations (Table 1).

Even though CFTR modulators have revolutionized the treatment of CF, a major limitation of these novel treatments has been the high annual drug acquisition cost, which can potentially increase the out-of-pocket spending for patients. In 2016, pharmaceutical spending contributed to 64% of the total spending on CF-related care. In patients on CFTR modulators, pharmaceutical spending was even higher, with 85% of spend in 5.8% patients taking ivacaftor and 74% of spend in 17.6% patients taking ivacaftor/lumacaftor[15]. The increase in utilization and high cost of CFTR modulators has attracted increased scrutiny from healthcare stakeholders, particularly on improving medication adherence. A recent review by Eakin and Riekert[16]indicated that nonadherence in patients with CF was associated with increased hospitalizations and longer length of stays due to pulmonary exacerbations and lower baseline lung function. There is evidence to also suggest that lower adherence to CF medications may be in part due to difficulties with time management, increased regimen complexity, decreased parental supervision in adolescents, perceived doubts about the necessity of treatments, stigma and reluctance to disclose CF status, and depression in both patients and their caregivers[17]. As electronic pharmacy data are becoming common, pharmacy refills are increasingly being utilized for calculating medication adherence. The medication possession ratio (MPR) and proportion days covered (PDC) are two such adherence measures that are based on the pharmacy refill data. These measures are calculated as follows:

$$\text{MPR} = \frac{\text{Sum of days' supply for all fills in period}}{\text{Number of days in period}}$$

$$\text{PDC} = \frac{\text{Number of days in period 'covered'}}{\text{Number of days in period}}$$

The major difference between the two measurements is that the maximum value of PDC is 1.0, which indicates full adherence, whereas MPR, which takes medication oversupplies into consideration, can have a value of greater than 1.0[18].

A few studies have been conducted that assess the adherence to CFTR modulators. Siracusa et al.[19] reported a suboptimal adherence of 0.61 to ivacaftor in 12 subjects using electronic monitoring. Suthoff et al.[20] utilized a US commercial administrative claims data ($n = 79$) to measure adherence to ivacaftor and reported a mean MPR of 0.8, with 73% of patients reporting MPR over 0.8. Tesell et al.[21] measured adherence in a US Medicaid population ($n = 21$) and reported a PDC of 0.62 for lumacaftor/ivacaftor over 1 year. Olivereau et al.[22] measured adherence to lumacaftor/ivacaftor over 1 year using pharmacy refills in France ($n = 96$). The mean PDC was 0.91 and 83% of patients reported a PDC over 0.8. These existing studies have had small sample sizes and involved only two CFTR modulators – ivacaftor and ivacaftor/lumacaftor. With the introduction of tezacaftor/ivacaftor & ivacaftor, there is a need to calculate medication adherence in patients taking CFTR modulator therapies using a national specialty pharmacy database. Hence, this study aimed: (i) to calculate medication adherence for patients with more than one refill for CFTR modulator therapies (ivacaftor, ivacaftor/lumacaftor, and tezacaftor/ivacaftor & ivacaftor) using PDC as a measure of adherence, and (ii) to explore the association between medication adherence, age (children/adolescents vs. adults) and payer characteristics (patients with primary vs. primary and secondary insurances).

Methods

Data source

This retrospective observational cohort study utilized pharmacy fill data from a national specialty pharmacy to assess the medication adherence of CFTR modulators. The database includes patients from different US geographical regions who are on commercial and public health insurance plans. The national specialty pharmacy provides varying clinical pharmacy services such as refilling and shipping specialty medications, counseling patients regarding medication adherence, and management of adverse events associated with the specialty medications. Fill data for patients using CFTR modulators from September 2017 to August 2018 was utilized. Patients with one fill date along with the ones who had switched CFTR modulators during this period were excluded from the study. No identifiable protected health information was extracted or accessed during the study and a unique identifier was assigned to each patient in the database. The study was

Table 1. Cystic fibrosis transmembrane conductance regulator (CFTR) modulators.

	Year approved	Indication	Mutation	Target CF population (%)	Annual cost[a]
Ivacaftor	2012	Age $\geq$ 6 months	Effective for gating mutation and some residue function and conduction mutations	3–5	$311,501
Lumacaftor /ivacaftor	2015	Age $\geq$ 2 years	F508del homozygous	45–50	$272,694
Tezacaftor /ivacaftor & ivacaftor	2018	Age $\geq$ 6 years	F508del homozygous, heterozygous, other mutations	45–50	$292,000
Elexacaftor /tezacaftor /ivacaftor & ivacaftor	2019	Age $\geq$ 12 years	One copy of F508del mutation	85–90	$311,501

[a]Wholesale Acquisition Cost from IBM Micromedex RED BOOK Online (as of April 10, 2020).
Abbreviation: CF, Cystic Fibrosis.

approved by the University's institutional review board and the legal team of the national specialty pharmacy.

Study variables

The pharmacy data included variables such as demographic characteristics, medication utilization data, and insurance details. Patients demographic characteristics included age, categorized as "children/adolescents" (< 18 years) and "adults" (≥ 18 years), sex, and region of US (Northeast, Midwest, South, and West) based on patient's residency. The medication utilization data included trade and generic CFTR modulator name, drug strength, quantity dispensed, days supply dispensed, and fill date. The insurance data included primary insurance plan (government/charitable organizations and commercial) and the presence or absence of a secondary insurance plan.

Outcome measure

Adherence for three CFTR modulators (ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor & ivacaftor) was calculated using PDC. Elexacaftor/tezacaftor/ivacaftor & ivacaftor was not included as it was not yet approved for CF treatment at the time of the study. PDC was calculated for patients that had more than one refill for the CFTR modulators. To calculate PDC, fill dates were first used to identify the earliest start and latest end date. The differences between these dates were utilized to calculate the "number of days in period" (denominator in the PDC formula). The days supply along with fill dates were utilized to label the dates when the medication was available to the patient, which was then used to calculate the "number of days in period covered" (numerator in the PDC formula).

Statistical analyses

All study measures were summarized using descriptive statistics. Medication utilization and insurance characteristics were described using the data collected on the last refill (most recent). Descriptive statistics were calculated for PDC for the overall patient cohort, adults, children, patients on primary insurance, and patients on both primary and secondary insurances. PDC means were stratified based on the three CFTR modulators. PDC means were also compared for children/adolescents and adults, patients with primary insurance, and those with both primary and secondary insurances. Independent *t*-test for continuous variables and chi-square for categorial variables were conducted and an *a priori* $p < 0.05$ was considered statistically significant. All analyses were performed using the SAS 9.4 University Edition (SAS Institute, Cary, NC).

Results

Characteristics of patients on CFTR modulators

A total of 3,015 unique patients on CFTR modulators were identified in the specialty pharmacy database from September 2017 to August 2018. After excluding patients ($n = 467$) who had switched CFTR modulators during this period, the analyses were conducted on a final sample of 2,548. The mean age of the cohort was 23.05 ± 13.68 years and was largely adult ($n = 1,473$, 57.81%) and male ($n = 1,387$, 54.43%). Most patients resided in the South ($n = 967$, 37.95%) and lumacaftor/ivacaftor was found to be the most utilized CFTR modulator ($n = 1,289$, 50.59%). A majority of the patients were on primary insurance ($n = 1,564$, 61.38%). Among those with only primary insurance, a higher percentage were on commercial insurance ($n = 808$, 51.66%). When comparing the characteristics of children/adolescents with those of the adults, differences were observed in the distribution of patient's region of residence, medication utilization, and insurance characteristics (Table 2).

Among the 984 patients with both primary and secondary insurances, commercial primary and commercial secondary

Table 2. Demographic, medication utilization, and insurance characteristics of patients on CFTR modulators.

Variables	Overall $n = 2,548$	Children/adolescents $n = 1,075$	Adults $n = 1,473$
Age in years			
Mean ± SD	23.05 ± 13.68	11.40 ± 3.84	31.55 ± 11.90
Median	20	11	29
Sex (*n*, %)			
Female	1,161, 45.57%	515, 47.91%	646, 43.86%
Male	1,387, 54.43%	560, 52.09%	827, 56.14%
Patient Residence (*n*, %)			
Northeast	472, 18.52%	185, 17.21%	287, 19.48%
Midwest	698, 27.39%	306, 28.47%	392, 26.21%
South	967, 37.95%	432, 40.19%	535, 36.32%
West	411, 16.13%	152, 14.14%	259, 17.58%
CFTR Modulators (*n*, %)			
Ivacaftor	784, 30.77%	329, 30.60%	455, 30.89%
Lumacaftor/ivacaftor	1,289, 50.59%	661, 61.49%	628, 42.63%
Tezacaftor/ivacaftor & ivacaftor	475, 18.64%	85, 7.91%	390, 26.48%
Insurance type			
Only primary insurance	1,564, 61.38%	701, 65.21%	863, 58.59%
Government/charitable	756, 48.34%	404, 57.63%	352, 40.79%
Commercial	808, 51.66%	297, 42.37%	511, 59.21%
Primary/secondary insurance	984, 39.62%	374, 34.79%	610, 41.41%

Data collected based on the last refill (most recent).
Abbreviation: CFTR, Cystic fibrosis transmembrane conductance regulator.

insurance ($n = 802$, 81.50%) was the most common combination. When stratified by age, 298 (79.68%) out of 374 children and 504 (82.62%) out of 610 adults had commercial primary and commercial secondary insurances.

Adherence measures

The mean PDC for the entire cohort was 0.86. Tezacaftor/ivacaftor & ivacaftor had the highest overall PDC of 0.92, while PDC values for both lumacaftor/ivacaftor and ivacaftor was 0.84. Children/adolescents on lumacaftor/ivacaftor ($p = 0.0001$) and tezacaftor/ivacaftor & ivacaftor ($p = 0.001$) had significantly higher mean PDC values when compared to adults but not for lumacaftor ($p = 0.3744$). Across insurance characteristics, no obvious pattern was seen for PDC values (Table 3).

Discussion

To the best of our knowledge, this is the first study to assess the adherence of three CFTR modulators using a large nationwide specialty database. This study used pharmacy refill as a proxy for adherence and found relatively high adherence to CFTR modulators over a 1-year period. Prior adherence studies in CF mainly focused on pulmonary medications, nebulizers, and multivitamins. A targeted literature review by Narayanan et al.[23] reported a higher adherence to ivacaftor and inhaled antibiotics compared to dornase alfa/hypertonic saline, oral pancreatic enzyme/vitamin supplements, and airway clearance therapy. In the last 5 years, a few studies have been published that focus mainly on adherence to CFTR modulators, specifically ivacaftor and ivacaftor/lumacaftor[19–22]. Results were mixed in the four published studies and the reported adherence rates were 0.61 and 0.80 for ivacaftor and 0.62 and 0.91 for ivacaftor/lumacaftor. The published study findings are different from the current study for a number of reasons. First, these published studies had small sample sizes ranging from 12–96. Second, their sample selection was not generalizable to the overall CF population as these studies were conducted in different populations including those with Medicaid coverage, private insurance coverage, and patients recruited from CF centers. Finally, different measures such as electronic monitoring[19], MPR[20], and PDC[21,22] were utilized to assess medication adherence.

The current study utilized a large sample size from nationwide specialty data to calculate adherence rates for the three CFTR modulators. The study also utilized PDC as the adherence measure, which has been validated and approved by Pharmacy Quality Alliance (PQA) and is also preferred by the Centers of Disease Prevention and Control (CDC) for calculating medication adherence at a population level[24,25]. However, it should be noted that PDC is a surrogate of adherence calculation and hence we cannot corelate clinical outcomes with PDC. In this study, the overall mean PDC values for the three CFTR modulators and across age and insurance categories exceeded the widely accepted adherence threshold of 0.80[26]. Among the CFTR modulators, the mean PDC for tezacaftor/ivacaftor & ivacaftor was the highest (0.92) followed by ivacaftor and ivacaftor/lumacaftor (0.84 each). The recent entry of tezacaftor/ivacaftor & ivacaftor may have contributed to a higher mean PDC value in comparison to other CFTR modulator therapies as it has been observed that adherence is generally higher in the first few months of use[26].

The study compared the mean PDC values of children/adolescent and adults for the three CFTR modulators. While there was no significant different in mean PDC for ivacaftor, mean PDC values for children/adolescent were significantly

Table 3. PDC calculated using fill dates from September 2017 to August 2018.

	Overall PDC	
	n	Mean ± SD
Total	2,548	0.86 ± 0.15
Ivacaftor	789	0.84 ± 0.16
Lumacaftor/ivacaftor	1,361	0.84 ± 0.15
Tezacaftor/ivacaftor & ivacaftor	398	0.92 ± 0.11

	PDC categorized according to age				
	Children/Adolescents		Adults		*p*-value[a]
	n	Mean ± SD	*n*	Mean ± SD	
Total	1,075	0.86 ± 0.14	1,473	0.85 ± 0.15	0.0876
Ivacaftor	330	0.85 ± 0.15	459	0.84 ± 0.16	0.3744
Lumacaftor/ivacaftor	684	0.86 ± 0.14	677	0.83 ± 0.15	0.0001
Tezacaftor/ivacaftor & ivacaftor	61	0.96 ± 0.10	337	0.91 ± 0.11	0.001

	PDC categorized according to insurance characteristics				
	Individuals with only primary insurance		Individuals with primary and secondary insurances		*p*-value[a]
	n	Mean ± SD	*n*	Mean ± SD	
Total	1,564	0.86 ± 0.15	984	0.86 ± 0.15	1.00
Ivacaftor	455	0.84 ± 0.16	334	0.84 ± 0.16	1.00
Lumacaftor/ivacaftor	869	0.85 ± 0.15	492	0.84 ± 0.15	0.24
Tezacaftor/ivacaftor & ivacaftor	240	0.92 ± 0.12	158	0.92 ± 0.11	1.00

[a]Independent *t*-test.
Significance $p \leq 0.05$.
Abbreviation: PDC, proportion of days covered.

higher than adults for lumacaftor/ivacaftor and tezacaftor/ivacaftor & ivacaftor, however caution should be exercised in interpreting the results. Studies have shown that adherence to CF medications is higher in children/adolescents compared to adults due to parent's strong belief that the treatments are necessary[27]. This possibly results in increased parental monitoring and timely refilling of medications[28]. Unlike age, no significant differences were seen in mean PDC values for individuals with primary insurance compared to those with both primary and secondary insurances. One of the possible reasons for higher mean PDC values seen in this study is the provision of a CF care program by the specialty pharmacy to all patients who are on CF-related medications. The program is delivered by pharmacists who provide drug utilization reviews, patient counseling, timely reminders for medication refills, and monitoring side-effects to treatments; all of which are designed to maximize adherence. The study results show the important role specialty pharmacy fulfils in delivering better patient outcomes for high cost, high touch medications through coordinated patient care and disease management services.

Study limitations

The 2018 CF Foundation registry serves as a good reference to compare the study's demographic characteristics with those seen in the national CF population[8]. The mean age of the study population (23.05 years) and proportion of males (54.40%) were slightly higher than those reported by CF Foundation (22.2 years, 51.80%). Additionally, the distribution of private (51.66%) and government insurance (48.34%) among those with primary insurance alone in the study was lower than the private insurance (58.8%) and government insurance (55.70%) seen in the CF registry. Despite the robust findings, the study does have some limitations which need to be addressed. Due to the retrospective nature of the data, its quality may be limited by systematic or recorder bias, data coding–recoding errors, and incomplete data. The study utilized the last refill for all patients to describe the patient population information. There may be instances where the patient characteristics such as their residence or insurance status could have changed after the last refill. The medication adherence calculation utilized pharmacy refill data. Although PDC is a valid measure, it assumes that the availability and possession of medication by the patient corresponds to the patient actually taking the medication. Thus, adherence measurement should be viewed as an estimate, rather than as true results. Additionally, adhering to a treatment regimen has been recently conceptualized as a process that includes three components: initiation, persistence, and implementation[29]. The PDC calculated in this study tries to evaluate both persistence and implementation in the same index. The calculation of these two dimensions in separate indexes should be preferred in order to differentiate between non-adherence behaviors linked to non-persistence and those linked to non-implementation, probably underpinned by different determinants. However, this study was unable to separate the two dimensions. Further, this study did not capture the patients from the initiation of their therapy, hence it might contain patients who discontinued therapy due to the physician's advice. The specialty pharmacy that provided the data closely monitors patients and follows up with them on a regular basis to improve treatment benefit. Thus, the study results may not be generalizable to patients using CFTR modulators through other specialty pharmacies. Finally, our study is broader than the previously published monocentric studies but does not discuss safety, tolerability of treatments, or the improvement as perceived by patients. The lack of information on clinical status and healthcare resource utilization associated with the level of treatment adherence is also a limitation of our study.

Conclusion

Overall, the study addresses an important gap in the CF adherence literature by providing mean PDC values for the three CFTR modulators. However, future research is necessary to measure the association between adherence thresholds and healthcare resource utilization of patients on CFTR modulators. Additionally, with the rising costs of CFTR modulator therapies specialty pharmacy should consider implementing programs such as patient follow-up and monitoring to aid in improving adherence.

Transparency

Declaration of funding

No potential funding source was associated with this study.

Declaration of financial/other interests

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