4-20-2022

Evaluating the Impact of Trikafta on the Quality of Life for Cystic Fibrosis Patients

Yzeed Alrwaili

EVALUATING THE IMPACT OF TRIKAFTA ON THE QUALITY OF LIFE FOR CYSTIC FIBROSIS PATIENTS

By

Yzeed Alrwaili

Under the Direction of Rachel Culbreth, PhD, MPH, RRT

A Thesis Submitted to the Graduate Faculty of Georgia State University

in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATLANTA, GEORGIA

30303

TABLE OF CONTENTS

Page

TABLES

ACCEPTANCE

This thesis, EVALUATING THE IMPACT OF TRIKAFTA ON THE QUALITY OF LIFE FOR CYSTIC FIBROSIS PATIENTS, by Yzeed Alrwaili was prepared under the direction of the Master's Thesis Advisory Committee of the Respiratory Therapy department at Georgia State University. It is accepted by the committee in partial fulfillment of requirements for the Master of Science degree in Respiratory Therapy at Byrdine F. Lewis College of Nursing and Health Professions, Georgia State University. The Master's Thesis Advisory Committee, as representatives of the faculty, certifies that this thesis has met all standards of excellence and scholarship as determined by the faculty.

Rachel Culbreth, PhD, MPH, RRT

Committee Chair

Shi Huh Samuel Shan, MRT, RRT, RRT-ACCS, RRT-NPS

Committee Member

Laryssa D. Frederick, MS, RRT, RRT-NPS, RPFT

Committee Member

April 20, 2022

AUTHOR'S STATEMENT

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his absence, by the professor under whose direction it was written, or in his absence, by the Associate Dean, College of Health and Human Sciences. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve any potential financial gain. It is understood that any copying from or publication of this thesis which involves potential financial gain will not be allowed without written permission of the author.

X

Yzeed Alrwaili

NOTICE TO BORROWERS

All these deposited in the Georgia State University Library must be used in accordance with the stipulations prescribed by the author in the preceding statement.

The author of this thesis is:

Yzeed Alrwaili
1048 W Market St
Akron, OH, 44313

The Chair of the committee for this thesis is:

Rachel Culbreth, PhD, MPH, RRT
Assistant Professor
Department of Respiratory Therapy
Lewis College of Nursing and Health Professions
Georgia State University
P.O. Box 4019
Atlanta, GA 30302-4019

Users of this thesis who not regularly enrolled as students at Georgia State University are required to attest acceptance of the preceding stipulation by signing below. Libraries borrowing this thesis for the use of their patrons are required to see that each user records here the information requested.

NUMBER OF USER	ADDRESS	DATE	TYPE OF USE (EXAMINATION ONLY OR COPYING)

ABSTRACT

Background: Cystic fibrosis (CF) is a severe genetic disorder that primarily impacts the digestive and pulmonary systems. The most frequent Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation is F508del which accounts for 90% of CF patients. Cystic fibrosis patients undergo multiple treatments daily to reduce the physical and psychological adverse CF. Trikafta combines three major chemical compounds: tezacaftor, ivacaftor, and elexacaftor. The drug assists the defected proteins to function normally. Trikafta is intended for CF patients 12 years or older with at least one gene of F508del, but the study only targets 18 years or older. This study evaluates the difference in health-related quality of life (HRQOL) between CF patients taking Trikafta compared to CF patients not taking Trikafta and the length of time on Trikafta. The study also evaluates the differences in depression and anxiety levels between CF patients taking Trikafta compared to CF patients not taking Trikafta.

Methods: A cross-sectional survey containing Cystic Fibrosis Questionnaire-Revised (CFQ-R), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire (PHQ)-9 was utilized to be administered by CF patients from closed and certified social media groups. CFQ-R is used to evaluate the Health-Related-Quality-of-Life (HRQOL) in CF patients, where GAD-7 and PHQ-9 measure levels of anxiety and depression, respectively. The survey divides the participants into two groups; patients who are not administering Trikafta versus patients who are administering Trikafta.

Results: 59 adults with CF participated (3 were not eligible and were excluded) aged 18 to 47 (M=25.6 yr.), 37.5% are males, and 62.5% are females. The majority were Caucasian (71.4%, n=40). Approximately 57.1% of patients reported taking Trikafta, and 42.9% reported not taking Trikafta. 73.2% reported having the F508del CFTR gene mutation. Trikafta users (M=2.9,

SD=0.5) compared non-Trikafta users (M=2.2, SD=0.7) revealed significantly better average CFQ-R scores, t(51)=4.2, (p<.001). For anxiety, Trikafta users (M=6.9, SD=5.8) compared to non-Trikafta users (M=11.3, SD=6.2) indicated significantly lower GAD-7 scores, t(50)= -2.6, (p=0.006). For depression, Trikafta users (M=8.2, SD=7.6) compared to non-Trikafta users (M=12.5, SD=6.1) indicating significantly lower PHQ-9 scores, t(51) = -2.2, (p=0.017). The association between length of time taking Trikafta and overall quality of life was not statistically significant (p=0.90). GAD-7 (MD= -4.4, p=0.006) and PHQ-9 (MD= -4.3, p=0.017) scores from all participants indicate that Trikafta users have lower levels of anxiety and depression than non-Trikafta users.

Conclusion: The use of Trikafta for the Treatment of cystic fibrosis patients with F508del CFTR mutation positively impacts CF patients' quality of life when compared to patients who are not taking Trikafta. The association between the length of time on Trikafta and the quality-of-life score reveals a non-significant value, as further research with a sizable sample initiating the use of Trikafta could reveal more significant findings. Findings suggest that participants administering Trikafta have lower levels of anxiety and depression than those who do not.

Keywords: cystic fibrosis (CF), anxiety, depression, cystic fibrosis transmembrane conductance regulator (CFTR), health-related quality of life (HRQOL), cystic fibrosis questionnaire revised (CFQ-R), general anxiety disorder-7 (GAD-7), patient health questionnaire (PHQ)-9.

CHAPTER I

INTRODUCTION

Cystic fibrosis (CF) is a serious genetic disorder that primarily affects the digestive and pulmonary systems. In the U.S., CF affects 1 out of 4,000 newborns (Farrell et al., 2017). Cystic fibrosis is a disease caused by the alteration of the protein that regulates the movement of salt from the cells. A mutation causes this alteration in a gene known as the fibrosis transmembrane conductance regulator (Mayo Clinic, 2020b). Cystic fibrosis damages the glands that produce mucus. Thus, patients with cystic fibrosis have a thick and sticky mucus membrane in the pulmonary and digestive systems. The thick mucus membrane blocks air passages in the lungs, making breathing difficult and increasing the risk of infection (Mayo Clinic, 2020b). Patients with cystic fibrosis face substantial daily treatment requirements.

Most cystic fibrosis patients are diagnosed at birth, with the condition progressively worsening as the child grows. Initially, the diagnosis of cystic fibrosis is detected during the symptomatic stages, with variations from patient to patient. However, the implementation of newborn screening (NBS) has helped to identify the condition at its early stages. As a result, over 60% of the diagnoses are detected at the asymptomatic stage (Farrell et al., 2017). Signs and symptoms may be characterized by breathing problems since the thick mucus blocks air passageways, making the lungs stop functioning normally. Other notable symptoms of cystic fibrosis include pale skin, coughing, chest infections, constipation, low weight input for babies, and diarrhea (Cystic fibrosis, 2017).

To this day, there is no known cure for cystic fibrosis. Cystic fibrosis patients are treated to reduce its adverse effects, but their lifespan is shortened, with most of them living up to their

mid-30s or 40s (Cystic fibrosis, 2017). However, with the introduction of a new drug, Trikafta, there is hope for treating patients with cystic fibrosis. Trikafta is a drug that combines three major chemical compounds: tezacaftor, ivacaftor, and elexacaftor. Once administered, the drug assists the proteins to function normally. Trikafta is recommended for patients above 12 years of age and patients with cystic fibrosis due to at least one F508del mutation in the CFTR gene. Patients with one F508del gene account for about 90% of the total population of patients with cystic fibrosis (Food and Drug Administration, 2019b).

The drug was approved in 2019 by the Food and Drug Administration (FDA) and was intended for patients with at least one gene of F508del. Before its inception, the U.S. had approved other drugs to treat cystic fibrosis, but these drugs were mostly ineffective. Most of the treatments that CF patients administered were aimed to control the adverse effects of the disease. Few drugs like ORKAMBI®, SYMDEKO®, and KALYDECO® were designed to treat the root cause of cystic fibrosis but as were not as effective as the combination therapy (TRIKAFTA®) of these drugs. The U.S. has the highest proportion of patients approved for the administration of Trikafta, with over 90% of the patients with at least one gene of F508del CFTR mutation approved in the U.S. alone (Bear, 2020).

This research aims to examine how the new drug Trikafta affects patients' lifestyles with cystic fibrosis compared to cystic fibrosis patients not taking Trikafta. This research also seeks to determine if and how Trikafta impacts CF patients' quality of life. This research consists of surveys; Cystic Fibrosis Questionnaire-Revised (CFQ-R), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire (PHQ)-9 administered to CF patients 18 years and older using a

convenience sample recruited from social media. The research questions that inform this study are:

1. Is there a difference in the quality of life between cystic fibrosis patients taking Trikafta compared to cystic fibrosis patients not taking Trikafta?
2. Is there an association between the quality-of-life index and the length of time on Trikafta?
3. Are there differences in the prevalence of depression and anxiety between cystic fibrosis patients taking Trikafta compared to cystic fibrosis patients not taking Trikafta?

I hypothesize that the use of Trikafta for treating cystic fibrosis patients with F508del CFTR Mutation positively impacts the patient's quality of life and reduces the severity of psychological issues such as depression and anxiety. I also hypothesize that there is a significant association between the time being on Trikafta and the quality of life among CF patients who administer the drug.

CHAPTER II

LITERATURE REVIEW

Prevalence and Epidemiology

Cystic Fibrosis (CF) is a serious disorder that primarily affects the digestive and pulmonary systems. CF is caused by certain defects in a single gene that codes for CFTR. Dr. Dorothy Anderson first described this condition in 1938. In the following years, scientific research supported that it is more prevalent in Caucasian populations. In 2004, one child out of every 2577 live births was diagnosed with cystic fibrosis. Regardless, patients with CF were never demotivated from having children who had known chances of having the disease at birth. Instead, newborns were screened at a board level to identify children with the condition so that they could be given all the required treatments and medications before the symptoms even begin to appear. However, it has been recorded that the rate of children born with CF is constantly increasing (Spoonhower & Davis, 2016).

The data from the California State newborn screening program suggest that the prevalence of the disorder in the state was 19.9 newborns per 100,000 births. The prevalence varied based on racial and ethnic background. Approximately 37.2 out of every 100,000 Native Americans had CF. Similarly, 38.8 and 17.1 out of every 100,000 white and black individuals were diagnosed with the condition (Spoonhower & Davis, 2016). If the global prevalence of cystic fibrosis is considered, then it has been recorded that nearly 70,000 individuals are affected by the disease worldwide. Earlier in the 1950s, the life expectancy of a child born with CF was only two years. However, the rapid advancement in healthcare has allowed the possibility of early diagnosis of cystic fibrosis, due to which the life span of CF patients has increased

drastically. Currently, 45% of CF patients are greater than 18 years of age, while many survive into the third and fourth decade of their lives (Heering & Schub, 2018).

Signs and Symptoms

The symptoms of CF are divided into two categories for all patients: respiratory and digestive symptoms. This is because the disease affects the mucous membranes and related organ function (Mayo Clinic, 2020b). The intensity of the signs and symptoms of cystic fibrosis differ for all patients. Newborn babies with cystic fibrosis may produce symptoms such as meconium ileus, which is the grayish-green colored first stool that blocks the end part of the small intestine because the stool is stickier and thicker than usual. Some of the common symptoms in younger children and adults include frequent bouts of cough and respiratory infections, shortness of breath, compromised growth despite a good diet, and foul-smelling and bulky stools. In severe cases, patients might experience recurrent pneumonia and bloody sputum. Since the disease is hereditary, a family history of CF is a primary risk factor. An individual whose one or both parents have CF is likely to be a carrier of the CF gene (Karakashian & Schub, 2018).

Definition and Types of CFTR Mutations

CFTR mutations are alternations in the Cystic Fibrosis Transmembrane Conductance Regulator, manifesting in the altered expression of the Cystic Fibrosis Transmembrane Conductance Regulator Protein (Derichs, 2013). According to the Cystic Fibrosis Foundation (2021b), “Cystic fibrosis is caused by mutations, or errors, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which results in either no CFTR protein being made or a malformed CFTR protein that cannot perform its key function in the cell. Its function is to create

channels on the cell surface to allow the movement of chloride (a component of salt) in and out of the cell".

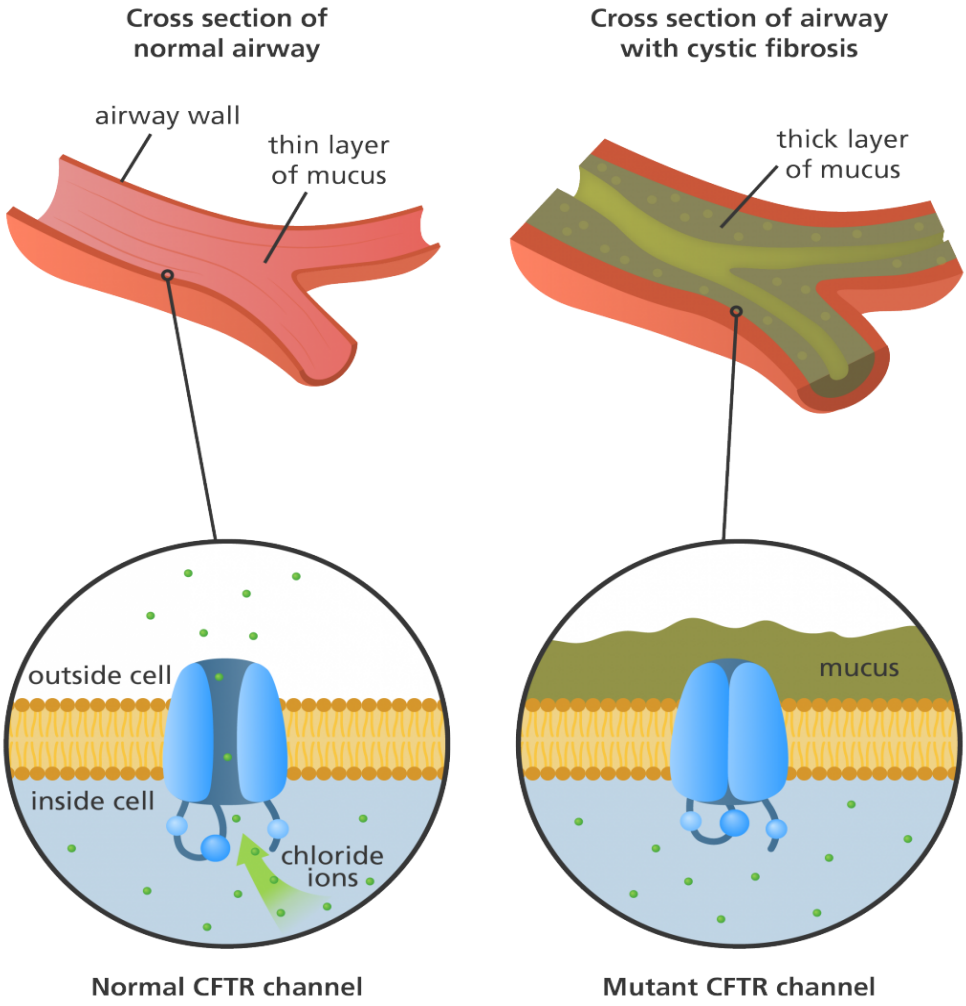


Figure 2.1: Normal CFTR channel vs. mutated CFTR channel (*What Is Cystic Fibrosis?*, 2016).

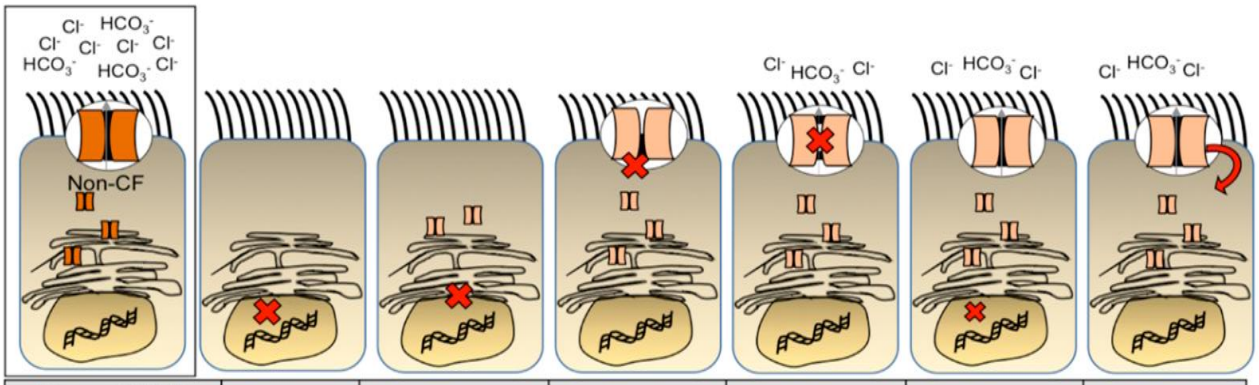
Most of the CFTR mutations are categorized into six classes (Rogan et al., 2011). Most of the CFTR mutations are very infrequent. More precisely, only 20 out of the more than 1900 CFTR mutations already identified have a higher than 0.1% frequency (Derichs, 2013). The most frequent CFTR mutations are the F508del because it has an estimated global allelic frequency of 90% (Derichs, 2013). F508del is the most prevalent CFTR mutation. It occurs due to the deletion of a codon in exon 10 involving the amino acid phenylalanine, specifically in position 508

(Sutanto et al., 2018). The high prevalence of the mutation implies that over 90% of people diagnosed with cystic fibrosis have one or more F508del (Kopito, 1999). It also implies that people who have the F508del mutation also have a high likelihood of having more expressive phenotypes (Morales et al., 1999).

The six classifications of the CFTR mutation include:

Table 2.1. Classifications of the CFTR mutation (Derichs, 2013; Veit et al., 2016).

Class	Particulars
I	Are either splicing, frameshift, or nonsense mutations that result in Premature Termination Codon as a result of an absent or repressed expression of CFTR.
II	Includes mutations resulting in premature degradation and misfolding on the quality control system in the endoplasmic reticulum, impaired biogenesis of proteins, and a severe reduction in the CFTR molecules traveling to the cell surface.
III	Includes the mutations that undermine the CFTR channel's regulation, leading to abnormal gating.
IV	Includes the mutations leading to the alternation of channel conductance. This effect is achieved through impairing unitary conductance by undermining the ion conduction pore.
V	Includes the mutations that, while not affecting protein conformation, introduce splicing or promoter abnormalities that in turn affect the abundance of the protein.
VI	Includes mutations that reduce the stability of the channel in the compartments after the endoplasmic reticulum.



Class of CFTR mutation	I	II	III	IV	V	VI
Protein output	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Mutation example	G542X	F508	G551D	R117H	3489+10kb C>T	4326delTC
% of people with CF who have at least one mutation*	22%	88%	6%	6%	5%	5%
Small molecules**		VX-809,VX-661 correctors	VX-770 potentiator			

Figure 2.2: Classifications of the CFTR mutation (Cooney et al., 2018).

Psychological Effects of CF on Patients

Unfortunately, patients suffering from cystic fibrosis are at a higher risk of developing psychological issues such as depression, anxiety, and stress, due to the severity of the disease and the burden of time-consuming treatments (Okumura & Kleinhenz, 2016). According to Sherman et al. (2020), "International cooperative group studies have demonstrated that a sizable proportion of adults with CF in many countries experience elevated levels of depressive (7–30%) or anxiety (5–39%) symptoms, as assessed by standardized screening measures." The disease not only takes a toll on the physical and mental health of the patient but also on those who are caring for them. Therefore, it has been advised to screen patients, parents, and caretakers frequently for the presence of psychological issues such as depression to help them and improve their quality of life (Heering & Schub, 2018). Sherman et al. (2020) also highlighted the importance of instilling gratitude (i.e., social support and positive reframing coping) in CF patients to prevent depression (Sherman et al., 2020).

Quality of Life in Patients with CF

Cystic fibrosis (CF) is a monogenic, autosomal recessive disorder caused due to the mutant cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (Ratjen et al., 2015). The protein coded by *CFTR* facilitates ion transport through the epithelial cell membrane. CFTR dysfunction mainly affects the lungs and causes obstructive pulmonary disease with the accumulation of mucus, leading to shortness of breath, wheezing, and repeated lung infections. Other manifestations include gastrointestinal malabsorption due to exocrine pancreatic insufficiency, malnutrition due to intestinal abnormalities, impaired growth with low body weight, male infertility, sinusitis, and diabetes. The incidence of CF is different in different races and ethnicities. (Ratjen et al., 2015). Given the progressive nature of CF, the lack of a cure, and the focus on symptom control and slowing down the progression, patients' quality of life is a crucial factor in disease management (Ratjen et al., 2015).

Although the lifespan of patients with CF has increased over the last few decades due to newer treatments, the quality of life varies considerably from patient to patient. The variability in the quality of life is attributed to variable progression of the disease, varying involvement of multiple body systems with major impacts on the pulmonary and gastrointestinal systems, the uncertainty of pulmonary exacerbations, and the need for complex treatment regimens (American Thoracic Society, 2009a). The quality-of-life studies underlined the perceived treatment burden by CF patients and their families and a significant variation in HRQOL for different socioeconomic and racial statuses (Ratjen et al., 2015). The key determining factors of the quality of life in patients with CF are as follows: age, sex, employment/participation in school, lung function, body mass index, frequency and severity of pulmonary

exacerbations, *Pseudomonas aeruginosa* infection, depression, and symptom burden (Habib et al., 2015).

Measuring HRQOL in Patients With CF

A multidimensional HRQOL assessment usually includes four basic modules: disease state and physical symptoms, body functions, psychological and emotional well-being, and daily functioning (Quittner et al., 2005). The patient-centered HRQOL assessments often involve the patient-specific examination of daily functioning and well-being. The quality of life in patients with CF is assessed using both generic and condition-specific instruments (American Thoracic Society, 2009a).

Some of the instruments are as follows: Cystic Fibrosis Questionnaire (CFQ), Cystic Fibrosis Questionnaire-Revised (CFQ-R), Child Health Questionnaire - Parent Form 50, Stein Functional Status Scale, Nottingham Health Profile, Quality of Well Being, Self-Administered Dependency Questionnaire, Medical Outcomes Study SF-36, Sickness Impact Profile, Functional Status II-R (FS II-R), Asthma Quality of Life Questionnaire (Juniper's), Chronic Respiratory Disease Questionnaire-CRQ, and Questions on Life Satisfaction - Cystic Fibrosis (FLZM -CF; American Thoracic Society, 2009a; Goss & Quittner, 2007).

Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The most widely used instrument for assessing the quality of life in patients with CF is CFQ-R (Habib et al., 2015). The original version of CFQ was developed in France by Henry et al. (2003). There are three different types of CFQ: one for teen/adults, CFQ Teen/Adult or CFQ 14+, which is self-administered; one for parent-proxy evaluation of children aged 6-13 years, CFQ Child P or CFQ Parent; and one for children aged 6-13 years, CFQ Child C or CFQ Child

6-13, which is interview-administered (American Thoracic Society, 2009b). The revised versions CFQ-R Teen Adult, CFQ-R Parent, and CFQ-R Child have a total of 50, 44, and 35 items, respectively. Each questionnaire takes about 15 minutes to complete. The questions/items are scored on a 4-point Likert scale (e.g., always - 1, often - 2, sometimes - 3, never - 4) and grouped into three modules: HRQOL, symptoms, and overall health perception.

The HRQOL module has nine domains in the CFQ-R Teen Adult, eight domains in the CFQ-R Parent, and seven domains in the CFQ-R Child (American Thoracic Society, 2009b). The nine domains are as follows: physical functioning, vitality, emotional state, social limitations, role limitations/school performance, embarrassment, body image, eating disturbances, and treatment constraints (American Thoracic Society, 2009b). The symptom module has a total of three symptom scales: respiratory, digestive, and weight (only two symptom scales in CFQ-R Child). The health perception module has one health status scale. After scoring each item on a 4-point Likert scale, the total score for individual domains and scales is obtained by summing up the scores for all items in a group. The final score ranges from 0 to 100, and higher total scores suggest better health (American Thoracic Society, 2009b). CFQ-R has been translated into 38 languages so far (Ronit et al., 2017).

CFQ-R in Clinical Trials of New CF Treatments

Patient-reported outcomes (PROs) are crucial in clinical research and care (Ratjen et al., 2015). PRO instruments often contain HRQOL domains and are used for various purposes, including primary and secondary outcomes in clinical trials of new pharmaceuticals and behavioral interventions. In clinical trials of new CF medications, CFQ-R is the most common PRO owing to its well-proven validity (Ronit et al., 2017). It measures pulmonary signs and symptoms (e.g., pulmonary exacerbations), constitutional and gastrointestinal signs and

symptoms, daily functioning (e.g., absenteeism and sports/walking), emotional and psychosocial aspects (e.g., worried/sad), and treatment burden as PROs (Goss & Quittner, 2007). The CFQ-R instrument is used in almost all clinical trials of new medications and treatments for CF, such as trials of hypertonic saline, inhaled antibiotics, CFTR correctors-modulators, macrolides, growth hormones, and pancreatic enzymes (Goss & Quittner, 2007; Ronit et al., 2017).

Current Treatments Available

Current treatments available in the market do not provide a cure for cystic fibrosis. However, they can help provide relief from the symptoms and manage the condition to enhance the quality of life. Some of the standard treatment approaches include the prescription of medicines that target the mutation of genes causing CF, antibiotics to prevent and treat respiratory bacterial infections, medicines to thin out mucus, and stool softeners. Depending on the patients' condition, they may also be prescribed drugs to reduce the inflammation in the airways and antacids to prevent acidity (Mayo Clinic, 2020a).

Patients with CF are regularly screened to check the condition of their lungs from a very young age. Their lungs are closely observed and are taken care of to maintain the highest level of lung function, even with CF. Doctors also perform airway clearance through various techniques to keep it free from excess sticky mucus. One of the techniques is huffing and coughing, in which the patient huffs or coughs voluntarily or involuntarily to remove mucus build-up. Similarly, chest physical therapy (CPT) might also be performed for the same reasons. The patient's chest is subjected to vibration or percussion on the specific region that requires drainage. It also includes deep breathing, in which the patients are asked to breathe deeply to loosen the mucus stuck anywhere in the air passageway (Cystic Fibrosis Foundation, 2021a). As a result, the patient feels the urge to cough and spit the excess mucus out. For long-term

management of CF, patients are also taught the use of nebulizer devices at home to inhale medicine mist that can open up the airways and make breathing easier. Lastly, if the lungs' condition worsens over time, even after adopting all the above mentioned techniques, the patients might be prescribed lung transplant surgery.

Current FDA Approved CFTR Modulators (Cystic Fibrosis) Treatments

Modulator treatment in the case of CFTR refers to therapies whose design principle is to remedy malfunctioning protein as a result of the CFTR gene. Modulator therapies are challenging because many CFTR mutations cause varied protein defects. Presently, the available therapies are developed to address specific mutations. Therefore, they are effective exclusively for people who have specific mutations (Pettit & Fellner, 2014). One and the first treatment that the Food and Drug Administration approved is Ivacaftor. The treatment is manufactured by Vertex Pharmaceuticals as Kalydeco. It was approved on January 31, 2012, as a potentiator indicated for treating cystic fibrosis in patients who are six years and above and who have the G551D mutation. An estimated 4% of the patients diagnosed with cystic fibrosis have the G551D mutation (Pettit & Fellner, 2014). The treatment enhances the CFTR channel to remain open for longer to allow the passage of chloride ions via the CFTR proteins that are located on the epithelial cells’ surface (Van Goor et al., 2008).

Another treatment for cystic fibrosis that has received FDA approval is ORKAMBI®. This drug is a combination of ivacaftor and lumacaftor and is indicated for cystic fibrosis treatment in children between two and five years with a F508del mutation (Food and Drug Administration, 2018; Vertex Pharmaceuticals, 2018). The approval of this treatment was a relief for people in this cohort because while F508del mutation is the most prevalent type of cystic fibrosis, and before the approval of this treatment, children between two and five years had no

approved treatment (Vertex Pharmaceuticals, 2018). The treatment combines the ability of lumacaftor to target the defect of F508del CFTR protein that enables them to process and traffic proteins to increase the availability of mature proteins on the surface of cells. This drug also improves the ability of ivacaftor to improve the CFTR protein function upon its arrival on the cell surface (Vertex Pharmaceuticals, 2018).

SYMDEKO® is also an approved treatment that combines ivacaftor and tezacaftor as a treatment for cystic fibrosis in patients above six years with the F508del CFTR mutation (Food and Drug Administration, 2019a; Vertex Pharmaceuticals, 2019). The previous approval was limited for patients above 12 years. The expanded approval increases the size of the population on which the drug can be used. The treatment combines the benefits of ivacaftor, as discussed earlier, and those of tezacaftor, which are addressing the CFTR protein's defect related to processing and trafficking to increase the protein's ability to travel to the cell surface (Food and Drug Administration, 2019a; Vertex Pharmaceuticals, 2019). Figure 2.3 below shows the current FDA approved CFTR modulators treatments assigned by age and gene-type.

Figure 2.3: Approved CFTR Modulators by age and type (Derichs, 2013; Veit et al., 2016).

Trikafta

Trikafta is effective in CF patients with F508del CFTR mutation. CFTR mutations are grouped according to protein defects. Delta-F508 mutation causes the deletion of three

nucleotides in the chromosome. Correction of this defect requires CFTR protein modification through molecular alterations (Chaudary, 2018). Different therapies for CFTR modulators address different deficiencies among CF patients. These therapies target different classes of mutations.

Notably, Trikafta is a combination of three modulators therapies, including ivacaftor, tezacaftor/ivacaftor, and Elexacaftor/tezacaftor/ivacaftor. Ivacaftor is the first modulator approved by the FDA for the treatment of CF. It is a potentiator therapy that binds to the defective CFTR protein. Lumacaftor/ivacaftor (Orkambi) is a combination of potentiator and corrector, while Tezacaftor/ivacaftor (Symdeko) is an improved combination for individuals with CF mutations. Elexacaftor/tezacaftor/ivacaftor (Trikafta) is a triple combination modulator that allows patients with particular heterozygous F508del genotypes to receive highly efficient modular therapies (Dickinson & Paranjape, 2020).

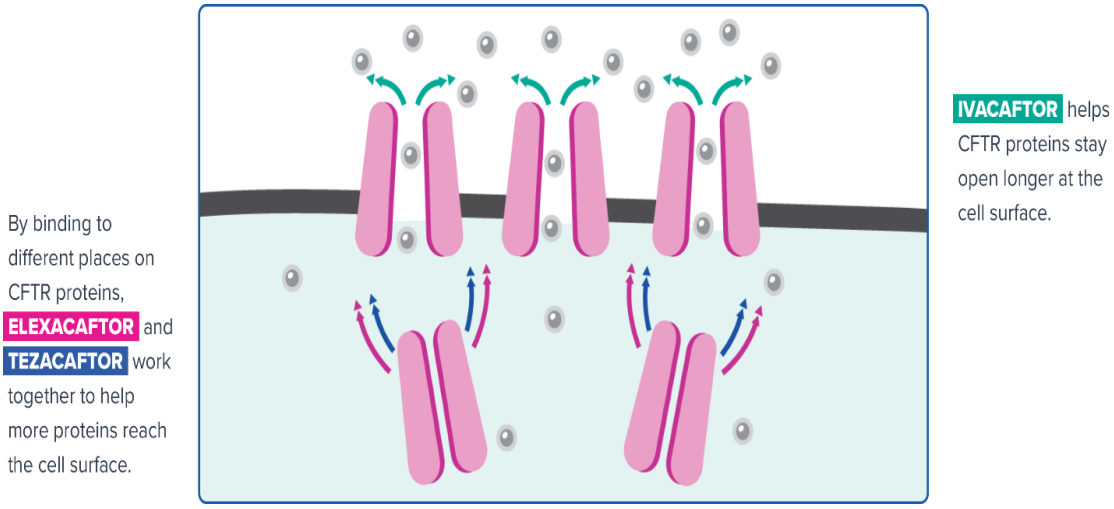


Figure 2.4: Trikafta combination of three modulators therapies (How Does TRIKAFTA® Work?, n.d.).

Trikafta is a treatment that has been approved recently for the treatment of cystic fibrosis caused by F508del CFTR mutation, the most prevalent of them all (Food and Drug

Administration, 2019b). The treatment is indicated for use in patients who are 12 years and above, in addition to having the F508del CFTR mutation.

Trikafta vs. Other Treatments for F508del CFTR Mutation

Various studies have been performed to understand how this triple-component treatment performs in the treatment of cystic fibrosis patients with the F508del CFTR Mutation. A review by Jain et al. (2020) on the effectiveness of triple therapy for individuals with F508del CFTR mutation in a clinical trial involving 16 individuals shows that this intervention, regardless of race or ethnic group (Jain et al., 2020). Hoy (2019) states that therapeutic trials of triple combination therapy are promising for the treatment of CF patients with F508del CFTR mutation. This study shows that there is a statistical significance or clinically significant improvement in lung functions with Trikafta compared to other regimens. The study also shows that there is improved respiratory-related quality of life compared to other treatment regimens (Hoy, 2019).

A randomized controlled trial was performed by (Middleton et al., 2019) to ascertain the safety and efficacy of Trikafta when used to treat patients who are 12 years and above whose cystic fibrosis is the result of the F508del-minimal effects genotypes. The researchers reported the efficacy of the treatment in patients with the F508del-minimal function genotype, while other CFTR modulator treatments were had low efficacy (Middleton et al., 2019).

Another three-phase randomized controlled trial (double-blind and active-controlled) done on four sites in four different countries showed clinically significant benefits in using a combination of Elexacaftor–tezacaftor–ivacaftor. The population had cystic fibrosis homozygous

for the F508del CFTR mutation. The active group received elexacaftor plus tezacaftor plus ivacaftor, while the control group received tezacaftor plus ivacaftor.

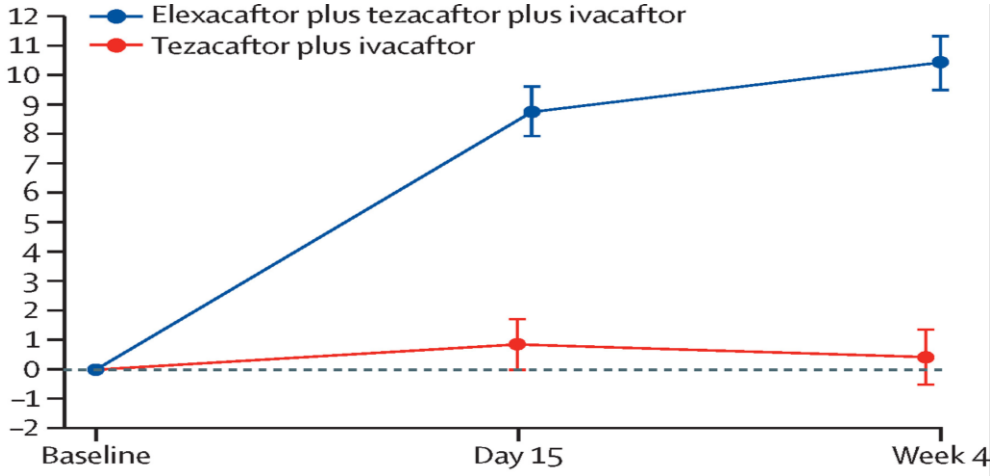


Figure 2.5: Change over time in forced expiratory volume in the first second (FEV1) (Heijerman, et al. 2019).

Figure 2.5 above shows that there were improved primary outcomes for forced expiratory volume in the first second (FEV1) for the active group. There were mild or moderate adverse effects on 4% of the individuals receiving Elexacaftor–tezacaftor–ivacaftor combination and 2% of those receiving control treatment Tezacaftor plus ivacaftor; no deaths were reported (Heijerman et al., 2019).

A recent clinical trial performed by (Mahase, 2019) found that Trikafta showed positive results. The high prevalence of F508del CFTR Mutation in patients diagnosed with cystic fibrosis means that as many as 90% of those with one copy of the mutation and 50% of the people with two copies of the mutation could benefit from the treatment (Mahase, 2019).

The findings of the various studies analyzed in this analysis support the hypothesis that Trikafta is effective in CF patients with F508del CFTR mutation. Therefore, all the analyzed articles and research in this review show that Trikafta is the most effective treatment for CF Most importantly, Trikafta is beneficial to individuals with F508del CFTR mutation because it is a

combination of a potentiator, potentiator-corrector, and a CFTR corrector (Dickinson & Paranjape, 2020). F508del has no options for the treatment of the underlying disease because the mutation either inhibits CFTR protein production or fails to respond to CFTR modulators. Therefore, only the application of triple modulators works for this patient group.

Medication Costs

Safe and effective medications also come with high costs for patients. For instance, the list price for a pack of Vertex Pharmaceutical's Trikafta containing a dosage of 28 days is $28,000. This price results in $311,000 in annual costs (Bell & Pagliarulo, 2020). Symdeko and Orkambi are not much cheaper, despite being double therapy treatments. According to (Maddipatla & O'Donnell, 2019), the list price for Orkambi for an annual dose is $272,000, while the same dosage for Symdeko attracts $292,000 in annual costs.

Conclusion

To sum up, CF is an autosomal recessive, monogenic disorder with varying incidence and mainly pulmonary and gastrointestinal complications. The quality of life in patients with CF is highly variable because of the progressive disease, and it has well-identified predictors. Of the various generic and condition-specific instruments available for measuring HRQOL in patients with CF, CFQ-R is the most widely used and best-validated instrument. The questions in CFQ-R are scored on a 4-point Likert scale and fall under three modules: HRQOL, symptoms, and health perception. The instrument has different questionnaires for teens/adults, parent-proxy, and children. CFQ-R is also the most common PRO used in clinical trials of new CF medications and treatments.

Trikafta is a combination of three CFTR modulators that is effective for individuals with F508del CFTR mutation. This treatment is most effective in this population because the mutation inhibits CFTR protein production, and it does not respond to current modulators. The use of Trikafta (Triple combination therapy: Elexacaftor/Ivacaftor/Tezacaftor) has been approved by the FDA, and it will improve respiratory therapy significantly because previously physicians had no option of treating underlying disease for individuals with F508del CFTR mutation. There are adequate findings of scientific research to prove that Trikafta is an effective therapy for individuals with CF, particularly those with F508del CFTR mutation. However, the literature is lacking in examining the impact of Trikafta on secondary outcomes, such as HRQOL, anxiety, and depression.

CHAPTER III

METHODS

This study design consisted of a cross-sectional survey administered to participants with Cystic Fibrosis. This study aims to compare cystic fibrosis patients who take Trikafta and who do not take Trikafta to compare their health-related quality of life, anxiety, and depression. The inclusion criteria for this survey are cystic fibrosis patients aged 18 years and above. Even though the FDA recommends the Trikafta drug for 12 years and older patients, this research excludes patients below 18 years of age. A convenience sample was selected upon availability from various social networks, such as closed, certified social media groups on Reddit and Facebook. The admins of these certified groups were asked to grant admission of the researcher to these groups allowing the researcher to invite members who qualify to participate in the survey directly. An anonymous link to the survey using Qualtrics was distributed to certified groups of CF patients on Facebook and Reddit. A digital informed consent was obtained from all participants. GSU IRB approval was obtained for this study.

The survey has a sample of 56 subjects. The research design consists of a cross-sectional study using primary survey data collected from Cystic Fibrosis patients. This research is aimed to survey how the Treatment of cystic fibrosis using Trikafta would affect the lifestyles of patients and their quality of life from the patient's perspective. This survey divides the participants into two groups. The first group is patients who are not administering Trikafta; the second group is patients currently taking Trikafta.

The Survey

The survey has four sections which are demographics, Cystic Fibrosis Questionnaire revised (CFQ-R), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire

(PHQ)-9, each section measuring a certain criterion. Demographics mainly covers age, gender, marital status, education level, insurance coverage, whether the patient is taking Trikafta or not and for how long. CFQ-R is a disease-specific health-related quality of life (HRQOL) measure for CF patients containing questions covering domains such as physical health, role, vitality, emotion, social, body image, weight, eating, burden, and health perceptions. GAD-7 and PHQ-9 measure levels of anxiety and depression respectively.

The results from patients' responses will be arranged in descending order, with answers such as, "A lot of difficulty," "Some difficulty," "A little difficulty," and "No difficulty," or "Always," "Often," "Sometimes," and "Never" being used to describe the extent to which the use of Trikafta can affect the patients' ways of life.

Data Analysis

The data recorded from patients will provide scores for Cystic Fibrosis Questionnaire Revised (CFQ-R), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire (PHQ)-9 which will be summarized using descriptive statistics. Additionally, the mean scores for CF participants taking Trikafta compared to those not taking Trikafta will be compared using an independent samples T-Test, if the data are normally distributed. One-Way Analysis of Variance (ANOVA) tests will be conducted to determine the statistically significant differences in quality of life with the amount of time on Trikafta among patients who are taking Trikafta. Lastly, anxiety and depression scores will be analyzed using Independent Samples T-Tests to determine differences in the GAD-7 scores and PHQ-9 scores between CF participants taking Trikafta and those not taking Trikafta.

CHAPTER IV

RERSUTLS

59 adults with CF participated (3 were not eligible and were excluded), ranging from 18 to 47 years. The mean age of participants was 25.6 years (SD= 6.63), and the number of males was 21 (37.5%), and females was 35 (62.5%). The majority of participants are Caucasian (71.4%, n=40), followed by Other races/ethnicities (14.3%, n=8), then African-American (12.50%, n=7). Half of the participants were single, and 16.1% were married. The most common level of education was High School (GED) or less, which was 41.1% of the participants, whereas 23.2% attended some college and 21.4% completed a college degree.

Table 4.1: Independent Sample t-test values for CFQ-R domains, GAD-7, and PHQ-9 for all patients.

Domain	Taking Trikafta (n=31, 57.1%)	Not taking Trikafta (n=23, 42.9%)	Mean Differences	T-Test statistic, degrees of freedom, p-value
	Mean (SD)	Mean (SD)		
CFQ-R Physical	2.74 (0.76)	1.98 (0.84)	0.76	3.48, *df*=52, *p*=0.001
CFQ-R Role/School	2.97 (0.60)	2.41 (0.78)	0.55	2.95, *df*=52, *p=0.005*
CFQ-R Vitality	2.57 (0.73)	1.95 (0.60)	0.62	3.41, *df*=53, *p*=0.001
CFQ-R Emotion	2.81 (0.69)	2.36 (0.73)	0.45	2.30, *df*=51, *p*=0.026
CFQ-R Social	2.60 (0.69)	2.04 (0.81)	0.55	2.70, *df*=52, *p*=0.009
CFQ-R Body	2.78 (0.79)	2.29 (0.87)	0.50	2.19, *df*=52, *p*=0.033
CFQ-R Eating	3.04 (0.69)	2.55 (1.00)	0.49	2.03, *df*=37, *p*=0.050
CFQ-R Burden	3.15 (0.75)	2.25 (0.78)	0.90	4.32, *df*=53, *p*<0.001
CFQ-R Health	2.86 (0.79)	1.68 (0.86)	1.18	5.23, *df*=52, *p*<0.001

CFQ-R Weight*	2.81 (1.01)	2.26 (1.39)	0.55	1.60, *df*=38, *p*=0.119
CFQ-R Respiratory	2.96 (0.67)	2.17 (0.80)	0.78	3.90, *df*=52, *p*<0.001
CFQ-R Digestion	3.08 (0.52)	2.68 (0.74)	0.39	2.30, *df*=52, *p*=0.026
Avg. CFQ-R Score	2.88 (0.53)	2.18 (0.68)	0.70	4.20, *df*=51, *p*<0.001
GAD-7	6.87 (5.78)	11.27 (6.24)	-4.41	-2.63, *df*=50, *p*=0.011
PHQ-9	8.16 (7.65)	12.45 (6.06)	-4.29	-2.19, *df*=51, *p*=0.033

SD: Standard Deviation

Note: Means are based on 4-point scale.

*Domain showing non-significant *p* value

Table 4.1 above shows the different mean and standard deviation values across all domains/scales from Cystic Fibrosis Questionnaire (CFQ-R), with 4 being the highest score possible and 0 being the lowest score possible. Higher values indicate higher quality of life scores. The table also shows the number of patients taking Trikafta versus the number of patients not taking Trikafta and the mean values associated with each domain/scale for these patients. From the data provided, it is clear that the mean values across all domains/scales for patients taking Trikafta are higher than domains/scales for those who are not. Noticeably in the Health domain by 1.2 points, Burden domain by 0.9 points, Respiratory domain by 0.78 points, Physical domain by 0.76 points, and Average CFQ-R Score by 0.7 points.

Table 4.1 also displays the different mean and standard deviation values of General Anxiety Disorder Questionnaire (GAD-7) and Patient Health Questionnaire (PHQ-9) scores reported from patients' responses to the survey. GAD-7 score ranges between 0 to 21, with higher scores indicating higher anxiety levels. PHQ-9 score ranges between 0 to 27, with higher

scores indicating higher levels of depression. In both questionnaires, patients taking Trikafta show lower levels of anxiety and depression in GAD-7 by 5 points and PHQ-9 by 5.7 points.

Table 4.1 illustrates the values from independent sample test running each domain/scale for patients who are administering Trikafta versus patients who are not. The 30 participants who reported administering Trikafta (M=2.88, SD=0.53) compared to the 23 who reported not administering Trikafta (M=2.18, SD=0.68) demonstrate a significantly better average CFQ-R score, t(51)=4.20, (p<.001). For GAD-7 scores, the 30 participants who reported administering Trikafta (M = 6.87, SD = 5.78) compared to the 22 who reported not administering Trikafta (M=11.27, SD=6.24) demonstrate a significantly lower GAD-7 scores, t(50)= -2.63, (p=0.011). Similarly, for PHQ-9 scores the 31 participants who reported administering Trikafta (M=8.16, SD=7.65) compared to the 22 who reported not administering Trikafta (M=12.45, SD=6.06) demonstrate a significantly lower PHQ-9 scores, t(51)= -2.19, (p=0.033).

The majority of participants reported having health insurance (85.7%). Approximately 57.1% of patients reported taking Trikafta, and 42.9% reported not taking Trikafta. Approximately 27% of patients reported that they were not eligible to take Trikafta due to the type of gene mutation which was not approved for Trikafta. A small percentage (5.4%) of participants believe that Trikafta is ineffective, and 10.7% of participants cannot afford Trikafta. The majority of participants in this study (73.2%) reported having the F508del CFTR gene mutation.

Across the majority of domains/scales, the analysis of the t-test reveals higher mean values and significant p values, meaning higher quality of life scores for those taking Trikafta compared to those not taking Trikafta. However, the association was not statistically significant for the weight domain (p=0.06).

A one-way ANOVA test was conducted to determine the association between quality of life and length of time on Trikafta among those on Trikafta. The majority of the participants were on Trikafta for ten or more months (71.9%), followed by 2-3 months (9.4%), one month or less (9.4%), 7-9 months (6.3%), and 4-6 months (3.1%). The association between the length of time taking Trikafta and overall quality of life was not statistically significant (p=0.90).

CHAPTER V

DISCUSSION

A recent study in 2022 totaling 107 CF patients treated by Trikafta concluded that "Treatment with ELX/TEZ/IVA results in effective improvement of CFTR function in the airway and intestinal epithelia in patients with CF and one or two F508del alleles" (Graeber et al., 2022). Clinically, Trikafta has demonstrated a significant improvement in the physical aspect of CF patients (respiratory and pulmonary systems). However, the literature lacks the use of secondary measures such as CFQ-R, GAD-7, and PHQ-9 to evaluate the effect of Trikafta on quality-of-life for CF patients. The survey used in this study utilizes Cystic Fibrosis Questionnaire-Revised (CFQ-R), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire (PHQ)-9 as a comprehensive tool to evaluate the impacts and changes to CF patients' quality-of-life. Improvements to the physical function of systems defected by the CFTR mutation when using Trikafta might not necessarily improve CF patients' quality of life unless properly measured using secondary measures (i.e., CFQ-R).

For demographic comparisons, the majority of participants were late adolescents or young adults.

Quality of Life

CFQ-R is the larger section of the survey containing 12 domains/scales which include Physical, Role/school, Vitality, Emotion, Social, Body, Eating, Burden, Health, Weight, Respiratory, and Digestion domains. Each domain has a set of questions targeting the titled goal. For the purpose of this research a new variable/score was created which is the average of all domains/scales. Significant differences in the mean and *p* values prominently appear in Health

(MD=1.18, p<.001) points, Burden (MD=0.90, p<0.001), Respiratory (MD=0.78, p < 0.001), Physical (MD=0.76, p=0.001), Average CFQ-R Score (MD=0.70, p<0.001), Vitality (MD=0.62, p=0.001), Role/School (MD=0.55, p=0.005), Social (MD=0.55, p=0.009), Emotion (MD=0.45, p=0.026), Body (MD=0.50, p=0.033), Digestion (MD=0.39, p=0.026), and Eating (MD=0.49, p=0.050) domains/scales. This is evident that the quality-of-life scores are positively impacted by the use of Trikafta which certainly supports the hypothesis; the use of Trikafta for the treatment of cystic fibrosis patients with F508del CFTR Mutation may have positive impacts on the patient's quality-of-life when compared to those are not.

Trikafta vs Time

Using One-way ANOVA test to find an association between the length of time on Trikafta and average CFQ-R score across all domains reveals a non-significant (p = 0.90) value, indicating that the length of time on Trikafta is not associated with the quality-of-life index. The results could be explained by the fact that most of the participants (71.9%) taking Trikafta reported that they have been administrating Trikafta for more than ten months, and there were not enough samples of patients newly administering Trikafta to compare it validly. In this study, most participants taking Trikafta have been taking the drug for more than ten months. However, future studies with a sizable sample initiating the use of Trikafta could reveal more significant findings, such as whether Trikafta has an immediate effect on CF patients' quality of life and whether the quality of life keeps improving with the long-term use of Trikafta**.**

Anxiety and Depression

Even though that CFQ-R is a complete measure of CF patients’ quality of life, GAD-7 and PHQ-9 were added to the survey to specifically measure the levels of anxiety and depression

and create a comparison between patients administering Trikafta versus patients not administering Trikafta. A significant indication from GAD-7 (MD= -4.41, p=0.011) and PHQ-9 (MD= -4.29, p=0.033) scores is that participants who are administering Trikafta have lower levels of anxiety and depression than the ones who do not (on average by 4 points) in both scales. A study completed by Mengistu Yohannes et al. concluded, "Anxiety and depressive symptoms are common in adult CF patients. They are associated with poorer QOL, low lung function, reduced physical functioning, and severity of chest symptoms" (Mengistu Yohannes et al., 2012). The results from this study support that CF patients with poor quality of life are more likely to experience higher levels of anxiety and depression, which is the case for non-Trikafta users in this study. On the contrary, Trikafta users' quality-of-life scores on average were higher, and their levels of anxiety and depression were lower.

The Weight Domain/Scale

The weight domain/scale has shown a non-significant value (p=0.119), and such a result could have several explanations. As mentioned before, administering Trikafta improved the CFTR function of intestinal epithelia in CF patients with one or two F508del gene mutations (Graeber et al., 2022). The Eating and Digestion domain/scales have shown significant p values when comparing Trikafta users to non-Trikafta users. These two domains/scales can be good indicators of the nutrition aspect of quality-of-life for CF patients, so rationally, the Weight domain would show a significant value. However, possibly due to the function of the sample size, a significant value for the weight domain/scale has not appeared in the analysis. A true association between the Weight domain/scale and the use of Trikafta might not show even in a larger population, possibly due to factors and side effects such as loss of appetite, stomach pain, and diarrhea which could affect weight gain progression even when administering Trikafta.

According to Quittner et al., in an effort to improve the Digestive and Burden scales' internal consistency, more items/questions were added to these domains/scales where the level of reliability has improved in both of these domains/scales; this could be the case with the Weight domain/scale which only has one item/question in the Cystic Fibrosis Questionnaire-Revised (CFQ-R), and adding more questions might aid the in deduction of the hypothesized association (Graeber et al., 2022).

According to a study by Quittner et al. from 18 CF centers around the United States stating that "CFQ is a reliable and valid measure of HRQOL for adolescents and adults with CF… and a majority of the CFQ scales were shown to have strong internal consistency and adequate test-retest reliability… that the CFQ is responsive to the effects of new medications and antibiotic Treatment of pulmonary exacerbations. Thus, the CFQ has a number of potential applications and is currently ready to be used for research purposes" (Quittner et al., 2005). Based on the study result, CFQ-R is a suitable measure of the quality of life for CF patients. Also, GAD-7 and PHQ-9 were added to the survey to detect anxiety and depression levels.

Prevalence of F508del CFTR Gene Mutation

Most of the participants (73.2%) have F508del CFTR gene mutation projecting similarity in the prevalence of the majority of F508del CFTR gene mutation (88%) around CF patients indicating that the sample in this research similarly represents the global prevalence of CFTR gene mutations (Cooney et al., 2018). The sample of participants who are administering Trikafta (57.1%) versus the ones who do not (42.9%) does not represent the percentage of participants who have F508del CFTR gene mutation, as (5.4%) of participants reported that the reason for not administrating Trikafta is believing that Trikafta is not effective. Also, another 6 (10.7%)

participants reported that they could not afford Trikafta, which can be explained by the 8 (14.3%) participants who reported not having health insurance coverage.

Limitations

This study has several limitations. The sample size is a limiting factor in this study, especially in the analysis of time being on Trikafta versus CF patients qualify-of-life, where the majority were long term users of Trikafta. Another potentially limiting factor is online recruitment of participants. The invitation to the survey was distributed in closed and certified social groups of CF patients, such as the Trikafta group on Facebook so that the sample would generalize to a specific population of CF patients. However, this type of recruitment mainly attracts active members of the groups and those accustomed to social media, which limits generalizability. We also did not collect information on confounding factors that may influence quality of life, such as social support. Future studies should assess this construct among CF patients in the context of Trikafta.

Conclusion

Trikafta was positively associated with quality of life, anxiety, and depression levels in CF patients in our study. The application and utilization of secondary measures are eminent for detecting the effectiveness of newly introduced treatments for CF patients, such as Trikafta. This study has shown distinct comparisons between Trikafta users and non-Trikafta users in multiple scales and areas such as quality-of-life (in CFQ-R has 12 scales), anxiety, and depression which are prominent in a CF patients' life.

In this study, the association between time being on Trikafta and quality-of-life was not adequately investigated due to the sample size not as a whole but within Trikafta users, which

reduces the sample in half. Most participants, who have been administering Trikafta, have been administering Trikafta for more than ten months, and a valid comparison was not feasible. For future research, a proper sample initializing Trikafta monitored over time and re-assessed using secondary measures such as CFQ-R to properly analyze the association between time on Trikafta and quality-of-life in CF patients.

REFERENCES

American Thoracic Society. (2009a, November 4). *Cystic fibrosis*. American Thoracic Society: Quality of Life Resource. Retrieved April 19, 2022, from https://qol.thoracic.org/sections/specific-diseases/cystic-fibrosis.html

American Thoracic Society. (2009b, November 4). *Cystic Fibrosis Questionnaire (CFQ); Cystic Fibrosis Questionnaire Revised (CFQ-R)*. American Thoracic Society: Quality of Life Resource. Retrieved April 19, 2022, from https://qol.thoracic.org/sections/instruments/ae/pages/cfq-cfq-r.html

Bear, C. E. (2020). A Therapy for Most with Cystic Fibrosis. Cell, 180(2), 211. https://doi.org/10.1016/j.cell.2019.12.032

Bell, J., & Pagliarulo, N. (2020, January 30). Vertex impresses with strong Trikafta launch . BioPharma Dive. https://www.biopharmadive.com/news/vertex-trikafta-launch-cystic-fibrosis-leiden/571452/

Chaudary, N. (2018). Triplet CFTR modulators: Future prospects for treatment of cystic fibrosis. *Therapeutics and Clinical Risk Management*, 14, 2375–2383. https://doi.org/10.2147/TCRM.S147164

Cooney, A. L., McCray, P. B., & Sinn, P. L. (2018). Cystic Fibrosis Gene Therapy: Looking Back, Looking Forward. Genes, 9(11). https://doi.org/10.3390/genes9110538

Cystic Fibrosis Foundation. (2021a). *Airway Clearance*. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/

Cystic Fibrosis Foundation. (2021b). *Types of CFTR Mutations*. https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations/

Cystic fibrosis. (2017, October 23). Nhs.Uk. https://www.nhs.uk/conditions/cystic-fibrosis/

Derichs, N. (2013). Targeting a genetic defect: Cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. European Respiratory Review: An Official Journal of the European Respiratory Society, 22(127), 58–65. https://doi.org/10.1183/09059180.00008412

Dickinson, K. M., & Paranjape, S. M. (2020). Triple combination therapy for cystic fibrosis is here! Contemporary Pediatrics, 37(2), 17–19.

Farrell, P. M., White, T. B., Ren, C. L., Hempstead, S. E., Accurso, F., Derichs, N., Howenstine, M., McColley, S. A., Rock, M., Rosenfeld, M., Sermet-Gaudelus, I., Southern, K. W., Marshall, B. C., & Sosnay, P. R. (2017). Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *The Journal of pediatrics*, 181S, S4–S15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064

Food and Drug Administration. (2018, August 7). *Drug Approval Package: ORKAMBI (lumacaftor/ivacaftor)*. U.S. Food and Drug Administration . https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211358Orig1s000TOC.cfm

Food and Drug Administration. (2019a, June 21). *FDA expands approval of treatment for cystic fibrosis to include patients ages 6 and olde*r. FDA. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-expands-approval-treatment-cystic-fibrosis-include-patients-ages-6-and-older

Food and Drug Administration. (2019b, October 21). *FDA approves new breakthrough therapy for cystic fibrosis*. U.S. Food and Drug Adminstration . https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis

Goss, C. H., & Quittner, A. L. (2007). Patient-reported outcomes in cystic fibrosis. *Proceedings of the American Thoracic Society*, 4(4), 378–386. https://doi.org/10.1513/pats.200703-039br

Graeber, S. Y., Vitzthum, C., Pallenberg, S. T., Naehrlich, L., Stahl, M., Rohrbach, A., Drescher, M., Minso, R., Ringshausen, F. C., Rueckes-Nilges, C., Klajda, J., Berges, J., Yin Yu, Scheuermann, H., Hirtz, S., Sommerburg, O., Dittrich, A.-M., Tümmler, B., Mall, M. A., & Yu, Y. (2022). Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on CFTR Function in Patients with Cystic Fibrosis and One or Two Alleles. *American Journal of Respiratory & Critical Care Medicine*, 205(5), 540–549. https://doi.org/10.1164/rccm.202110-2249OC

Habib, A.-R. R., Manji, J., Wilcox, P. G., Javer, A. R., Buxton, J. A., & Quon, B. S. (2015). A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. *Annals of the American Thoracic Society*, 12(3), 420–428. https://doi.org/10.1513/annalsats.201408-393oc

Heering, H., & Schub, T. (2018). Cystic Fibrosis in Adults: Psychosocial Issues. *CINAHL Nursing Guide*. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=nup&AN=T903023&site=eds-live&scope=site&custid=gsu1

Heijerman, H. G. M., McKone, E. F., Downey, D. G., Van Braeckel, E., Rowe, S. M., Tullis, E., Mall, M. A., Welter, J. J., Ramsey, B. W., McKee, C. M., Marigowda, G., Moskowitz, S.

M., Waltz, D., Sosnay, P. R., Simard, C., Ahluwalia, N., Xuan, F., Zhang, Y., Taylor-Cousar, J. L., … Majoor, C. (2019). Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. The Lancet, 394(10212), 1940–1948. https://doi.org/10.1016/S0140-6736(19)32597-8

Henry, B., Aussage, P., Grosskopf, C., & Goehrs, J-M. (2003). Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Quality of Life Research*, 12, 63–76. https://doi.org/10.1023/a:1022037320039

How Does TRIKAFTA® Work? (n.d.). TRIKAFTA®. Retrieved June 16, 2021, from https://www.trikafta.com/how-trikafta-works

Hoy, S. M. (2019). Elexacaftor/Ivacaftor/Tezacaftor: First Approval. Drugs, 79(18), 2001–2007. https://doi.org/10.1007/s40265-019-01233-7

Jain, R. et al. (2020). Triple therapy for cystic fibrosis with a Phe508del CFTR Mutation. *The New England Journal of Medicine*, 382(7), 684.

Karakashian, L., & Schub, T. (2018). Cystic Fibrosis. *CINAHL Nursing Guide*. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=nup&AN=T700390&site=eds-live&scope=site&custid=gsu1

Kopito, R. R. (1999). Biosynthesis and degradation of CFTR. Physiological Reviews, 79(1 SUPPL. 1), 167–173. https://doi.org/10.1152/physrev.1999.79.1.S167

Maddipatla, M., & O'Donnell, C. (2019, October 21). Vertex prices cystic fibrosis combo treatment at $311,000-per-year. *Reuters*. https://www.reuters.com/article/us-vertex-pharms-fda-idUSKBN1X024U

Mahase, E. (2019). Cystic fibrosis: Triple therapy shows promising results. The BMJ, 367. https://doi.org/10.1136/bmj.l6347

Mayo Clinic. (2020a, March 14). *Cystic fibrosis - Diagnosis and treatment - Mayo Clinic*. https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/diagnosis-treatment/drc-20353706

Mayo Clinic. (2020b, March 14). *Cystic fibrosis - Symptoms and causes*. https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

McGarry, M. (2020). Triple Therapy for Cystic Fibrosis with a Phe508del CFTR Mutation. *New England Journal of Medicine*, 382(7), 684–684. https://doi.org/10.1056/nejmc1916747

Mengistu Yohannes, A., George Willgoss, T., Ade Fatoye, F., Dodd Dip, M., & Webb, K. (2012). Relationship Between Anxiety, Depression, and Quality of Life in Adult Patients With Cystic Fibrosis. Respiratory Care, 57(4), 550–556. https://doi.org/10.4187/respcare.01328

Middleton, P. G., Mall, M. A., Dřevínek, P., Lands, L. C., McKone, E. F., Polineni, D., Ramsey, B. W., Taylor-Cousar, J. L., Tullis, E., Vermeulen, F., Marigowda, G., McKee, C. M., Moskowitz, S. M., Nair, N., Savage, J., Simard, C., Tian, S., Waltz, D., Xuan, F., … Jain, R. (2019). Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *New England Journal of Medicine*, 381(19), 1809–1819. https://doi.org/10.1056/NEJMoa1908639

Morales, M. M., Capella, M. A. M., & Lopes, A. G. (1999). Structure and function of the cystic fibrosis transmembrane conductance regulator. *Brazilian Journal of Medical and*

Biological Research, 32(8), 1021–1028. https://doi.org/10.1590/S0100-879X1999000800013

Okumura, M. J., & Kleinhenz, M. E. (2016). Cystic Fibrosis Transitions of Care. *Clinics in Chest Medicine*, *37*(1), 119–126. https://doi.org/10.1016/j.ccm.2015.11.007

Pettit, R. S., & Fellner, C. (2014). CFTR modulators for the treatment of cystic fibrosis. P and T, 39(7), 500–511. /pmc/articles/PMC4103577/

Quittner, A. L., Buu, A., Messer, M. A., Modi, A. C., & Watrous, M. (2005). Development and validation of the Cystic Fibrosis Questionnaire in the United States. *Chest*, 128(4), 2347–2354. https://doi.org/10.1378/chest.128.4.2347

Ratjen, F., Bell, S. C., Rowe, S. M., Goss, C. H., Quittner, A. L., & Bush, A. (2015). Cystic fibrosis. *Nature Reviews Disease Primers*, 1(15010). https://doi.org/10.1038/nrdp.2015.10

Rogan, M. P., Stoltz, D. A., & Hornick, D. B. (2011). Cystic fibrosis transmembrane conductance regulator intracellular processing, trafficking, and opportunities for mutation-specific treatment. *Chest*, 139(6), 1480–1490. https://doi.org/10.1378/chest.10-2077

Ronit, A., Gelpi, M., Argentiero, J., Mathiesen, I., Nielsen, S. D., Pressler, T., & Quittner, A. L. (2017). Electronic applications for the CFQ-R scoring. *Respiratory Research*, 18, 108. https://doi.org/10.1186/s12931-017-0592-z

Sherman, A. C., Simonton-Atchley, S., O'Brien, C. E., Campbell, D., Reddy, R. M., Guinee, B., Wagner, L. D., & Anderson, P. J. (2019). Longitudinal associations between gratitude

and depression 1 year later among adult cystic fibrosis patients. *Journal of Behavioral Medicine*, *43*(4), 596–604. https://doi.org/10.1007/s10865-019-00071-y

Spoonhower, K. A., & Davis, P. B. (2016). Epidemiology of Cystic Fibrosis. *Clinics in Chest Medicine*, *37*(1), 1–8. https://doi.org/10.1016/j.ccm.2015.10.002

Sutanto, E. N., Scaffidi, A., Garratt, L. W., Looi, K., Foo, C. J., Tessari, M. A., Janssen, R. A., Fischer, D. F., Stick, S. M., & Kicic, A. (2018). Assessment of p.Phe508del-CFTR functional restoration in pediatric primary cystic fibrosis airway epithelial cells. *PLoS ONE*, 13(1). https://doi.org/10.1371/journal.pone.0191618

Van Goor, F., Hadida, S., & Grootenhuis, P. (2008). Pharmacological Rescue of Mutant CFTR Function for the Treatment of Cystic Fibrosis. *Topics in Medicinal Chemistry*, 3, 91–120. https://doi.org/10.1007/7355_2008_022

Veit, G., Avramescu, R. G., Chiang, A. N., Houck, S. A., Cai, Z., Peters, K. W., Hong, J. S., Pollard, H. B., Guggino, W. B., Balch, W. E., Skach, W. R., Cutting, G. R., Frizzell, R. A., Sheppard, D. N., Cyr, D. M., Sorscher, E. J., Brodsky, J. L., & Lukacs, G. L. (2 c016). From CFTR biology toward combinatorial pharmacotherapy: Expanded classification of cystic fibrosis mutations. *Molecular Biology of the Cell*, 27(3), 424–433. https://doi.org/10.1091/mbc.E14-04-0935

Vertex Pharmaceuticals. (2018, August 7). FDA Approves ORKAMBI® (lumacaftor/ivacaftor) as First Medicine to Treat the Underlying Cause of Cystic Fibrosis for Children Ages 2-5 Years with Most Common Form of the Disease . *News & Events*. https://investors.vrtx.com/news-releases/news-release-details/fda-approves-orkambir-lumacaftorivacaftor-first-medicine-treat

Vertex Pharmaceuticals. (2019, June 21). FDA Approves SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) to Treat the Underlying Cause of CF in Children Ages 6-11 Years with Certain Mutations in the CFTR Gene. *News and Events*. https://investors.vrtx.com/news-releases/news-release-details/fda-approves-symdekor-tezacaftorivacaftor-and-ivacaftor-treat

What is cystic fibrosis? (2016, January 25). Yourgenome. https://www.yourgenome.org/facts/what-is-cystic-fibrosis