Advances in cystic fibrosis treatment

Nishita Hira, PharmD, CSP

Cystic fibrosis (CF) is a life-threatening, rare, genetic disease that primarily affects the lungs and pancreas.[1] For patients and families living with CF, disease management can be demanding. However, great advances in the last decade have resulted in an entirely new class of CF medications that has helped delay disease progression and improve life expectancy and quality of life. Today, more than half of those living with CF are age 18 or older.[1]

Incidence and diagnosis

CF affects more than 30,000 people in the United States. Across the globe, more than 70,000 people are living with CF.[1] There are roughly 1,000 newly diagnosed CF patients every year, with more than 75% being diagnosed by age 2.[1] CF is most common in Caucasians in the United States and Northern Europe, but it can affect people of all ethnicities.[2]

A person with CF has inherited two copies of the CF gene — one from each parent.[1,2] A person with a single copy of the defective gene does not have CF and is known as a carrier.[1,2] In the United States, diagnosing a newborn with CF begins with a newborn screening test.[2] Using a needle prick on the newborn's heel, a drop of blood can be used to test for a host of genetic conditions, including CF.[2]

If a newborn screen comes back positive for CF, a confirmatory test called a sweat chloride test is performed when the newborn is a few weeks old.[2] CF mutation testing can also determine which mutations are present in a patient. There are currently more than 2,000 identified cystic fibrosis transmembrane conductance regulator (CFTR) mutations.[3] The most common mutation is *F508del*, with approximately 85% of patients in the 2018 Cystic Fibrosis Foundation (CFF) patient registry having at least one copy.[3-5]

Pathophysiology

In CF, mutations in the CFTR gene cause a defect in the CFTR protein.[1] This defect can result in both an inadequate production of CFTR protein as well as an inhibition of its function.[1] Under normal circumstances, this protein is responsible for the transport of chloride and sodium ions across the cell membrane. When a defect occurs, the movement of these ions is impaired.[1,3] Without chloride transport in and out of the cells, water cannot move freely, thus resulting in thick, sticky mucus in multiple organs of the body.[1,4]

In the lungs, this thick, sticky mucus provides an ideal medium for bacterial growth and, subsequently, lung infections. CF patients are prone to a host of bacterial, viral and fungal infections, with the most common organisms to colonize the respiratory tract being *Pseudomonas aeruginosa, Haemophilus influenzae, and Staphylococcus aureus*.[3] Over time, chronic infections and inflammation can lead to scarring and permanent damage of the lungs.[3]

Thick, sticky mucus can also block pancreatic ducts, inhibiting the release of digestive enzymes.[1] In turn, the body is unable to absorb nutrients from food and fat-soluble vitamins, such as vitamins A, D, E and K. This can lead to malnutrition and poor growth.[1] CF can also affect other parts of the body, including the liver and male reproductive organs.[1]

Symptoms and complications

Common symptoms of CF include frequent lung infections, persistent coughing, wheezing, difficulty with bowel movements, poor weight gain, infertility and salty-tasting skin.[1] Table 1 lists additional signs and symptoms of CF.

Table 1. CF symptoms[6]

Respiratory	Digestive
Exercise intolerance	Abdominal pain
Inflamed nasal passages	Flatulence
Persistent cough with or without phlegm	Foul-smelling, greasy stools
Recurrent sinusitis	Increased frequency of stools
Repeated lung infections	Intestinal blockage (newborns)
Shortness of breath	Severe constipation

Most CF patients will exhibit both respiratory and digestive symptoms. However, each individual patient's disease presentation will vary, even amongst siblings. Symptoms can also differ for an individual, with symptoms improving at some periods of time and worsening at others.[6]

Disease progression and organ involvement will also vary from patient to patient. As the disease progresses, symptoms often give way to complications. In the respiratory system, patients might develop nasal polyps, hemoptysis, pulmonary exacerbations or life-threatening respiratory failure.[6] Digestive system complications can include CF-related diabetes, nutritional deficiencies and intestinal obstruction.[6]

Treatment

A typical CF treatment plan can take up to two hours to administer two times a day, including setup and disinfection of multiple nebulizer devices. The management of CF involves a combination of oral, inhaled and nebulized medications, nonpharmacologic therapies, diet and nutrition therapies and exercise.[5,7] Inhaled and nebulized therapies deliver medication directly to the lungs to maximize therapeutic effects and minimize adverse events.[7] Medications and therapies must be taken in a specific sequence for the maximum benefit to the patient. Most regimens begin with bronchodilators and mucolytic agents, followed by airway clearance therapy and inhaled antibiotics.[7]

Bronchodilators

Bronchodilators, such as Ventolin HFA (albuterol sulfate) or Xopenex solution (levalbuterol hydrochloride), are commonly used as the first medication in a CF treatment regimen.[8] Bronchodilators are inhaled via a metered dose inhaler or, in some cases, nebulized.[8] Bronchodilators work by relaxing the airways, allowing subsequent inhaled medications to work more effectively.[8] Some patients may also use bronchodilators prior to exercise.[8] Common side effects of bronchodilators include dizziness, increased heart rate, nausea or nervousness.[8] Many patients include bronchodilators as part of their CF regimen, but CFF guidelines state there is insufficient evidence to recommend for or against their use.[9]

Mucolytics

After bronchodilator therapy, patients will use a mucolytic or mucus thinner. This type of medication is inhaled via a nebulizer to thin the mucus in the lungs so it can be coughed out.[10] Common side effects of mucolytics can include change or loss of voice, chest tightness, dizziness, increased cough, runny nose or sore throat.[10] Pulmozyme (dornase alfa) and hypertonic saline are the two types of mucolytics currently available in the United States. Some patients may use hypertonic saline followed by Pulmozyme while others may use Pulmozyme on its own.

Hypertonic saline is a salt solution, available in varying concentrations.[10] Once this salt solution is inhaled into the airways, water is drawn in, thinning out the mucus and allowing it to be coughed out.[10] Hypertonic saline is typically used twice daily; administration should continue until all solution is used up.[10] In contrast, Pulmozyme is an enzyme that adheres to the DNA in sputum and reduces its viscosity, allowing it to be coughed out more easily.[10,11] Administration of Pulmozyme is typically once daily and can take up to 15 minutes, in addition to setup and cleanup.[11] CFF guidelines support treatment with Pulmozyme in patients age 6 and older.[10] However, in practice, Pulmozyme may be used in younger patients.[10]

Airway clearance techniques

Once mucus is starting to thin out, the next step in the CF regimen is the use of airway clearance techniques (ACT). ACT involves vibration or percussion on the chest to dislodge mucus from the walls of the airways.[12] This is followed by forceful coughing or huffing to expectorate the mucus.[12] Various types of ACT include active cycle of breathing, airway oscillating device, autogenic drainage, chest physical therapy, high-frequency chest wall oscillating vest and positive expiratory device.[12] Administration of ACT usually lasts 20 to 40 minutes per session, and patients (or caregivers) can choose the ACT that best fits their lifestyle and daily routine.[12-14] CFF guidelines recommend all CF patients make use of ACT, along with exercise for further benefits.[5]

High-frequency chest wall oscillation (“the vest”) is the most common ACT used in patients age 2 and older.[5] In this method, the patient wears a vest that inflates and deflates rapidly with air from a connected generator.[13] This series of movements causes an intense vibration on the chest, breaking up mucus and moving it up into the larger airways where it can then be coughed out.[13] Patients alternate between using the vest and coughing out mucus for the duration of the treatment.[13]

Chest physical therapy, or postural drainage, is the most common ACT performed in patients under age 2.[5] In this type of ACT, the patient sits or lies down in various positions, using gravity to draw mucus out from the lungs.[14] The caregiver then performs percussion along with vibration over the chest wall and lungs to break up and help move mucus toward the larger airways to be coughed out.[14] Similar to the vest, the caregiver will alternate between percussing and allowing the patient to cough mucus out for the duration of the treatment.[14]

Inhaled antibiotics

Clearing of mucus is an important and necessary step that allows inhaled antibiotics to reach bacteria deep in the lungs.[15] Long-term inhaled antibiotic therapy is an essential component to CF treatment, as CF patients are afflicted with chronic infections due to mucus buildup in the lungs.[7,15] Most often, patients will use either an aminoglycoside or aztreonam product to treat one of the most common CF-related bacteria, *Pseudomonas aeruginosa*.[15] CFF guidelines strongly recommend the use of tobramycin and aztreonam for moderate to severe lung disease.[9]

Aminoglycosides encompass tobramycin products, available under the brand names of Tobi or Bethkis (tobramycin inhalation solution), Kitabis Pak (co-packaging of tobramycin inhalation solution and PARI LC PLUS Reusable Nebulizer) and Tobi Podhaler (tobramycin inhalation powder). With the exception of Tobi Podhaler, all tobramycin products are inhaled via a nebulizer. Tobi Podhaler is a dry powder inhaler in which the contents of capsules are inhaled via a handheld device. Aztreonam is commercially available as Cayston (aztreonam for inhalation solution).

Dosing schedules for tobramycin and aztreonam are unique. Patients will typically cycle 28 days on medication with 28 days off.[15] Some patients may alternate 28 days of tobramycin with 28 days of aztreonam.[15] Tobramycin nebulizer products are used twice daily with a 15-minute administration time, while aztreonam is used three times a day with a shorter administration time of about three minutes.[16, 17] As with all antibiotic therapy, treatment should continue even when a patient feels better to avoid resistance and worsening lung function.

CFTR modulator therapies

Over the last decade, four CF medications have come to market in a new therapeutic class known as CFTR modulators. Unlike other available therapies that treat symptoms, CFTR modulators correct the underlying defect of CF — the malfunctioning protein.[18,19] Each of the four medications targets a specific set of gene mutations, and only patients with those specific mutations are eligible for the corresponding medication.[18]

The advent of this class of medications provided renewed hope for CF patients and families as well as anticipation for additional similar therapies to follow. The first CFTR modulator, Kalydeco (ivacaftor) was approved in January 2012, with 4% of the CF population initially being eligible.[19] Over the last seven years, the approval of three additional CFTR modulators has greatly expanded the number of eligible patients. Additionally, the most recent approval of Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor), offers the potential to treat up to 90% of the CF population.[20]

Kalydeco is known as a potentiator for the CFTR protein.[21] It enables the CFTR channel to remain open longer, thus allowing increased transport of chloride ions through the cell surface.[21,22] As Kalydeco cannot increase functioning CFTR, its function depends in part on how much CFTR protein is already present at the surface of the cell.[21] Kalydeco is indicated for patients age 6 months and older who have at least one of the following: gating mutations, residual function mutations, splice mutations or a conduction mutation.[18] Common side effects include diarrhea, dizziness, headache, nasal congestion, nausea/vomiting, rash, sore throat and stomach pain.[21]

A second CFTR modulator, Orkambi (lumacaftor/ivacaftor), was approved in July 2015. It is a combination corrector and potentiator, respectively.[23] The lumacaftor compound increases the amount of CFTR protein that reaches the cell surface, while ivacaftor allows the CFTR channel to remain open longer for the chloride ions to pass through.[22,23] Orkambi is indicated for patients 2 years and older who have two copies of the *F508del* mutation, which represents approximately 44% of CF patients.[5,23] Its common side effects are similar to that of Kalydeco, but Orkambi does have some additional serious adverse events, such as abnormal breathing, chest discomfort and increased blood pressure and drug/drug interactions, including decreased efficacy of hormonal contraceptives, which have prompted some patients to discontinue treatment.[23,24]

A third CFTR modulator, Symdeko (tezacaftor/ivacaftor and ivacaftor) was approved in February 2018. Similar to Orkambi, Symdeko is a corrector-potentiator combination.[25] Symdeko is indicated for patients 6 years and older who have two copies of the *F508del* mutation as well as patients with at least one residual function mutation or splice mutation.[18] Common side effects are similar to those of Kalydeco and Orkambi. With a better adverse event and drug/drug interaction profile compared to Orkambi, Symdeko presented an alternative for patients homozygous for *F508del*.[25]

The fourth of the CFTR modulators, Trikafta (elexacaftor, tezacaftor, ivacaftor and ivacaftor), was approved in October 2019.[20] It was possibly the most highly anticipated CF medication, for both its efficacy and breadth of reach.[20] Trikafta combines the CFTR correctors elexacaftor and tezacaftor with ivacaftor, a CFTR potentiator.[26] An important contributor to the efficacy of Trikafta is the combined effect of the two correctors, which allows for more CFTR protein to reach the cell surface.[26,27] In one study, patients with one copy of the *F508del* mutation who took Trikafta saw a 13.8% increase in lung function (FEV1) after four weeks versus those taking placebo.[27] In another study, patients with two copies of *F508del* who crossed over from Symdeko to Trikafta after four weeks saw a 10% increase in FEV1.[27] When compared to Orkambi and Symdeko, Trikafta had a significantly larger increase in FEV1 from baseline to Week 24.[23,25,26]

Trikafta is indicated for patients with at least one *F508del* mutation, which encompasses about 85% of the CF population.[5] It is the first CFTR modulator available to patients with only one *F508del* mutation (with a minimal function mutation), or about 40% of all CF patients.[5,20] Additionally, Trikafta became the third CFTR modulator available to patients homozygous for *F508del*. Presently, patients 12 years and older are eligible to receive Trikafta.[20] However, with the potential for treatment of expanded age groups, Trikafta could possibly reach approximately 90% of patients with CF.[20] With a side effect profile comparable to Kalydeco and Symdeko but more favorable than Orkambi, it remains to be seen how many patients will transition from their current CFTR modulator to Trikafta.

Table 2 summarizes dosing for the four available CFTR modulators.

Pancreatic enzyme replacement therapy (PERT)

CF patients can require nearly twice as many calories as people without CF due to physical demands of the disease and its effects on digestion and nutrient absorption.[28] Digestive system treatments and therapies are another important component of CF care. This involves the use of pancreatic enzymes and vitamins along with a nutrition program.

Pancreatic enzymes work in the intestines to assist with digestion and subsequent absorption of nutrients.[29] They are better known under the brand names Creon (pancrelipase), Pancreaze (pancrelipase), Pertzye (pancrelipase), Viokace (pancrelipase) and Zenpep (pancrelipase). According to CFF guidelines, all CF patients who meet specific clinical criteria should use PERT. This includes infants.[5] Approximately 85% of CF patients are on PERT.[5]

Pancreatic enzymes are capsules containing small beads with varying concentrations of the enzymes lipase, protease and amylase, which aid in the digestion of fats, proteins and carbohydrates, respectively.[29] Enzymes are taken by mouth before a meal or snack, including breast milk or formula.[29] PERT dosing is weight-based and individualized, depending on a patient's clinical presentation and dietary fat content.[29,30] Failure to take enzymes or taking the incorrect dose can lead to gastrointestinal symptoms including abdominal pain, constipation, frequent, loose bowel movements and gas.[29]

Other treatments

This discussion of CF treatments is not all-inclusive of every patient's CF regimen. Although treatment regimens across the CF patient population might include the same medications or therapies, each

Table 2. CFTR modulator dosing[21,23,25-26]

Age	Kalydeco[21] (ivacaftor)	Orkambi[23] (lumacaftor/ivacaftor)	Symdeko[25] (tezacaftor/ivacaftor and ivacaftor)	Trikafta[26] (elexacaftor/ tezacaftor/ivacaftor and ivacaftor)
12 years and older	X	Two tablets (lumacaftor 200mg/ ivacaftor 125mg) every 12 hours	One tablet (tezacaftor 100mg/ ivacaftor 150mg) in the morning and one tablet (ivacaftor 150mg) in the evening	Two tablets (elexacaftor 100mg/ tezacaftor 50mg/ivacaftor 75mg) in the morning and one tablet (ivacaftor 150mg) in the evening
6 years and older	One (150mg) tablet every 12 hours	X	X	X
6 to 11 years	X	Two tablets (lumacaftor 100mg/ ivacaftor 125mg) every 12 hours	Weight based - tablets	X
2 to less than 6 years	X	Weight based- granules	X	X
6 months to less than 6 years	Weight based - granules	X	X	X

All doses should be taken with a fat-containing snack or meal. Dose modifications recommended for hepatic impairment and drug/drug interactions

patient's regimen is customized.[1] Additionally, many patients may be prescribed other medications such as insulin, nasal sprays, acid suppression therapy and anti-inflammatories.

Conclusion

It remains to be seen how the advent of CFTR modulators, along with new and existing therapies, will affect CF and the lives of CF patients and their families. CF is still a fatal disease, with respiratory complications as the primary cause of morbidity and mortality.[5] However, significant advances in CF treatment over the last few decades have enabled CF patients to live longer and with an improved quality of life.

About the author

Nishita Hira, PharmD, CSP, is a clinical program manager on the clinical services team at AllianceRx Walgreens Prime. She is a certified specialty pharmacist, with a focus on CF and organ transplant. Hira has also provided expertise for Walgreens retail and community-based specialty pharmacies. She is a graduate of the University of the Sciences in Philadelphia, College of Pharmacy.

References

1. About cystic fibrosis. Cystic Fibrosis Foundation website. Accessed April 9, 2020. https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/
2. Disorder fact sheet: cystic fibrosis. Newbornscreening.info website. Updated November 30, 2012. Accessed April 9, 2020. https://www.newbornscreening.info/Parents/otherdisorders/CF.htm
3. Brown SD, White R, Tobin P. Keep them breathing: Cystic fibrosis pathophysiology, diagnosis, and treatment. JAAPA. 2017;30(5):23–27. doi: 10.1097/01.JAA.0000515540.36581.92
4. CFTR gene. U.S National Library of Medicine Genetics Home Reference website. Updated March 31, 2020. Accessed April 10, 2020. https://ghr.nlm.nih.gov/gene/CFTR
5. 2018 Patient Registry Annual Data Report. Cystic Fibrosis Foundation website. Published August 2019. Accessed April 10, 2020. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2018-Patient-Registry-Annual-Data-Report.pdf
6. Cystic fibrosis. Mayo Clinic website. Accessed April 10, 2020. https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700
7. Agent P, Parrott H. Inhaled therapy in cystic fibrosis: agents, devices and regimens. *Breathe (Sheff)*. 2015;11(2):110–118. doi: 10.1183/20734735.021014
8. Bronchodilators. Cystic Fibrosis Foundation website. Accessed April 10, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/Bronchodilators/
9. Prickett M, Naureckas ET. Chronic medications to maintain lung health clinical care guidelines. Cystic Fibrosis Foundation website. Published April 2013. Accessed April 10, 2020. https://www.cff.org/Care/Clinical-Care-Guidelines/Respiratory-Clinical-Care-Guidelines/Chronic-Medications-to-Maintain-Lung-Health-Clinical-Care-Guidelines/
10. Mucus thinners. Cystic Fibrosis Foundation website. Accessed April 10, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/Mucus-Thinners/
11. Pulmozyme. DailyMed website. Updated December 3, 2019. Accessed April 10, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d8c78a7e-ff99-48f3-8952-643ec2ea0f86
12. Airway clearance techniques (ACTs). Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/Airway-Clearance-Techniques/
13. High-frequency chest wall oscillation (the Vest). Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/High-Frequency-Chest-Wall-Oscillation/
14. Chest physical therapy. Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Airway-Clearance/Chest-Physical-Therapy/
15. Antibiotics. Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/Antibiotics/

16. Tobramycin. DailyMed website. Updated October 31, 2018. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=be8368d7-bfd0-47e8-8d69-ac5f4a4851ed
17. Cayston. DailyMed website. Updated November 25, 2019. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=67300ca3-8c53-4ce4-8e86-2c03be1f9b8a
18. CFTR modulator therapies. Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/
19. FDA approves Kalydeco™ (ivacaftor), the first medicine to treat the underlying cause of cystic fibrosis [news release]. Cambridge, MA: Vertex Pharmaceuticals Incorporated; January 31, 2012. Accessed April 13, 2020. https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecotm-ivacaftor-first-medicine-treat?releaseid=644257
20. FDA approves Trikafta™ (elexacaftor/tezacaftor/ivacaftor and ivacaftor) to treat the underlying cause of cystic fibrosis in people ages 12 and older who have at least one F508del mutation [news release]. Boston, MA: Vertex Pharmaceuticals Incorporated; October 21, 2019. Accessed April 13, 2020. https://investors.vrtx.com/news-releases/news-release-details/adding-multimedia-fda-approves-trikafta
21. Kalydeco. DailyMed website. Updated April 25, 2019. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0ab0c9f8-3eee-4e0f-9f3f-c1e16aaffe25
22. Pettit RS, Fellner C. CFTR modulators for the treatment of cystic fibrosis. *P T*. 2014;39(7):500-511. Accessed April 13, 2020. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4103577/
23. Orkambi. DailyMed website. Updated July 15, 2019. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3fc1c40e-cfac-47a1-9e1a-61ead3570600
24. Boyles S. Real-world CF study assesses tolerance for combo drug. MedPage Today website. Published October 11, 2019. Accessed April 13, 2020. https://www.medpagetoday.com/pulmonology/cysticfibrosis/82698
25. Symdeko. DailyMed website. Updated January 2, 2020. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=302ae804-37db-44fd-ac2f-3dbdeda9aa4b
26. Trikafta. DailyMed website. Updated January 29, 2020. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f354423a-85c2-41c3-a9db-0f3aee135d8d
27. Trikafta: What are the study details and results? Trikafta website. Accessed April 13, 2020. https://www.trikafta.com/study-information
28. Nutritional basics. Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Daily-Life/Fitness-and-Nutrition/Nutrition/Getting-Your-Nutrients/Nutritional-Basics/
29. Enzymes. Cystic Fibrosis Foundation website. Accessed April 13, 2020. https://www.cff.org/Life-With-CF/Daily-Life/Fitness-and-Nutrition/Nutrition/Taking-Care-of-Your-Digestive-System/Enzymes/
30. Creon. DailyMed website. Updated March 25, 2020. Accessed April 13, 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=073201aa-556d-4a70-918e-84e9616fd88d

Walgreens | allianceRx Walgreens + PRIME