Chapter 6
Treatment of Cystic Fibrosis

The treatment of cystic fibrosis (CF) requires a multi-pronged approach to target dysfunction in a number of organ systems. Although the advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies heralds a new era in CF care, their full impact on CF remains to be determined, and older patients with CF are likely to still have complications of CF that need to be addressed.

6.1 Gastrointestinal Disease and Nutrition

6.1.1 Pancreatic Enzyme Replacement Therapy

Approximately 85 % of patients with CF are pancreatic insufficient (PI), and pancreatic enzyme replacement therapy (PERT) is empirically prescribed for patients with PI genotypes or who present with clinical features suggestive of malabsorption [1]. Once the diagnosis of PI is confirmed the use of PERT is universally indicated. For most individuals, a lipase dose of 2000–2500 units of lipase per kg per meal is preferred and a maximum daily lipase dose of 10,000 units/kg should be maintained if possible [2]. There are differing clinical responses to various brand name enzyme preparations so close attention should be given to the medication that is dispensed. The use of acid blocking therapy, such as H2 receptor antagonists and

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proton pump inhibitors, is common due to deficient bicarbonate secretion and altered intestinal pH that is associated with exocrine pancreatic failure [3]. These agents may help raise duodenal pH and improve the action of pancreatic enzyme supplements. Poor mealtime behaviors in some young children with CF may adversely affect caloric intake and cognitive behavioral therapy may be beneficial [4].

6.1.2 Caloric Supplementation

There is a well-established link between nutritional status and lung function (Fig. 6.1). Nutrition early in life is especially important, since poor nutrition in early childhood is associated with lower lung function in later childhood and decreased survival [5, 6].

Patients with CF have high caloric requirements; caloric supplementation is often required whether they are PI or not. Breast milk is the preferred source of nutrition for infants with CF and supplementation with fortifier, formula powder, and lipids may be necessary to achieve adequate growth. Infants should not be fed soy formula, since soy

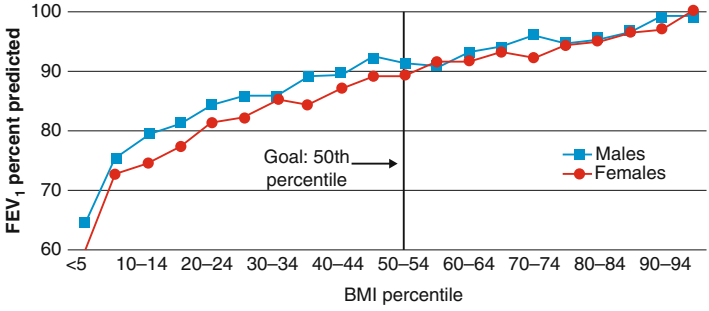

FIGURE 6.1 Median forced expiratory volume in 1 s predicted versus median body mass index percentile for children between 6 and 19 years old. The goal of the US Cystic Fibrosis Foundation is for all patients with cystic fibrosis to have a body mass index in at least the 50th percentile. *BMI* body mass index, *FEV1* forced expiratory volume in 1 s

protein appears to be have less bioavailablity compared to cow's milk or breast milk proteins. High fat diets are encouraged in children and adults. Commercial oral supplements are often used to bolster caloric intake. However, there are still many individuals that will have tremendous caloric needs that may necessitate consideration of gastrostomy tube placement, or in some cases jejunostomy tube placement, to provide enteral feeding. Supplemental enteral feedings have been demonstrated to improve nutritional outcomes in CF [7–9].

Poor appetite is reported by many patients and appetite stimulation may be attempted. Cyproheptadine may be an effective treatment for anorexia in CF and is most effective during the first few months of use. Cyprohepatidine may be preferable to megesterol or drorabinol, as the former has exogenous steroid effects that may be unacceptable [10].

6.1.3 Other Supplemental Therapy

Despite use of PERT, most patients with CF who are PI require supplementation of the fat soluble vitamins A, E, D, and K. Some individuals may require additional supplementation of individual vitamins depending on serum levels. Annual monitoring of vitamin levels is indicated, with more frequent follow-up of suboptimal levels after additional supplementation [2]. Salt supplementation is recommended during infancy, and a high salt diet is generally recommended in older children and adults. This is of particular importance for patients who incur high sodium losses through sweat, and are therefore at risk for the development of hyponatremic dehydration [11].

6.1.4 Hepatobiliary Disease

The management of hepatobiliary disease in CF can be challenging as it is often clinically silent [12–14]. Many individuals with elevated transaminases or ultrasonographic evidence of disease

may not develop progressive liver disease regardless of treatment. Ursodeoxycholic acid is frequently prescribed to improve bile flow in patients with chronic CF-related liver disease, although there are no data regarding its effectiveness in delaying the progression of CF liver disease. There is an increased risk for cholelithiasis and cholecystitis in CF that may require surgical management in symptomatic individuals. The need for liver transplantation due to CF-related hepatobiliary disease is uncommon and is reserved for those patients with recurrent variceal bleeding from severe portal hypertension or synthetic dysfunction due to end-stage cirrhosis and hepatic failure.

6.1.5 Intestinal Obstruction

Chronic constipation is a common complication in CF. The management of constipation in CF may include stool softeners and increased fluid intake. Polyethylene glycol (PEG) solutions have been advocated for treatment of CF-related constipation. Distal intestinal obstruction syndrome (DIOS) is a related gastrointestinal (GI) complication of CF that is thought to result from impaction of mucus and stool in the GI tract of patients with CF, leading to small bowel obstruction at the terminal ileum and ileocecal valve [15]. Initial treatment of DIOS is similar to management of any bowel obstruction. If the patient is vomiting, a nasogastric (NG) tube should be placed to decompress the stomach. Polyethylene glycol can then be administered either orally or via the NG tube, initially at low volume and then increasing until the bowels are cleared out of stool and mucus. N-acetylcysteine or gastrograffin enemas can also be used to relieve distal obstruction at the ileocecal valve. Surgical intervention is a last resort and usually not required.

6.2 Pulmonary Disease

Pulmonary disease and respiratory failure is the overwhelming cause of morbidity and mortality in CF. Treatment of CF lung disease has evolved from acute treatment focused on

Table 6.1 Chronic pulmonary therapies used in patients with cystic fibrosis. Therapies are grouped by class or mechanism of action

Chronic pulmonary therapies used in patients with cystic fibrosis
Airway clearance therapies
Manual chest percussion
High frequency oscillating chest wall devices
Hand-held oscillatory positive pressure devices
Autogenic drainage/active cycle of breathing techniques
Anti-infectives
Inhaled tobramycin[a]
Inhaled aztreonam[a]
Mucolytics
DNase[a]
Hydration therapies
Hypertonic saline[a]
Anti-inflammatory therapy
Oral corticosteroids
High dose ibuprofen
Low dose azithromycin[a]

[a]Denotes that the therapy has been shown to reduce the risk of pulmonary exacerbation

symptom relief to a chronic therapy approach to maintain pulmonary health and prevent exacerbations. Table 6.1 summarizes the chronic pulmonary therapies currently used in patients with CF. The number of therapeutic options has increased markedly in the last few years, and one of the challenges facing CF clinicians and their patients is balancing the potential benefits of multiple therapies with the increased treatment burden.

6.2.1 Airway Clearance Therapies

The mainstay of preventative pulmonary treatment is airway clearance, which is introduced at or shortly after diagnosis [16]. Airway clearance facilitates mucus transport and can alleviate bronchial obstruction by secretions [17]. There are various modalities that can be used, depending on age. Instruction on chest percussion with postural drainage is initially taught to parents of infants and young children with CF. High frequency oscillating chest wall devices are commonly prescribed as they are less labor-intensive and thus can be managed by one caregiver or by the patient without assistance. These devices consist of an inflatable vest that surrounds the thorax. The vest is connected via a hose to a compressor that generates low amplitude, high frequency pressure oscillations, which in turn create shear forces in the airway that help mobilize airway secretions. Hand-held oscillatory positive pressure devices are another option. These devices use the patient's own expiratory flow to generate intraluminal pressure oscillations. Autogenic drainage and active cycle of breathing are techniques that utilize inspiratory and expiratory maneuvers for airway clearance. There have been very few studies comparing the efficacy of one method over another and the US Cystic Fibrosis Foundation guidelines do not recommend a specific method [16], although they do note that individuals may respond better to one method than another so airway clearance therapy should be personalized for the patient [16].

Standard instruction involves performance of airway clearance twice daily, even in asymptomatic patients. During illness and for those with progressive bronchiectasis the frequency of airway clearance should be increased and the use of different modalities should be considered. An active lifestyle should be encouraged in children and adults with CF. A daily exercise program is considered an important adjunct for the maintenance of pulmonary health and can augment the benefits of airway clearance.

Exercise has also been associated with higher quality of life scores and less severe respiratory scores on validated questionnaires [18].

6.2.2 Bronchodilators

Bronchial hyperresponsiveness is present in more than 30 % of patients with CF [19] and bronchodilators have been recommended for routine use in the past, although evidence is lacking for their efficacy. The most recent version of the US Cystic Fibrosis Foundation clinical practice guidelines does not recommend for or against their use [20]. It remains common to prescribe bronchodilators in conjunction with airway clearance or prior to hypertonic saline (HS) administration. The latter therapy can sometimes be associated with bronchoconstriction, hence the rationale of pretreatment with a bronchodilator. In most cases, the bronchodilator used is a selective beta-2 agonist, such albuterol. However, there is some evidence to suggest that anticholinergics, such as ipratropium, may also be beneficial [21, 22].

6.2.3 Dornase Alfa

Dornase alfa (recombinant human DNase 1) is an endonuclease that cleaves long filamentous strands of DNA into shorter pieces. CF sputum contains copious amounts of DNA, primarily derived from neutrophils, and DNase can help markedly reduce sputum viscosity. Dornase alfa therapy has been demonstrated to increase lung function and decrease pulmonary exacerbations [23]. It is recommended for routine use once daily in children over 6 years of age and adults [20]. Its use in patients under 6 years of age has become increasingly common, particularly in those with chronic respiratory symptoms or other evidence of lung disease. Its use is recommended in children aged 2–5 years, depending on the child's symptoms or history [24]. The use of twice daily dornase alfa has been employed in more

advanced bronchiectasis, although there is no evidence to support this increased frequency.

6.2.4 Hypertonic Saline

HS is thought to help rehydrate the airway surface liquid (ASL) through increasing the tonicity and passively drawing in tissue water. Elkins et al. [25] demonstrated that chronic HS therapy resulted in increased forced expiratory volume in 1 s (FEV_1) and reduced pulmonary exacerbations in patients aged 6 years and older. A large randomized trial of HS in children younger than 6 years of age with CF failed to demonstrate an effect on its primary outcome measure, pulmonary exacerbation, although there were physiologic improvements [26]. The US Cystic Fibrosis Foundation currently recommends chronic HS therapy in patients ≥6 years old and its use can be considered for patients 2–5 years of age [20, 24].

6.2.5 Anti-inflammatory Therapies

With the increased understanding of the important role inflammation plays in the pathogenesis of CF lung disease clinicians and investigators have long sought safe, easily administered, effective anti-inflammatory therapies. Despite this, such a treatment is still not available. Caution regarding anti-inflammatory therapy has been raised. In a randomized trial of an oral leukotriene B4 receptor antagonist in CF there was a higher rate of pulmonary exacerbations in the treatment group, suggesting that excessive attenuation of the inflammatory response may have unwanted deleterious effects [27].

High dose ibuprofen (HD-Ibu) has been shown to inhibit neutrophil migration in rodent models of chronic *Pseudomonas aeruginosa* infection, and based on this observation a randomized clinical trial of HD-Ibu was conducted in patients with CF ≥5 years of age [28]. The results of this

study showed that the treatment group had a slower rate of decline in FEV_1 (-1.48 ± 0.69) compared to the placebo group (-3.57 ± 0.65) [26]. Children between 5 and 17 years of age had the greatest benefit, suggesting that the treatment is more effective in patients with less advanced or established bronchiectasis. The dose for HD-Ibu is 20–30 mg/kg twice daily, which is much higher than standard antipyretic or analgesic doses. Furthermore, individual pharmacokinetics must be performed on a biannual basis to ensure that an ibuprofen serum concentration of 50–100 mg/L is achieved. The need for individual pharmacokinetic studies and concern about potential adverse effects, such as gastrointestinal bleeding and renal disease, may be reasons why very few patients are on HD-Ibu [29]. Nonetheless, the data regarding HD-Ibu serve as important proof-of-concept evidence of the role of inflammation in the pathophysiology of CF lung disease and the therapeutic efficacy of anti-inflammatory therapy.

Macrolide antibiotics also appear to have an anti-inflammatory effect that is independent of their antimicrobial properties. Randomized clinical trials of azithromycin 250 mg (or 500 mg if weight is >40 kg) three times weekly have demonstrated improved FEV_1 in patients ≥6 years old who are chronically infected with *P. aeruginosa* [30] and a lower rate of pulmonary exacerbations in patients 6–18 years old without *P. aeruginosa* infection [31]. Based on these results the US Cystic Fibrosis Foundation currently recommends that chronic azithromycin therapy be considered in patients with CF ≥6 years of age [20]. Contraindications for this treatment include the presence of non-tuberculous mycobacterial (NTM) infections or severe liver disease.

Oral and inhaled corticosteroids have been studied in CF [32]. Alternate day prednisone can improve lung function, but at the cost of growth retardation, glucose intolerance, and cataract formation [33]. They are not recommended for routine use, although some clinicians may use them in severe or advanced lung disease, and they clearly have a role in treatment of allergic bronchopulmonary aspergillosis (ABPA). Inhaled corticosteroid (ICS) therapy has been associated with a lower rate of FEV_1 decline [34]. Although, there have

been no randomized clinical trials of ICS that demonstrate improvement in lung function or reduction in pulmonary exacerbation rates. The US Cystic Fibrosis Foundation currently recommends against routine use of ICS in the absence of a diagnosis of asthma [20]. Despite this recommendation approximately 50 % of patients with CF in the US are receiving ICS therapy [35].

6.2.6 *Anti-Infective Therapy*

Another hallmark of CF lung disease is chronic bacterial airway infection, and antibiotic therapy has a major role in the treatment of CF [36]. Antibiotics can be administered chronically and acutely, as well as via the oral, inhaled, and intravenous route.

The persistence of *P. aeruginosa* in CF respiratory cultures is associated with a more rapid deterioration of pulmonary function as well as increased mortality [37]. Surveillance for *P. aeruginosa* infection using oropharyngeal swab or sputum cultures has become standard of care in CF. Eradication of *P. aeruginosa* infection at first isolation can be achieved with the use of 28 days of inhaled tobramycin with or without the addition of ciprofloxacin. A culture based regimen, where respiratory cultures are obtained quarterly and antibiotics are only given if *P. aeruginosa* is cultured, is equally effective as a cycled treatment regimen, where antibiotics are given quarterly regardless of respiratory culture results [38]. Similar eradication regimens have been achieved with the use of colistimethate and aztreonam [39, 40].

Inhaled antipseudomonal antibiotics increase lung function and reduce pulmonary exacerbations in patients with chronic *P. aeruginosa* infection. The alternate month use of inhaled tobramycin solution twice daily, or inhaled aztreonam lysine three times daily, have both been studied and are effective regimens in improving lung function and reducing the risk of pulmonary exacerbations [41, 42]. Both treatment strategies have been demonstrated to reduce pulmonary exacerbations and improve lung function, even in patients

with mild disease [43, 44]. The use of inhaled vancomycin for individuals with methicillin-resistant *Staphylococcus aureus* (MRSA) is under investigation. A dry powder formulation of colistimethate sodium for inhalation is available in Europe for the treatment of patients with CF and *P. aeruginosa* infection, but this medication is not available in the US at time of writing.

With regard to chronic oral antistaphylococcal antibiotics, their routine use is not currently recommended by the US Cystic Fibrosis Foundation, although it is common practice in other countries [45]. While there is a decrease of staphylococcal burden with chronic antibiotic use the emergence of earlier *P. aeruginosa* infection has tempered antistaphylococcal use in the US.

6.2.7 Pulmonary Exacerbations

Treatment of pulmonary exacerbations remains highly variable and there is a paucity of high quality evidence to guide treatment. The Pulmonary Therapies Committee of the US Cystic Fibrosis Foundation has suggested guidelines for management of exacerbations, including recommendations regarding site of treatment (in hospital versus outpatient), number of antibiotics used and dosing of antibiotics targeting *Pseudomonas*, and synergy testing. They do not make specific recommendations regarding duration of treatment [46].

Early recognition of symptoms is imperative in order to treat an exacerbation and avoid hospitalization or parenteral antibiotics. Increasing airway clearance and the early use of oral antibiotics directed against the individual's microbiology are cornerstones of treatment. In individuals with more severe or rapidly progressive symptoms, or in those who fail to respond to first-line treatment, parenteral antibiotics and more aggressive airway clearance are used. Traditionally, the choice of antibiotics has been based on organisms that are recovered from respiratory cultures, although there is evidence to suggest that clinical response is not related to in vitro antibiotic sensitivities [47].

Monotherapy is often used for the treatment of methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA, whereas a two drug regimen is typically used for patients with *P. aeruginosa* infections. An aminoglycoside (tobramycin or amikacin) in addition to a beta-lactam (ceftazidime, piperacillin/tazobactam, meropenem), monobactam, or quinolone is preferred. The duration of treatment is traditionally 14 days, although shorter duration of treatment may be effective in some individuals. Conversely, some patients may benefit from up to 21 days of therapy, although treatment beyond that duration is unlikely to provide additional benefit. Patients who received multiple courses of aminoglycoside as part of their pulmonary exacerbation treatment should be routinely screened for hearing loss and kidney injury. Treatment of *Burkholderia cepacia* complex infections is often more challenging due to antibiotic resistance. A variety of agents have been used including ceftazidime, meropenem, trimethoprim/sulfamethoxazole, and minocycline. The presence of other resistant Gram-negative rods, such as *Stenotrophomonas maltophilia* or *Achromobacter xylosoxidans*, can further complicate the clinical picture, however, the causative effect of these bacteria on exacerbations is not clearly understood.

Atypical infections are also encountered in the CF airway and may lead to worsening pulmonary disease. Fungal disease unrelated to ABPA may be targeted with antifungal treatment, based on sensitivities. Non-tuberculous mycobacteria (NTM) are seen with increasing prevalence as the CF population ages. *Mycobacterium avium* complex (MAC) infections are the most common, followed by 'rapid growers' such as *Mycobacterium abscessus* complex infections [48]. These latter organisms have been associated with severe lung disease in some cases. Treatment of mycobacterial infections is difficult and may require three or four agents for 9 months or longer. Recent consensus guidelines for management of mycobacterial infections have been published by the US Cystic Fibrosis Foundation and European Cystic Fibrosis Society [49].

6.2.8 Other Pulmonary Complications

ABPA is a hypersensitivity pneumonitis with allergic features that occurs more commonly in the CF population [50]. Treatment generally is with systemic glucocorticoids, and may also include antifungals or anti-immunoglobulin E (IgE) antibody therapy [51].

Hemoptysis and pneumothoraces are two other pulmonary complications that can occur in patients with CF. Hemoptysis can range from scant streaks of blood in sputum to massive, life-threatening hemorrhage. The US Cystic Fibrosis Foundation Pulmonary Guidelines recommend that for scant amounts of hemoptysis (<5 mL), airway clearance and nebulized therapies should be continued, but there is no consensus as to whether antibiotics need to be prescribed in the absence of other symptoms of an exacerbation [52]. In the case of major hemoptysis, intravenous antibiotics are indicated, with some clinicians advocating empiric coverage for *S. aureus* while awaiting culture results. Guidelines also recommend discontinuing chest physiotherapy, HS, and non-steroidal anti-inflammatories. When a patient is clinically unstable or when bleeding is persistent or recurrent bronchial artery embolization is recommended. It is successful in stopping bleeding in most cases but recurrence is relatively common, often requiring re-embolization. Surgical resection is generally reserved for times when all other options have been exhausted, with lobectomy being the most common procedure performed.

Pneumothoraces in patients with CF can similarly have a wide range of severity. Cystic Fibrosis Pulmonary Guidelines recommend that patients with larger pneumothorax should be admitted to the hospital and should have a chest tube placed for drainage [52]. Pleurodesis is recommended for patients who develop a recurrence of large pneumothorax. Recurrence is fairly common and is seen in over half of patients. A surgical pleurodesis is recommended over chemical pleurodesis [52]. The US Cystic Fibrosis Foundation Pulmonary Guidelines recommend that positive pressure,

such as continuous positive airway pressure or bilevel positive airway pressure, be withheld until the air leak has resolved. Patients should not perform spirometry, fly on a plane, or lift weights for at least 2 weeks following resolution of the pneumothorax.

6.2.9 *Lung Transplantation*

Patients who develop progressive loss of lung function with subsequent evidence of chronic respiratory failure, frequent pulmonary exacerbations, and poor quality of life may be candidates for bilateral lung transplantation [53]. A variety of risk models have been developed to identify patients who are more likely to benefit from lung transplant and should be listed [54]. Specific criteria for listing vary by transplant center and incorporate considerations of disease severity and adherence. Important predictors of success following lung transplantation include nutritional status, exercise tolerance, and microbiology. While 1 year post-transplantation survival statistics are favorable (around 90 %), 5-year outcome data continues to demonstrate survival at 50–60 % [55]. The main cause of long-term death is bronchiolitis obliterans syndrome (BOS). BOS is characterized by progressive narrowing and ultimately fibrosis of the small airways as a result of chronic graft rejection.

6.3 Cystic Fibrosis-Related Diabetes

Over time, progressive fibrosis of the pancreas in patients with CF results in the development of diabetes mellitus. Cystic fibrosis-related diabetes (CFRD) is a unique form of glucose intolerance that is different from type 1 and type 2 diabetes mellitus. Although insulin production is insufficient in CFRD, patients usually produce enough residual insulin to avoid diabetic ketoacidosis. The treatment of CFRD generally involves insulin therapy [56]. Oral hypoglycemic agents

are not typically effective in the setting of pancreatic destruction and limitation of caloric intake is discouraged. Rather, calculation of carbohydrate intake followed by administration of appropriate short-acting insulin coverage is preferred. Long-acting insulin has also been used successfully. A hallmark of CFRD is global islet cell destruction, which leads to both insulin and glucagon deficiency. Therefore, treatment for hypoglycemia may be necessary.

6.4 Sinusitis and Nasal Polyposis

Sinus disease may be a source of morbidity in CF. Inspissated mucus may lead to chronic infection and inflammation. The use of saline nasal sprays and rinses may be effective in clearing secretions. Nasal steroids and montelukast may also be effective to decrease nasal inflammation and reduce polyp formation. A longer (several weeks) duration of oral, nasal, or parenteral antibiotics may be used for the treatment of sinusitis. Failure of medical therapy may lead to endoscopic sinus surgery.

6.5 Other Cystic Fibrosis Therapies

Patients with CF are at increased risk for salt loss and hyponatremic dehydration. Breast milk and infant formulas tend to be low in salt, therefore salt supplementation is recommended for infants until they have transitioned to a primarily table food diet. Older patients with CF who are engaging in intense physical activity, especially during the summer, should also take salt supplements.

Males with CF have azoospermia due to atresia and obstruction of the vas deferens, although, using microsurgical epididymal sperm aspiration (MESA) and in vitro fertilization, they are able to father their own biologic children. CF clinicians should counsel their male patients during adolescence about the option of MESA.

6.6 CFTR Modulators

CFTR modulators are small molecules that can restore partial or complete CFTR function in defective CFTR proteins [57, 58]. CFTR modulators can be divided into two broad classes; CFTR potentiators and CFTR correctors. CFTR potentiators bind to CFTR and increase the open channel probability of the protein, thereby increasing chloride (Cl) conductance. CFTR correctors bind to mutant CFTR mRNA or proteins and correct their transcription or processing defects, increasing surface expression of the protein. Because CF is an autosomal recessive condition and carriers are known to be unaffected, correction of a single mutant allele in a patient with CF should be enough to prevent disease. In fact, studies of CFTR function in patients with CFTR-related disorder (CFTR-RD) suggest that as little as 20–30 % of wild type CFTR function is enough to prevent disease [59]. Potentiators and correctors are small molecules that were discovered by using high throughput screening to search large medicinal chemical libraries for compounds with potentiator or corrector capacity.

At present there is only one CFTR potentiator available for clinical use — ivacaftor. Ivacaftor is a CFTR potentiator that can increase Cl conductance in class III mutations. It was initially introduced into clinical use in 2012 for patients with at least one copy of the G551D mutation. Treatment with ivacaftor in patients with this mutation resulted in improvement of lung function, pulmonary symptoms, quality of life scores, nutritional status, and decreased sweat Cl values [60]. It has now been approved for use in CF for several other class III gating mutations and R117H (class IV mutation). Together, these mutations are present in about 10 % of the US CF population [35]. Currently, ivacaftor is indicated for patients with CF who are 2 years of age and older with G551D, R117H, and a small number of other gating mutations, and the US Cystic Fibrosis Foundation recommends its use in these patient populations [20].

The most common CF-causing mutation, F508del, results in a CFTR protein that folds improperly and has reduced Cl conductance. The former property leads to F508del CFTR being degraded in the golgi, and <1 % of the protein is expressed on the cell surface [61]. Due to this, F508del CFTR is not responsive to ivacaftor alone. Lumacaftor is a CFTR modulator that partially corrects the folding defect in F508del, increasing surface expression of the protein [62]. A combination of lumacaftor and ivacaftor has been shown in randomized clinical trials to improve FEV_1 and decrease the rate of pulmonary exacerbations [63], and lumacaftor/ivacaftor is currently approved by the US FDA for patients with CF who are homozygous for the F508del mutation and are ≥12 years old. In the US, these patients comprise approximately 45 % of the total CF population in the country [35, 63].

Ataluren is a small molecule that allows read-through of mutations with a premature stop codon (nonsense mutations/class I mutations). In patients with class I mutations, ataluren can improve CFTR-mediated ion flux and increase CFTR expression in airway epithelial cells [64]. Ataluren is currently preregistered in the EU and completing Phase III clinical trials in the US, and if the results are favorable it may be available for clinical use.

It remains unclear whether the use of CFTR modulators will decrease the treatment complexity for individuals with CF. Longer duration follow-up of adverse and clinical effects is necessary before it can be determined if these agents may be able to supplant any of the chronic therapies for CF, both for pulmonary complications as well as other organ systems affected by CF. The degree of pre-existing disease prior to starting CFTR modulators may also affect the need for continued CF maintenance therapies. More potent CFTR modulators are also currently under development, and they may have a greater impact on need for other chronic CF therapies.

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