Updates on the Management of Cystic Fibrosis: Development of Modulators and Advancement of Antibiotic Therapies

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INTRODUCTION

Cystic fibrosis (CF) is a rare autosomal recessive, multi-organ disease that affects over seventy thousand people worldwide. While CF is the most common heritable disease in Caucasians, improvements in newborn screening and wider availability of genetic testing have shed light on the increasing incidence in non-Caucasian individuals.[1] In decades past, CF was a disease of childhood that was often fatal before adulthood. However, utilization of dedicated multidisciplinary care centers and advances in therapeutics have led to dramatic improvements in lifespan and quality of life. The median life expectancy for persons with cystic fibrosis (PwCF) is now approaching fifty years in many countries.[1]

CF was first characterized in 1938 after the discovery of pancreatic fibrosis in individuals with steatorrhea and nutritional deficiencies previously attributed to celiac disease.[2] Several decades later the discovery of increased sweat salinity in this population led to the development of the preferred diagnostic study, the sweat chloride test.[3,4] While CF was believed to be caused by a recessive genetic defect as early as the 1940s, the cystic fibrosis transmembrane regulator (CFTR) gene was not discovered until 1989.[5,6] The genetic hallmark of CF is absent or impaired function of the CFTR protein and over 2,000 pathogenic variants of the CFTR gene have been described.[7] The most common pathogenic mutation is the deletion of phenylalanine in position 508 (F508del), which results in misfolding of the CFTR protein.[8]

CFTR is present on epithelial membranes in the lungs, gastrointestinal tract, and exocrine pancreas, and is responsible for the chloride transport vital to normal mucus production, function, and clearance. CFTR also has an important role in bicarbonate transport and regulation of the epithelial sodium channel (ENaC), two major determinants of mucosal pH and fluid movement across the cellular membrane. In PwCF, decreased or absent CFTR leads to thick mucus, impaired ciliary function, and altered mucosal pH, ultimately resulting in decreased ability to clear respiratory secretions, recurrent respiratory infections and inflammation, nutrient malabsorption, and exocrine pancreas dysfunction. Research has also demonstrated direct and indirect effects of the dysfunctional CFTR protein on the innate and adaptive immune systems, further predisposing to recurrent lung infections, bronchiectasis, and reduced lung function. These injuries ultimately lead to respiratory failure, the major cause of mortality in PwCF.

The last decade has brought tremendous progress to the treatment of CF. Novel therapeutics, particularly medications designed to improve the production of functional CFTR, collectively termed modulators, have the capacity to improve lung function, decrease pulmonary infections, and improve quality of life. This article will review the development and validation of modulator therapies, as well as discuss updates on the state of antibiotic therapies, two mainstays of modern CF care.

NOVEL THERAPEUTICS: MODULATORS

Production of functional CFTR protein is a multistep process that includes transcription of deoxyribonucleic acid (DNA) into messenger ribonucleic acid (mRNA), translation into a sequence of amino acids, processing to fold and transport the resultant protein to the cell membrane and maintaining proper gating and stability to allow sufficient ion conductance. Mutations in the CFTR gene that prevent any of these processes from occurring correctly can result in functional protein deficiency and serve as potential therapeutic targets. CFTR mutations are classified into six categories based on their primary downstream effect, though one mutation may cause defects in multiple classes.

Class I, II, and III mutations involve premature termination codons, protein processing mutations, and gating mutations, respectively, leading to minimal or no CFTR activity and severe clinical phenotypes. These mutations are classified as minimal function (MF) mutations and are often not amenable to targeted therapies. Class IV mutations affect ion conductance, class V mutations blunt CFTR protein production, and class VI mutations cause instability at the cell surface. Class IV, V, and VI mutations are classified as residual function (RF) mutations because some functional CFTR is formed, typically generating less severe clinical phenotypes.[9] These mutations have become some of the first therapeutic targets for modulator therapies (**Figures 1 and 2**).

Figure 1. CFTR Mutation Classification

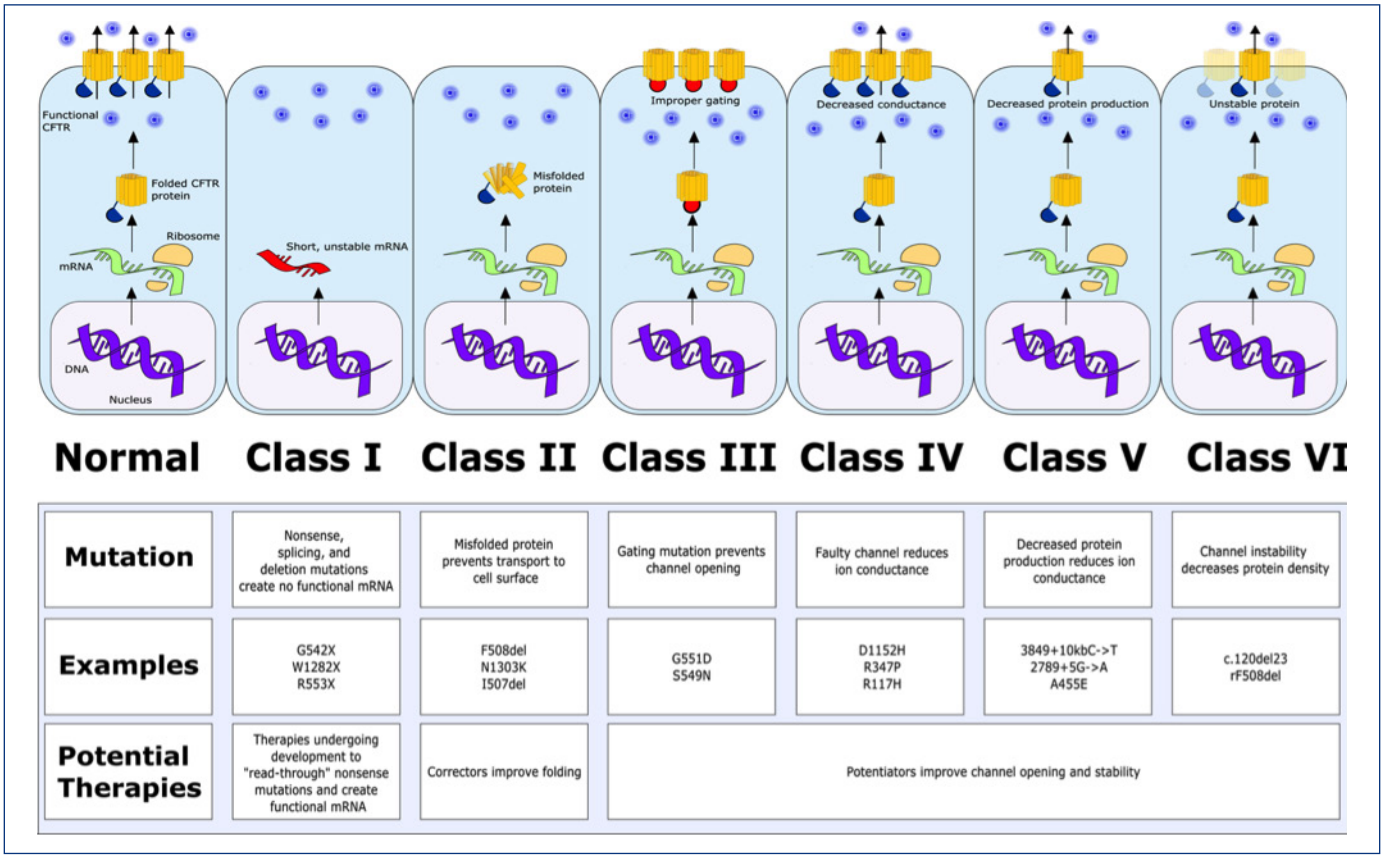
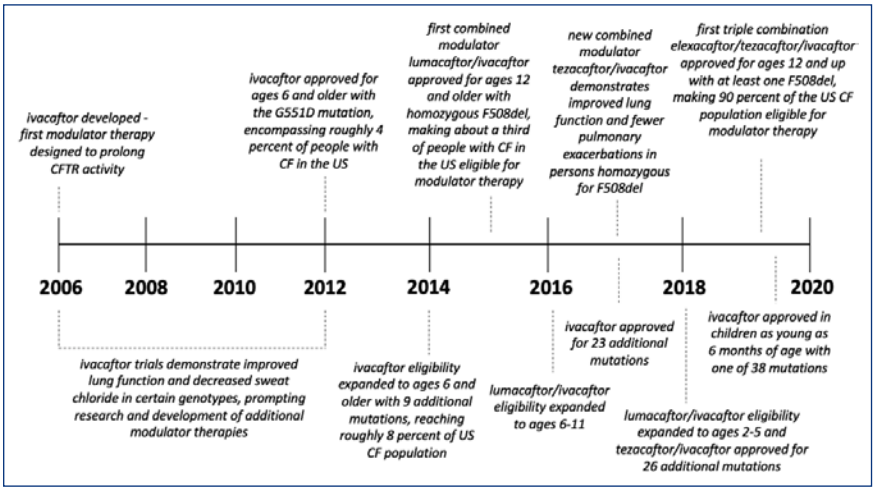


Figure 2. Timeline of Modulator Therapy Development and Approval



Ivacaftor

In 2006, ivacaftor (Kalydeco®) was developed and became the first modulator to enter clinical trials. Ivacaftor acts on CFTR gating, prolonging the duration of CFTR opening. This type of therapy is known as a "potentiator," because it prolongs the activity of CFTR already present at the cell surface. In 2007, a pilot clinical trial demonstrated significant improvement in clinical outcomes with ivacaftor including an 8.7 percent increase in percent predicted forced expiratory volume in one second (ppFEV1) and median decrease in sweat chloride by –59.5 mmol/L.[10] Ivacaftor became available in the United States (US) in 2012 for patients six years and older with one specific CF mutation (G551D). Despite the drug's limited eligibility, this landmark discovery demonstrated clinically meaningful improvements in lung function and laid the groundwork for future study. Additionally, a recent observational study that followed US patients starting ivacaftor within the first years of commercial availability provided evidence that the benefits of ivacaftor extend well beyond improved lung function. This study demonstrated that in the subsequent three years, patients taking ivacaftor experienced significantly lower risk of death, transplantation, hospitalization, pulmonary exacerbations, CF-related diabetes, bone or joint complications, and cultures involving methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and Aspergillus species.[11]

Throughout the decade following its initial approval, the FDA progressively expanded approval for ivacaftor to ultimately include patients four months of age and older with 38 RF mutations.[9] Still, by 2014 only approximately eight percent of the US CF population qualified for ivacaftor based on their mutations.

Lumacaftor

The next modulator to be developed was lumacaftor, the first member of a class of "correctors." Correctors are named for their ability to restore the shape of poorly processed CFTR protein, thereby improving successful transit to and activity in the cell membrane. Although in vitro studies suggested that lumacaftor increases the density of functional CFTR at the cell surface, phase II clinical trials in patients with homozygous F508del mutations were only able to demonstrate a dose-dependent decrease in sweat chloride levels. There was no improvement in clinically relevant endpoints such as lung function or patient-reported outcomes.[12] However, when combined with the potentiator ivacaftor, the combination lumacaftor/ivacaftor (known as Orkambi®) was shown in phase II and III clinical trials to improve ppFEV1 by 2.6–4.0 percentage points, decrease pulmonary exacerbations by 30–39 percent, and decrease events leading to hospitalization and use of intravenous antibiotics when compared with placebo.[13,14] As a result, in 2015 the FDA approved lumacaftor/ivacaftor for patients ages 12 and older who are homozygous for the F508del mutation, expanding availability of modulator therapy to approximately one third of US PwCF. Subsequently, studies demonstrated reduced pulmonary exacerbations to approximately 0.6 exacerbations per patient per year with lumacaftor/ivacaftor when compared with placebo.[15] Another study demonstrated sustained benefit in slowing ppFEV1 decline over an extended study period of 96 weeks, and two additional clinical trials redemonstrated efficacy and safety in younger populations.[16-18] Together, trials supporting lumacaftor/ivacaftor led to FDA approval for patients aged two and older by 2018.

Tezacaftor

In 2017, another corrector called tezacaftor was developed, with a similar structure to lumacaftor but improved pharmacokinetics and fewer respiratory side effects.[9] It was tested alone in phase II clinical trials and in combination with ivacaftor in phase II and III trials, both in patients homozygous for F508del and in patients with one F508del mutation and another RF mutation. Phase II clinical trials demonstrated decreased sweat chloride levels in higher-dose tezacaftor and in most tezacaftor/ivacaftor groups compared with placebo, but increased ppFEV1 only in tezacaftor/ivacaftor combination groups.[19] Combination tezacaftor/ivacaftor (Symdeko®) was found to increase ppFEV1 in patients homozygous and heterozygous for F508del with an additional RF mutation.[19,20] Phase III clinical trials demonstrated four percent absolute increase in ppFEV1 and 35 percent decrease in pulmonary exacerbations with tezacaftor/ivacaftor compared to placebo.[21] In 2018, the FDA approved tezacaftor/ivacaftor for patients 12 years and older homozygous for F508del or heterozygous F508del with a second RF mutation. This again markedly increased the pool of PwCF eligible for modulator therapy. Following publication of a phase III clinical trial that demonstrated a similar safety profile with tezacaftor/ivacaftor in patients ages six through 11, FDA approval was extended to this age group in 2019.[22]

Elexacaftor

Nearly a decade after the introduction of ivacaftor, new modulators and combinations were undergoing development and preclinical trials. Although major advancements had been made, improvements in lung function with available modulator treatments remained limited and there were minimal options for patients with certain mutations, particularly MF mutations.[9] However, 2019 proved to be another landmark year for the CF community when a triple therapy containing two correctors, elexacaftor and tezacaftor, and potentiator ivacaftor was released for patients 12 years and older with at least one F508del mutation. This extended availability of modulator therapy to nearly 90 percent of PwCF. Further, phase III clinical trials demonstrated marked improvement with 41.8mmol/L decrease in sweat chloride, 14.3 percent increase in ppFEV1 over 24 weeks, 63.0 percent decrease in pulmonary exacerbations, and a 20.2 point increase in the Cystic-Fibrosis Questionnaire-Revised score indicating improved quality of life with elexacaftor/tezacaftor/ivacaftor (Trikafta®) compared with placebo.[23] Studies are underway evaluating the safety and efficacy of elexacaftor/tezacaftor/ivacaftor long-term and in younger populations. Additionally, an ongoing observational study entitled PROMISE aims to assess for broader systemic improvements with triple therapy.

There are several treatments designed to restore CFTR function that are currently undergoing phase II clinical trials including correctors, potentiators, and a compound designed to target premature termination mutations. Others are currently in phase I clinical trials, including a potentiator and an inhaled therapy designed to deliver CFTR mRNA to the lungs.

UPDATES ON ANTIBIOTIC THERAPIES

PwCF are chronically colonized with bacteria that alter the lung microbiome.[24] Common pathogens include *Staph aureus* and *Hemophilus influenzae* in early disease with progression to resistant organisms that can form biofilms such as *Pseudomonas aeruginosa* and *Burkholderia cepacia.* Colonization with *Pseudomonas aeruginosa* and *Burkholderia cepacia* is correlated with worsening lung function and as such, suppressive therapy with inhaled antibiotics is a cornerstone of CF management.[25,26] There is also increased susceptibility in PwCF for chronic infections with opportunistic

pathogens such as mycobacterium avium complex (MAC). There are ongoing efforts to develop alternative anti-infective therapies for chronic use, especially for the resistant and diverse pathogens now recognized to colonize the CF lung. Additionally, acute CF exacerbations are repeatedly treated with short-term oral or intravenous antibiotics. There are ongoing investigations to optimize acute antibiotic treatment to minimize exposure and toxicities.

Chronic suppression

Inhaled antibiotics are the primary treatment for chronic Pseudomonas infection. Inhaled tobramycin and inhaled aztreonam became available in 1997 and 2010 respectively, after studies demonstrated improved lung function, decreased Pseudomonas burden in sputum, improved respiratory symptom scores, and decreased risk of pulmonary exacerbations and hospitalizations with chronic therapy.[27-31] Inhaled antibiotics are typically cycled every 28 days to reduce selective pressure for antibiotic resistance.[29] It is worthwhile to note that oral azithromycin is also approved for chronic pseudomonas suppression after studies demonstrated improved lung function and decreased risk of exacerbations. However, recent studies suggest oral azithromycin may decrease the efficacy of tobramycin and therefore should be used with caution.[32-34]

In 2018, inhaled liposomal amikacin became the first therapy approved under the FDA Limited Population Pathway for Antibacterial and Antifungal Drugs designed to accelerate development of medications for serious infections affecting small populations. It was approved for treatment-refractory mycobacterium avium complex in adults, although notably the primary study leading to its approval excluded PwCF.[35] Recent studies have also suggested inhaled amikacin liposomal suspension to be non-inferior to inhaled tobramycin for treatment of chronic Pseudomonas, although results of a phase III clinical trial evaluating this have not yet been published and it is not FDA-approved for this indication.[36]

Multiple studies have evaluated the efficacy and safety of inhaled levofloxacin, including phase II clinical trials demonstrating decreased sputum Pseudomonas density, dose-dependent improvements in lung function, and reduced need for other inhaled or systemic antipseudomonal antibiotics compared with placebo.[37] However, phase III clinical trials failed to demonstrate a difference in pulmonary exacerbations between inhaled levofloxacin and placebo.[38] Inhaled levofloxacin is not FDA approved in the US, although it is available in the European Union and Canada.

Studies are ongoing to address the diagnosis and treatment of other pathogens that colonize the CF lung. For example, an ongoing prospective study aims to evaluate a standardized approach for diagnosis and management of nontuberculous mycobacteria. Additionally, inhaled vancomycin recently underwent phase III clinical trials for chronic MRSA, however it did not improve lung function or reduce pulmonary exacerbations and is not currently undergoing further development.

There are also several innovative treatments designed to combat chronic infections undergoing phase II trials including intravenous gallium, bacteriophage therapy, and intravenous nitrous oxide. Gallium is thought to inhibit iron-dependent processes and may kill antibiotic-resistant Pseudomonas.[39] Bacteriophage therapy utilizes viruses targeted to kill specific bacterial sources, and has been shown to eliminate more than 80 percent of Pseudomonas strains in PwCF.[40] Nitrous oxide may help eliminate biofilms and nontuberculous mycobacteria.[41] Many other anti-infective therapies are in phase I trials or pre-clinical development.

Acute exacerbations

Treatment with oral or intravenous antibiotics during pulmonary exacerbations has long been a pillar of CF management. However, the optimal antibiotic selection and duration for acute exacerbations remains unknown.

Due to the recurrent need for antibiotics and increasing prevalence of antibiotic resistance, standard practice for selecting antibiotics during acute CF exacerbations relies on in vitro antimicrobial susceptibility testing (AST). However, a 2019 systematic review demonstrated that 11 out of 13 studies evaluating AST for acute exacerbations demonstrated no relationship between AST and clinical response to treatment, calling the utility of this practice into question.[42] As opposed to isolated monomicrobic infections in otherwise healthy patients, AST may not accurately capture the heterogeneous microbiology of the CF lung or predict clinical response to treatment and thus, may not be effective in guiding treatment decisions.

Additionally, the recurrent need for nephrotoxic and ototoxic antibiotics raises the question of minimum effective dosing regimens. A 2017 Cochrane review found once daily dosing of aminoglycosides equally as effective as three times daily dosing with no difference in lung function or time to next exacerbation requiring intravenous antibiotics. There was a lower risk of nephrotoxicity in children with once daily dosing.[43] Additionally, an ongoing randomized controlled trial entitled STOP2 aims to evaluate the efficacy and safety of 10-day, 14-day, and 21-day intravenous antibiotic regimens during acute exacerbations by comparing improvements in lung function and respiratory symptom scores. Altogether, it may be possible in the near future to decrease the frequency and duration of intravenous antibiotics administered during acute exacerbations, an important step in minimizing total lifetime antibiotic exposure and toxicity.

CONCLUSIONS

The development of modulator therapies that target the underlying pathophysiology of CF has revolutionized care for PwCF. Still, ongoing research and development promises

upcoming advances in both combination and novel modulator therapies as well as innovative agents for those with mutations not currently served by existing therapies. Further, optimization of both acute and chronic antibiotic treatments will provide more efficient regimens that maximize efficacy and minimize toxicity.

While substantial progress has been made, there remains ample opportunity to improve care for PwCF. Anticipating increased longevity, considerations for ongoing CF care must be prioritized to optimize quality of life. Efforts include, but are not to limited to, improving screening and management of CF-related chronic illnesses as well improving opportunities for family planning. Day-to-day quality of life can be improved by working to minimize the burden of CF care. To this end, an ongoing study entitled SIMPLIFY will examine the outcomes of withdrawing adjunctive therapies for those on modulator therapy.

With recent advancements and continued efforts toward safer, more efficacious, and streamlined treatments, individuals born with CF in 2021 will enjoy quality life years well beyond that of their predecessors.

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