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Cystic Fibrosis Treatment Landscape: Progress, Challenges, and Future Directions

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ABSTRACT

Cystic fibrosis (CF) is a monogenic autosomal recessive disorder that primarily affects the respiratory and gastrointestinal systems. It results from variants in the *CFTR* gene, leading to dysfunctional chloride channels, thickened mucus secretion, and subsequent multisystem complications. Significant advances have been made in CF treatment, particularly with the development of CFTR modulators, which are unique to genotypes and have improved clinical outcomes in many people with CF. However, the benefits of these therapies are not universal, with a considerable portion of the CF population—especially those with rare mutations—still without access to effective treatment options. This review provides a comprehensive overview of the pathophysiology and genetic basis of CF, explores current and emerging treatments, and discusses the ongoing challenges in the field.

Keywords: Cystic fibrosis, ivacaftor, modulator drugs, treatment

INTRODUCTION

Cystic fibrosis (CF) is a life-threatening genetic disorder that primarily affects the respiratory and digestive systems. Over the past few decades, significant advances have been made in the treatment of CF, dramatically improving patient outcomes and quality of life.[1] The development of CF transmembrane conductance regulator (CFTR) modulators represents a major breakthrough, as these drugs target the underlying protein defect rather than just managing symptoms. However, despite these advances, challenges remain in providing effective treatments for all individuals with CF, particularly those with rare mutations. This review provides a comprehensive overview of the current CF treatment landscape, focusing on recent developments in CFTR modulator therapies. It examines the pathophysiology and genetic basis of CF, explores current and emerging treatments, and discusses ongoing challenges in the field.

PATHOPHYSIOLOGY

Cystic fibrosis is a monogenic autosomal recessive disease that primarily affects the respiratory and digestive systems, but its impact can extend to multiple organ systems throughout the body.[1] It is the most prevalent life-threatening genetic disorder in Caucasians with significant variability in incidence worldwide.[2] Cystic fibrosis is caused by variants in the *CFTR* gene, which is located on the long arm of chromosome 7.[3]

The *CFTR* encodes a protein that functions as a chloride channel, which allows chloride ions to pass through mucus-producing cells, followed by water, that helps to thin the mucus particularly in the lungs and pancreas. When the channel is defective, the mucus becomes thick and sticky, resulting an obstruction. This obstruction leads to both recurrent infections with highly pathogenic bacteria such as *Pseudomonas aeruginosa* (PsA) and *methicillin-resistant Staphylococcus aureus*, and a massive inflow of neutrophils that release elastase,

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overwhelming the lung's antiproteases and contributing to tissue damage.[4,5] Over time, this leads to a decline in lung function, airway narrowing, and ultimately, respiratory failure.

In the gastrointestinal system, mucus plugs block the ducts of the pancreas and gallbladder, preventing the flow of enzymes and bile into the duodenum, which leads to severe malabsorption.[6]

GENETICS

Genetic testing has revolutionized the diagnosis and understanding of CF by identifying over 2000 *CFTR* gene variants to date, with the most common being the F508del (c.1521_1523del).[7] The prevalence of less common CF-related variants can differ across geographic regions, depending on the racial and ethnic diversity of the population. Each of the variants is associated with a wide spectrum of disease manifestations. Despite significant progress in classifying these variants, particularly in Northern European populations, the functional consequences of these have not been fully defined, especially in non-European populations.[8]

Variants in the gene can be classified into different classes (I-VI), based on the type of defect they cause in the CFTR protein, such as protein production, processing, regulation, or function (Figure 1).[9] It has been shown that class I-III CF-causing variants result in minimal or absent CFTR function, leading to a more severe phenotype, including exocrine pancreatic insufficiency (PI). On the other hand, class IV and V variants retain some residual CFTR function, often associated with preserved exocrine pancreatic function especially in early life.[10]

Genotyping people with CF (pwCF) is crucial because it directly informs the diagnosis, prognosis, and treatment strategy for them.[11] Identifying specific *CFTR* variants allows the use of targeted therapies, such as CFTR modulators, which are tailored to specific genetic variants.[12,13] Accurate genotyping also helps with genetic counseling and understanding of the hereditary nature of the disease. Additionally, knowing the *CFTR* genotype can help predict the likelihood of prognosis and optimize individualized patient care.

In the last 3 decades, as the natural history and pathophysiology of CF have become better understood, treatment approaches have progressed from merely symptom relief to directly targeting the underlying defective protein. This shift marks a significant advancement in CF management, offering hope for more effective therapies. By examining the current

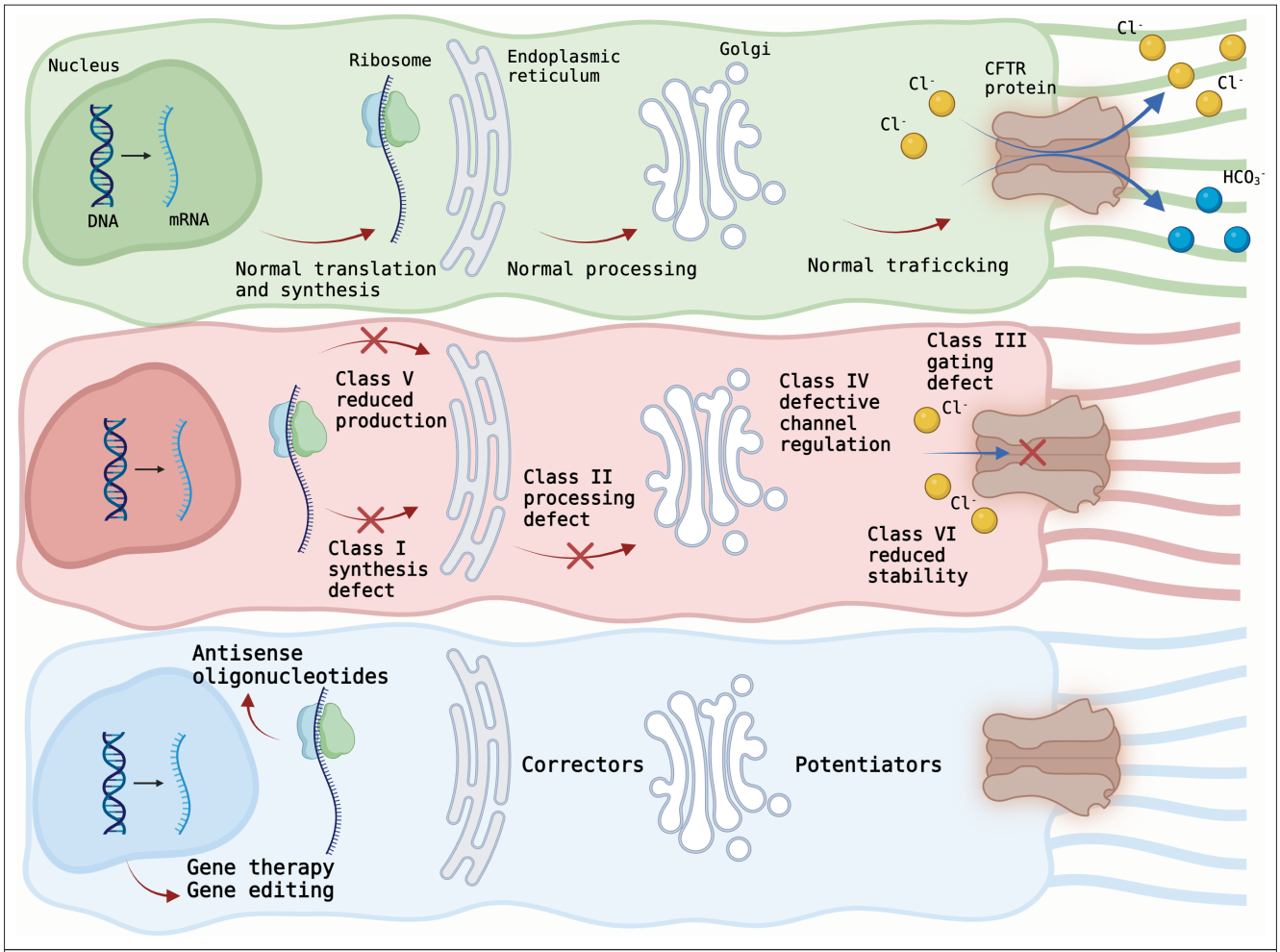

Figure 1. Illustration of cystic fibrosis transmembrane conductance regulator protein dysfunction classes and corresponding therapeutic interventions in cystic fibrosis.

landscape and emerging therapies, this review aims to provide a comprehensive overview that can guide future research and clinical practice in improving outcomes for pwCF.

Study Method

Advancements in CF treatment, particularly CFTR modulators, were explored through a comprehensive literature review using databases like PubMed, MEDLINE, and Cochrane Library. Keywords included "cystic fibrosis," "CFTR modulators," "new therapies," and "rare mutations." Articles from the past 10 years were selected based on relevance and methodological rigor. A comparative analysis evaluated different therapies and their effectiveness for various mutations, identifying strengths and limitations. Insights into real-world applications were gained while ethical considerations of gene therapy were addressed. Findings were presented with graphs and tables, and peer-reviewed for accuracy and relevance, ensuring a comprehensive analysis of current advancements and future research needs in CF treatment.

TREATMENT

The primary purpose of CF treatment is to manage and relieve the symptoms, slow disease progression, and improve the quality of life and survival of patients. This can be achieved by maintaining airway clearance properly, controlling respiratory infections, reducing inflammation, optimizing nutritional status and getting vaccinated for *Influenza A and B* annually.[14] Emerging relatively new therapies also aim to correct the underlying CFTR protein dysfunction, addressing the basic cause of the disease and potentially changing its natural course. Regular monitoring and individualized treatment adjustments are essential to effectively manage the multisystemic complications associated with CF.[15]

Respiratory System

In pwCF, respiratory symptom management involves a comprehensive approach that targets airway clearance, infection control and inflammation reduction. Airway clearance techniques are crucial and include manual chest physiotherapy, autogenic drainage, devices like oscillatory positive expiratory pressure and high-frequency chest wall oscillation vests and exercise.[16] Since no physiotherapy type has been proven superior, it is best for the choice to be determined through a collaborative decision between the physiotherapist and pwCF.[17,18] Main purpose is to mobilize and clear thick, sticky mucus from the lungs. Inhaled medications play a critical role during practicing these techniques, with bronchodilators used to open the airways, mucolytics such as dornase alfa breaking down mucus, and hypertonic saline solutions helping to hydrate the mucus and make it easier to cough out.

Long-term use of inhaled antibiotics, such as tobramycin or colistin, are utilized to suppress persistent infections, particularly those caused by PsA.[19] Additionally, oral or intravenous antibiotics are administered during acute exacerbations or within the scope of eradication protocols to manage these infections more aggressively.[4] Anti-inflammatory treatments, like azithromycin, can be used to control chronic inflammation, which is a major contributor to lung tissue damage over time.[5]

Gastrointestinal System

In the gastrointestinal tract, CFTR dysfunction leads to thickened secretions, resulting in complications such as PI malabsorption, intestinal blockage, and distal intestinal obstruction syndrome (DIOS).[20] These complications necessitate specialized dietary interventions and watchful electrolyte monitoring to prevent and manage associated morbidities as body weight and body mass index are linked to enhanced lung function and represent critical clinical outcomes for pwCF, especially children.[21]

Nutritional management is a cornerstone in the treatment of CF, aiming to ensure adequate caloric intake, prevent malabsorption, and support overall growth and development. Key components include high-calorie diets and pancreatic enzyme replacement therapy. Due to increased energy consumption and malabsorption, pwCF require a high-calorie diet rich in fats and proteins. Supplementation with fat-soluble vitamins (A, D, E, K) is also critical due to PI. Around 85% of children with CF are either born with PI or develop it within the first few years of life, although this rate is around 70% in Turkey, while 10%-15% maintain pancreatic sufficiency.[22]

Recent advancements in CFTR modulators have also improved gastrointestinal outcomes in pwCF by enhancing CFTR function, which has implications for nutritional status, electrolyte balance, and the management of complications like DIOS. However, ongoing monitoring and individualized nutritional support remain essential as these therapies do not fully restore normal gastrointestinal function.[23]

New Era of Therapies

As above-mentioned, historically, CF therapies have focused on managing the symptomatic complications. Especially towards the last decade, the focus has shifted towards precision medicine, tailoring therapies to individual patients. Several new agents have been approved or are currently under study for pwCF. These therapies can broadly be classified into 2 groups: mutation-specific agents, which target particular *CFTR* variants, and mutation-agnostic treatments, which aim to restore normal function regardless of the specific *CFTR* defect.[24]

Here, we review recent developments, discuss their potential impact on future clinical care, and address the current gaps in the care of individuals with CF.

Cystic Fibrosis Transmembrane Conductance Regulator Modulators

Cystic fibrosis transmembrane conductance regulator modulators are small molecules designed to address the underlying defects in CFTR channel function, aiming to enhance chloride transport. These modulators, which were approved in different doses for patients of different ages, include potentiators and correctors, each targeting specific dysfunctions within the CFTR protein (Table 1).[24] The introduction of these modulators has significantly improved clinical outcomes for individuals with cystic fibrosis, leading to better lung function, reduced pulmonary exacerbations, and an overall enhancement in the quality of life.[25]

- *Ivacaftor (Kalydeco®)*

The first class of agents to be successfully developed were CFTR potentiators, small molecules that interact with the

Table 1. Comprehensive Dosing Guidelines for Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapies Based on Age, Weight, and Clinical Considerations

	Age	Weight	Morning Dose	Evening Dose	Comment		
Ivacaftor *(Kalydeco)*	1-2 months	≥3 kg	5.8 mg (1 packet)	5.8 mg (1 packet)	Mix with 5 mL (1 teaspoon) of soft food of liquid and administer every 12 hours orally with fat-containing food.		Dose adjustment for moderate or severe hepatic impairment or if coadministered with strong CYP3A4 inhibitors. For all modulators, liver-related toxic effects, elevated creatine kinase level, hypertension and cataracts should be monitored.
	2-4 months	≥3 kg	13.4 mg (1 packet)	13.4 mg (1 packet)			
	4-6 months	≥5 kg	25 mg (1 packet)	25 mg (1 packet)			
	6 months-6 years	5-7 kg	25 mg (1 packet)	25 mg (1 packet)			
		7-14 kg	50 mg (1 packet)	50 mg (1 packet)			
		>14 kg	75 mg (1 packet)	75 mg (1 packet)			
	≥6 years	–	150 mg (1 tablet)	150 mg (1 tablet)	Take orally with fat-containing food.		
Lumacaftor/Ivacaftor *(Orkambi)*	1-2 years	7-9 kg	lum 75 mg/iva 94 mg (1 packet)	lum 75 mg/iva 94 mg (1 packet)	Mix with 5 mL (1 teaspoon) of soft food of liquid and administer every 12 hours orally with fat-containing food.	Risk of transient dypsnea.	
		9-14 kg	lum 100 mg/iva 125 mg (1 packet)	lum 100 mg/iva 125 mg (1 packet)			
		≥14 kg	lum 150 mg/iva 188 mg (1 packet)	lum 150 mg/iva 188 mg (1 packet)			
	2-5 years	<14 kg	lum 100 mg/iva 125 mg (1 packet)	lum 100 mg/iva 125 mg (1 packet)			
		≥14 kg	lum 150 mg/iva 188 mg (1 packet)	lum 150 mg/iva 188 mg (1 packet)			
	6-11 years	–	lum 200 mg/iva 250 mg (2 tablets)[a]	lum 200 mg/iva 250 mg (2 tablets)[a]	Take orally with fat-containing food.		
	≥12 years	–	lum 400 mg/iva 250 mg (2 tablets)[b]	lum 400 mg/iva 250 mg (2 tablets)[b]			
Tezacaftor/Ivacaftor *(Symdeko)*	6-12 years	<30 kg	tez 50 mg/iva 75 mg (1 tablet)	iva 75 mg (1 tablet)	For pediatric patients, it is only approved for those over 6 years of age. Take orally with fat-containing food.		
		≥30 kg	tez 100 mg/iva 150 mg (1 tablet)	iva 150 mg (1 tablet)			
	≥12 years	–	tez 100 mg/iva 150 mg (1 tablet)	iva 150 mg (1 tablet)			
Elexacaftor/Tezacaftor/Ivacaftor *(Trikafta)*	2-6 years	<14 kg	elx 80 mg/tez 40 mg/iva 60 mg (1 packet)	iva 59.5 mg (1 packet)	Mix with 5 mL (1 teaspoon) of soft food of liquid and administer every 12 hours orally with fat-containing food.		
		≥14 kg	elx 100 mg/tez 50 mg/iva 75 mg (1 packet)	iva 75 mg (1 packet)			
	6-12 years	<30 kg	elx 100 mg/tez 50 mg/iva 75 mg (2 tablets)[c]	iva 75 mg (1 tablet)	Take orally with fat-containing food.		
		≥30 kg	elx 200 mg/tez 100 mg/iva 150 mg (2 tablets)[d]	iva 150 mg (1 tablet)			
	≥12 years	-	elx 200 mg/tez 100 mg/iva 150 mg (2 tablets)[d]	iva 150 mg (1 tablet)			

elx, elexacaftor; iva, ivacaftor; kg, kilogram; lum, lumacaftor; mL, mililiter; tez, tezacaftor.
[a]One tablet contains 100 mg lumacaftor and 125 mg ivacaftor.
[b]One tablet contains 200 mg lumacaftor and 125 mg ivacaftor.
[c]One tablet contains 50 mg elexacaftor, 25 mg tezacaftor, and 37.5 mg ivacaftor.
[d]One tablet contains 100 mg elexacaftor, 50 mg tezacaftor, and 75 mg ivacaftor.

mutant channel to increase its open probability and enhance anion flux through the plasma membrane. These initial studies primarily targeted the G551D (c.1652G>A) (class III) gating variant, where the CFTR protein is sufficiently localized to the cell surface, but its functional activity is almost entirely absent.

Ivacaftor is an oral bioavailable CFTR potentiator that rectifies the defective CFTR protein at the cell surface. It was developed by Vertex Pharmaceuticals and received Food and Drug Administration (FDA) approval in 2012 for use in children aged 12 years and older with G551D (c.1652G>A) variant in *CFTR*. Ivacaftor prolongs the duration that the channel remains in the open state.

After that, ivacaftor was proven to be highly effective in improving forced expiratory volume in 1 second (FEV_1), body weight and quality of life in 2 large multicentric trials (STRIVE and ENVISION).[12,26] With KIWI trial in 2016, its use was expanded for other variants (class IV) and children aged 2-5 years.[27] Also, it was shown to be effective more gating and missense variants which have similar mechanisms with G551D.[28] Researches involving younger children with CF have shown the potential to preserve or even restore pancreatic function. Furthermore, the early use of effective CFTR modulators like ivacaftor could slow or prevent the progression of lung disease if administered before bronchiectasis develops.[29,30] It is now approved for children older than 1 month.[29]

One of the main limitations of ivacaftor therapy is its specificity for the gating mutations, which are relatively rare among pwCF. While efficacy of ivacaftor in improving lung function and other clinical outcomes in patients were reported, it is not effective for those with the most common *CFTR* variant, F508del (c.1521_1523del) (class II). This limits its utility to a small subset of the CF population, necessitating the development of other therapies for the broader CF community.[8]

- *Lumacaftor/Ivacaftor (Orkambi®)*

The variant F508del (c.1521_1523del) (class II), which is the most common worldwide and associated with a severe phenotype, leads to the misfolding and early degradation of the CFTR protein, resulting in reduced expression of CFTR on the cell surface. The limited amount of F508del-CFTR protein that does reach the cell surface is not only less stable but also has a lower channel-open probability compared to the wild-type CFTR. It was shown that ivacaftor alone is not sufficiently effective in F508del and subsequent research led to the identification and development of lumacaftor.[1,31,32]

Lumacaftor is a CFTR corrector which has been shown that when used in combination with ivacaftor, with complementary mechanisms of action, it corrects CFTR misprocessing and trafficking mistakes in patients carrying the homozygous F508del variant and increases the amount of protein on the cell surface.[33] After 2 large trials (TRAFFIC and TRANSPORT, and PROGRESS), lumacaftor/ivacaftor (lum/iva) combination was approved by FDA for children with CF older than 12 years and with F508del variant in both *CFTR* alleles and it became the next CFTR modulator drug to be approved for clinical use.[15,33] Moreover, as of 2018, the drug has been approved for children older than 2 years old, and in 2022, it received approval for children over 1 year old.[25]

However, since patient outcomes did not demonstrate the same level of clinical efficacy as ivacaftor for individuals with highly responsive gating and conductance variants, and due to treatment discontinuation from adverse events such as chest tightness, shortness of breath and abdominal pain, the search for a more effective treatment persisted.[34] Besides lum/iva was proved ineffective in a clinical study for individuals heterozygous for F508del, leaving a significant portion of the CF population without an available modulator therapy.[35]

- *Tezacaftor/Ivacaftor (Symdeko®)*

Tezacaftor is a small molecule with chemical similarities to lumacaftor, functioning as a broad-acting corrector by enhancing CFTR protein trafficking to the epithelial cell surface.[36] Tezacaftor offers several advantages over lumacaftor, including fewer drug–drug interactions, as lumacaftor is a cytochrome P450 3A4 (CYP3A4) enzyme inducer.[37] Moreover, tezacaftor does not appear to be associated with the clinical incidence of chest tightness seen with lumacaftor, which led to some patients discontinuing lum–iva treatment in clinical practice.[31]

Based on the data from 2 simultaneous phase III studies of the tezacaftor/ivacaftor (tez/iva) combination, which demonstrated modest improvements in respiratory functions and a reduction in pulmonary exacerbations in patients homozygous for F508del, as well as in people heterozygous for F508del with a residual function mutation, was approved for patients carrying at least 1 F508del allele.[36,38] As of 2020, in the United States, it is approved for children older than 6 years old.[39,40]

Tezacaftor–ivacaftor therapy, have expanded eligibility for modulator drugs to more pwCF compared to lum/iva or ivacaftor alone. Yet, despite their use, neither lumacaftor nor tezacaftor were regarded as highly effective modulators due to their relatively modest improvements compared to the robust effect of ivacaftor on gating and conductance mutations.[12,33,41] Moreover, approximately 40% of individuals with CF were still not eligible for any available modulator drugs because of their genotypes.[36] As a result, there was still an ongoing need to develop a highly effective treatment that could benefit a broader population of pwCF, particularly by finding a corrector that would work well with the current dual-combination modulators.

- *Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®)*

The next significant breakthrough came with the development of elexacaftor, another CFTR corrector. For the combination, tezacaftor was selected over lumacaftor as the second corrector, as it had a better side effect profile and fewer drug–drug interactions.

In clinical trials elexacaftor/tezacaftor/ivacaftor (ETI) demonstrated significant improvements in lung function, as measured by FEV_1 as well as improvements in quality of life, as measured by the CF Questionnaire-Revised and decrease in pulmonary exacerbations. Based on the results of 2 phase III studies, 1 with pwCF who were not eligible for any modulator drugs and 1 with individuals who already were, triple combination CFTR modulator (ETI) was approved by FDA in 2019 for people with at least 1 copy of F508del, which accounts for approximately 80% of pwCF worldwide.[42,43] The drug was approved by FDA for

children over 12 years old at the same year, for children over 6 years old in 2021, and for children over 2 years old in 2023.[44,45]

Elexacaftor/Tezacaftor/Ivacaftor has been recognized globally for its unprecedented clinical benefits in pwCF including children with highly reduced lung capacity.[46] It has transformed the management of CF by significantly improving lung function, reducing pulmonary exacerbations, and enhancing overall quality of life.[47] Additional *CFTR* variants have subsequently been identified, even some nonsense (class I) ones, as responsive to ETI through in vitro testing using a cultured cell-based assay.[48] These findings, along with real-world data from compassionate use cases, have contributed to the expansion of the drug label in the United States and Europe up to 200 variants.[49,50]

- *Adverse Effects and Drug Interactions*

Modulator drugs are generally considered to have a positive safety profile. On the prescription information for the 4 modulator drugs currently on the market, there are 4 common precautionary recommendations: elevated transaminases, hypersensitivity reactions, use with CYP3A4 inducers, and cataracts.

Long-term outcomes are most extensively documented for ivacaftor, largely because of the extended period since the drug's initial discovery and its availability in clinical practice. Since ivacaftor is a component of all combined modulators currently available, the long-term outcomes documented for ivacaftor can also be reflective of the effects seen with these combination therapies. In a 2 year extension study for ivacaftor with children older than 6 years, around 20% of subjects experienced adverse events, with the majority presenting as respiratory symptoms typical of CF, occurring less frequently than in the placebo group. Liver function abnormalities, including elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, were noted at comparable rates between the ivacaftor and placebo groups.[51] Considering these potential increases, it is recommended to perform hepatic function assessments quarterly during the initial year of therapy. If substantial elevations are detected, the medication should be temporarily suspended (Table 2).

Furthermore, cataracts have been reported in juvenile rats treated with ivacaftor, as well as in young children receiving the drug; therefore, regular ophthalmologic evaluations are recommended for children taking ivacaftor or modulators containing ivacaftor.

Compared to other CFTR modulators, lum/iva seems to be associated with a higher incidence of adverse events affecting the respiratory system, such as bronchospasm, chest tightness, and increased sputum, which led some people to discontinue.[33,52]

While ETI is generally well-tolerated in children, there are reports of mild physical side effects and some concerns regarding neuropsychiatric effects. In a follow-up study involving a 12-month period and including 6 children aged 12-18 years, only rash and abdominal pain were reported.[53] Moreover, isolated elevations of AST, ALT, or bilirubin, increase of liver stiffness, and altered bile acid metabolism have been observed in pwCF treated with ETI.[54-56]

Although an improvement in objective sleep measures has been observed, it has been suggested that ETI may cross the blood–brain barrier due to its lipophilic nature and might contribute to some psychiatric and sleep disorders that have been reported after the start of the therapy.[57]

All CFTR modulator drugs are known to interact with drugs metabolized by the CYP3A4 enzyme, which leads to potential drug-drug interactions, particularly with medications that are also substrates, inhibitors, such as certain antifungals like itraconazole or voriconazole and clarithromycin, or inducers of CYP3A4, such as rifampin and phenobarbital.[58]

- *Pregnancy and Lactation*

Due to the improved health thanks to CFTR modulators, pregnancy rates are rising among women with CF. There is limited but growing data on the safety of CFTR modulators during

Table 2. Recommendations for Monitoring and Management of Liver Transaminase and Bilirubin Elevation During Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy

	Increase Rate			
	>2 times	**>3 times**	**>5 times**	**>8 times**
Alanine aminotransferase (ALT)		Repeat the test after 1 month.	• STOP modulator • Monitor AST and ALT • Restart modulator when AST and ALT <2× upper limit of normal	STOP modulator
Aspartate aminotransferase (AST)		Repeat the test after 1 month.	• STOP modulator • Monitor AST and ALT • Restart modulator when AST and ALT <2× upper limit of normal	STOP modulator
Total bilirubin	And if AST or ALT >3× upper limit of normal: • STOP modulator • Monitor in 2 weeks • Restart modulator when bilirubin <2× upper limit of normal			

ALT, alanine aminotransferase; AST, asparate aminotransferase.

pregnancy. The drugs have been shown to pass through the placenta, and in animal reproductive models, the 3 components of ETI did not cause teratogenicity at normal human doses.[59,60] The few studies on pregnancy and lactation related to CFTR modulator use published so far suggest that these drugs are generally well-tolerated, especially considering the well-documented higher incidence of complications during pregnancy among women with CF; however, there have been reports of congenital cataracts in infants.[59,61,62] On the other hand, there are also case reports of patients diagnosed with antenatal CF and meconium ileus, and whose findings regressed with the initiation of antenatal ETI.[63]

The safety of CFTR modulators during pregnancy and lactation is an area of active research, and while these therapies have significantly improved outcomes for pwCF, their use during these periods requires careful consideration. However, the clinical benefits of maintaining CFTR modulator therapy during pregnancy, particularly for the mother's health, might outweigh the potential risks.

- *Equity in Cystic Fibrosis Transmembrane Conductance Regulator Modulators*

In the context of CFTR modulators, it is a fundamental principle that a drug cannot be presumed eligible with a variant without specific studies. This principle is critical because the development and approval of modulator drugs are typically based on clinical trials that may not fully capture the genetic diversity present within the CF population. These trials often prioritize the most common *CFTR* variants, which are predominantly found in the majority of pwCF. Consequently, many rarer *CFTR* variants, which tend to be more prevalent among diverse and underrepresented populations, are not adequately studied.[64]

This underrepresentation poses significant challenges. Patients with these less common variants may not have access to the full range of modulators, as their effectiveness has not been validated for their specific genotypes. As a result, there is a gap in treatment options, leading to potential disparities in health outcomes for people with these rarer variants.[11] This underscores the need for more inclusive research that encompasses a broader spectrum of *CFTR* variants, ensuring that the benefits of modulator drugs are accessible to all individuals with CF, regardless of their genetic background. Expanding the scope of clinical trials to include a wider variety of *CFTR* variants is crucial for achieving equity in CF care and treatment.

Future Directions

Despite the major steps taken in the treatment of the majority of pwCF, the work is not yet done. There is still an unmet need for the ones who are not eligible for current modulator drugs and who can't tolerate their adverse effects.[65] Furthermore, very young children and infants, who could gain the most from early administration of CFTR modulators to minimize disease complications, are currently ineligible for ETI. Although modulator medications have demonstrated remarkable effects on various systems, they do not offer a complete cure for CF.

For people with nonsense variants (class I), read-through agents represent a promising area.[66] Read-through agents are compounds designed to recognize and skip premature termination codon (PTC), enabling the production of a full-length, potentially functional CFTR protein. Early-phase clinical studies with ataluren indicated some improvements in pulmonary functions; however, subsequent larger clinical trials did not show significant improvements.[67]

Another novel approach to deal with PTC variants are transfer ribonucleic acids (tRNAs), that utilizes the functions of tRNA molecules involved in protein synthesis. Transfer RNA-based therapies are engineered to recognize PTCs and insert the correct amino acid instead of terminating protein synthesis. This allows the ribosome to continue translating the mRNA, potentially producing a full-length, functional protein.[68] Although tRNA-specific therapies have not yet been fully realized in CF, existing gene therapy trials have shown that while the approach is safe, its efficacy has been limited and temporary.

Antisense oligonucleotides are synthetic polymers, that imitate deoxyribonucleic acid (DNA) or RNA, structurally or functionally. They can attach to the target RNA as a result of base paring principal.[69] These therapeutic approaches offer the flexibility to either suppress or enhance gene expression, providing an effective means to manage CF at the RNA level. Ongoing research and development in this area hold significant promise for expanding the treatment options available.

These treatments will still be specific to certain variants, potentially putting individuals with less common variants at a disadvantage. On the other hand, gene therapy and gene editing represent 2 of the most innovative approaches currently being explored, under the branch of mutation-agnostic treatments. In terms of gene therapy, the primary goal is to introduce a functional copy of the *CFTR* into the affected cells to restore normal protein function. This is typically done using vectors, such as recombinant adeno-associated viruses or liposomal vectors. What is meant by gene editing is, to aim to correct the *CFTR* mutation directly within the patient's DNA, which could offer a permanent solution. Techniques like clustered regularly interspaced short palindromic repeats, naming CRISPR/CRISPR-associated protein 9,Cas9, and transcription activator-like effector nucleases, known as TALENs, are used to cut DNA near the *CFTR* mutation site and allow the repair mechanisms to insert the correct genetic sequence.[70]

However, both gene therapy and editing strategies face challenges such as achieving efficient delivery to lung cells, avoiding immune responses and addressing the vast number of different *CFTR* mutations.

CONCLUSION

Cystic fibrosis treatment has made significant strides over recent decades, particularly with the introduction of CFTR modulators. These advancements have transformed the management of CF, leading to improved lung function, reduced exacerbations, and enhanced quality of life for many patients. However, despite these achievements, challenges remain. A significant portion of the CF population, especially those with rare variants still lacks access to these drugs. Furthermore, existing treatments, though beneficial, do not offer a complete cure and are accompanied by some side effects, limiting their use in certain populations, such as infants and those intolerant to current therapies.

Future research and development should focus on addressing these gaps. The pursuit of mutation-agnostic therapies represents a promising direction. These approaches could potentially offer broader treatment options for pwCF, regardless of their genotype. As we move forward, continued innovation and inclusive research will be essential to ensuring that all individuals with CF can benefit from the advances in treatment, ultimately aiming to improve their overall prognosis and quality of life.

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