CFTR Modulators: Current Status and Evolving Knowledge

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Abstract

In the past decade, the medical management of people with cystic fibrosis (pwCF) has changed with the development of small molecules that partially restore the function of the defective CF transmembrane conductance regulator (CFTR) protein and are called CFTR modulators. Ivacaftor (IVA), a CFTR potentiator with a large effect on epithelial ion transport, was the first modulator approved in pwCF carrying gating mutations. Because IVA was unable to restore sufficient CFTR function in pwCF with other mutations, two CFTR correctors (lumacaftor and tezacaftor) were developed and used in combination with IVA in pwCF homozygous for F508del, the most common CFTR variant. However, LUM/IVA and TEZ/IVA were only moderately effective in F508del homozygous pwCF and had no efficacy in those with F508del and minimal function mutations. Elexacaftor, a second-generation corrector, was thus developed and combined to tezacaftor and ivacaftor (ELX/TEZ/IVA) to target pwCF with at least one F508del variant, corresponding to approximately 85% of pwCF. Both IVA and ELX/TEZ/IVA are considered highly effective modulator therapies (HEMTs) in eligible pwCF and are now approved for nearly 90% of the CF population over 6 years of age. HEMTs are responsible for rapid improvement in respiratory manifestations, including improvement in symptoms and lung function, and reduction in the rate of pulmonary exacerbations. The impact of HEMT on extrapulmonary manifestations of CF is less well established, although significant weight gain and improvement in quality of life have been demonstrated. Recent clinical trials and real-world studies suggest that benefits of HEMT could even prove greater when used earlier in life (i.e., in younger children and infants). This article shortly reviews the past 10 years of development and use of CFTR modulators. Effects of HEMT on extrapulmonary manifestations and on CF demographics are also discussed.

Keywords
- cystic fibrosis
- CFTR modulators
- ivacaftor
- tezacaftor
- elexacaftor

Cystic fibrosis (CF) is an autosomal recessive disorder affecting more than 100,000 individuals worldwide.[1,2] The disease is caused by the presence of mutations in the CF transmembrane conductance regulator (*CFTR*) gene located on chromosome 7.[3] The CFTR protein is a transmembrane chloride and bicarbonate ion channel expressed at the epithelial cell surface of mucus-producing organs: airways, pancreas, sweat glands, gastrointestinal and reproductive tracts. This

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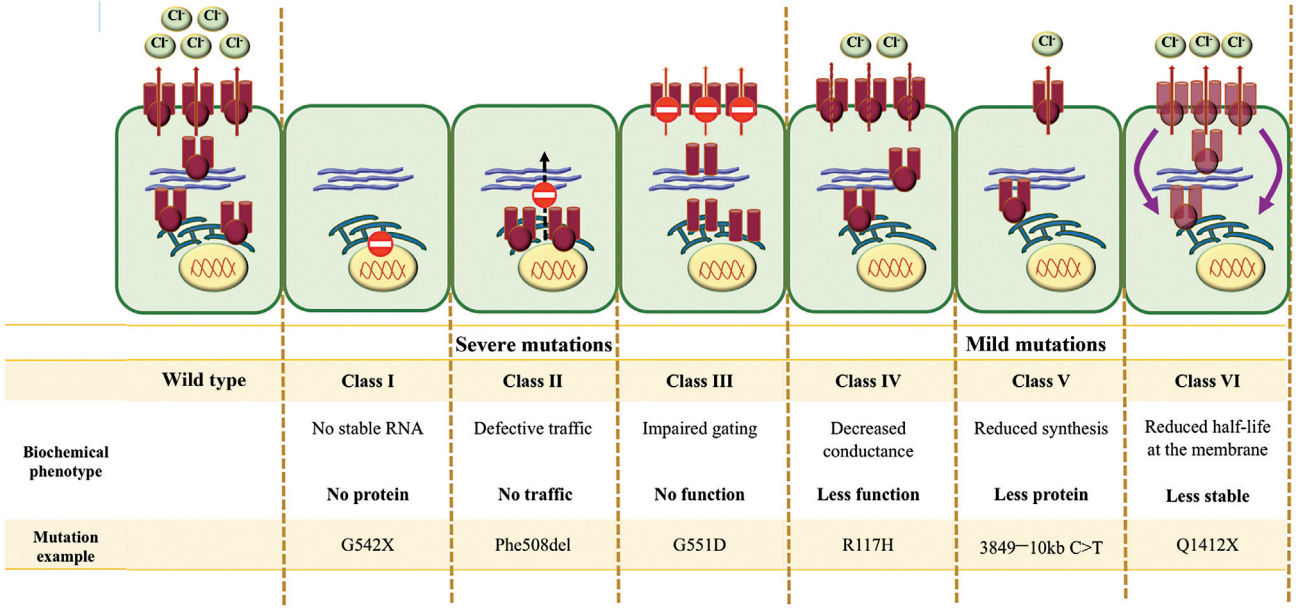

Fig. 1 Classification of CFTR mutations. CFTR protein is located at the apical surface of epithelial cells, where it acts as a bicarbonate and chloride (Cl^-) channel. Mutations in the *CFTR* gene are classified as severe (classes I, II, and III), resulting in absent or minimal CFTR function, and mild (classes IV, V, VI), usually with residual CFTR function. CFTR, cystic fibrosis transmembrane conductance regulator.

channel plays a crucial role in epithelial surface hydration and luminal pH regulation.[3] Mutations in the *CFTR* gene lead to reduced quantity and/or activity of the CFTR protein, resulting in a multiorgan disease. Since its discovery in 1989, more than 2,000 mutations in the *CFTR* gene have been identified. They are divided into functional classes based on the pathophysiological effect of the mutation (►**Fig. 1**). Class I, II, and III mutations are disease-causing mutations associated with little to no CFTR function and more severe phenotype; class IV, V, and VI mutations maintain residual CFTR function and often result in milder phenotypes.[4] The most common mutation is the F508del, a class II mutation found in approximately 80% of people with CF (pwCF), with 40 to 50% being homozygous for this mutation.[4,5]

Until early in the 2010s, care for pwCF was characterized by a multidisciplinary approach, focusing on slowing lung disease progression with inhaled and/or systemic antibiotics, using physiotherapy and/or inhaled mucoactive drugs for increasing mucus clearance, improving nutritional status with pancreatic enzyme replacement or specific diet and treating CF-related complications.[6,7] Since 2012, new drugs called CFTR modulators have been introduced for pwCF with selected CFTR genotypes. CFTR modulators are small molecules that bind to defective CFTR proteins and partially restore either abnormal channel gating (potentiators) and/or protein folding and intracellular trafficking (correctors)[8] in patients with selected *CFTR* mutations (►**Fig. 2**). To date, four CFTR modulators have been approved for pwCF. Ivacaftor (IVA) is a potentiator that improves CFTR function in patients with gating mutations by increasing the CFTR channel's opening frequency and ion conductance.[9,10] Lumacaftor (LUM), tezacaftor (TEZ), and elexacaftor (ELX) are all three correctors. Their mechanisms of action are not fully available yet. Studies suggest they could repair the aberrant assembly of the full-length protein, improve protein folding in the endoplasmic reticulum and subsequent trafficking and stability to the cell surface.[11] Clinically, correctors are used in combination with IVA to correct concurrent folding and gating abnormalities, as encountered with the F508del mutation (►**Fig. 2**). Both LUM/IVA and TEZ/IVA combinations are approved in patients homozygous for the F508del mutation,[12,13] and TEZ/IVA is also approved for patients carrying one copy of the F508del mutation and selected residual function mutation.[14] The elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) combination was approved in 2020 for pwCF aged 12 years and older homozygous for the F508del mutation or with a F508del mutation associated with a minimal function, gating, or residual function mutation.[15–17] Approximately 85% of pwCF are known to carry the F508del mutation and are therefore eligible to receive the triple combination ELX/TEZ/IVA. IVA, LUM/IVA, TEZ/IVA, and ELX/TEZ/IVA have proven their efficacy on improving lung function, reducing the rates of respiratory exacerbations, increasing weight and improving quality of life.[10,18–20]

The aim of this review article is to briefly retrace the history of CFTR modulators approval and described their expanded indications, from single therapy with IVA to triple combination ELX/TEZ/IVA. We also review impact of CFTR modulators on respiratory and extrapulmonary manifestations of CF, as well as their expected impact on CF demographics. Of note, the use of CFTR modulators in patients living with solid organ transplantation (including lung and/or liver transplantation) is not discussed in the present article.

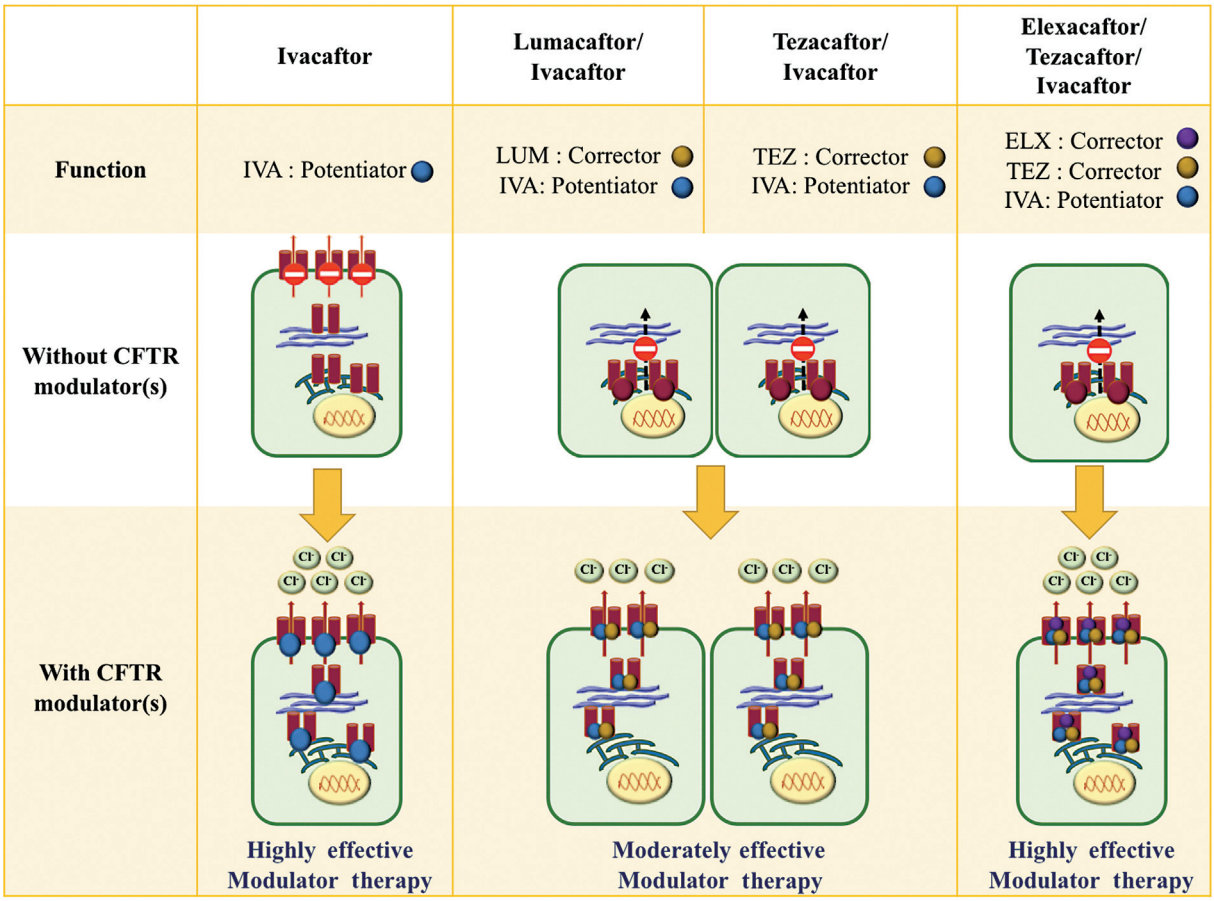

Fig. 2 Mechanisms of action of CFTR modulators. Ivacaftor is a potentiator that increases CFTR opening frequency and ion conductance. Lumacaftor, tezacaftor, and elexacaftor are correctors that improve protein folding, trafficking, and stability at the cell surface. Compared with each molecule alone, they have an additive effect to facilitate the intracellular maturation and trafficking of the CFTR protein to increase the amount of CFTR proteins brought to the cell surface. Ivacaftor potentiates the probability of opening. The combined effect of elexacaftor, tezacaftor, and ivacaftor is an increase in the amount of CFTR proteins and their function at the cell surface, leading to an increased CFTR channel activity. Both ivacaftor and the triple combination of elexacaftor/tezacaftor/ivacaftor are considered highly effective: high level of CFTR function restoration (major decrease in sweat chloride concentration) and rapid and major clinical improvement (lung function, exacerbations, weight). LUM/IVA and TEZ/IA are moderately effective in F508del homozygous patients, but TEZ/IVA is highly effective in patients with one F508del mutation and an eligible residual function mutation. CFTR, cystic fibrosis transmembrane conductance regulator.

From Single Modulator Therapy Limited to Adolescents and Adults to Triple Modulator Combination Initiated in Younger Children with Cystic Fibrosis: the Continuous Expanding Access and Approval of CFTR Modulators

IVA was the first CFTR modulator approved for the treatment of pwCF carrying at least one G551D mutation and rapidly extended to several other gating mutations (approximately 4% of pwCF; ►**Table 1**). A remarkable improvement in respiratory symptoms and lung function, and weight gain was first reported in adolescents and adults carrying at least one G551D mutation and in 6- to 11-year-old children treated with IVA.[21–23] Additional clinical trials and in vitro evidence of CFTR function restoration led to IVA approval to other gating and residual function mutations (►**Table 1**).[24,25] These results raised great hope for pwCF but the results of the DISCOVER trial were then disappointing: in patients homozygous for the F508del mutation, IVA had no effect on lung function or exacerbation.[26] The real-world experience with IVA supports the evidence that the benefits of this highly effective modulator therapies (HEMTs) are sustained over multiple years. Observational and registry-based studies show that survival is improved, while exacerbation frequency, need for lung transplantation (LTx), and prevalence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* are reduced.[27–31] Longitudinal data also indicate that starting IVA early was likely to obtain a greater long-term impact.[32]

The promising results obtained with IVA in patients with gating mutations and the need to treat a greater proportion of pwCF encouraged the development of CFTR correctors lumacaftor and tezacaftor used in combination with IVA to target F508del, the most common *CFTR* mutation. Both LUM/IVA and TEZ/IVA combinations were approved in patients homozygous for the F508del mutation,[12,13] and TEZ/IVA was also approved for patients carrying one copy of the F508del mutation and selected residual function mutation[14] (►**Table 1**). In contrast with the results obtained with IVA in patients with gating mutations, improvement in

Table 1 Evolution in CFTR modulators approval and indications in Europe

Modulator	Approval (year)	Approved (ages)	Target mutations
Ivacaftor	2012	≥6 years	At least one copy of the G551D mutation
	2014	≥6 years	At least one gating (class III) mutation: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R
	2016	≥2 years	
	2019	≥1 year	
	2020	≥6 months	
	2021	≥4 months	At least one gating (class III) mutation: G1244E, G1349D, G178R, G551D, S1251N, S1255P, S549N, S549R or G970R or at least one copy of the R117H mutation
Lumacaftor + ivacaftor	2016	≥12 years	Two copies of the F508del mutation
	2018	≥6 years	
	2019	≥2 years	
Tezacaftor + ivacaftor	2020	≥12 years	Two copies of the F508del mutation or one copy of the F508del mutation AND one of the following mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711 + 3A→G, S945L, S977F, R1070W, D1152H, 2789 + 5G→A, 3272 26A→G, 3849 + 10kbC→T.
	2021	≥6 years	
Elexacaftor + tezacaftor + ivacaftor	2020	≥12 years	Two copies of the F508del mutation or one copy of the F508del mutation and one minimal function mutation
	2021	≥12 years	At least one F508del mutation

Abbreviation: CFTR, cystic fibrosis transmembrane conductance regulator.

respiratory parameters was more modest with both LUM/IVA and TEZ/IVA combinations. Furthermore, real-world studies evaluating safety and effectiveness of LUM/IVA in adults reported higher rates of treatment discontinuation (18.2–24%)[33–35] compared with those of clinical trials (5% or fewer).[12] Treatment discontinuation was mostly related to the respiratory adverse events (AEs) that were especially increased in patients with advanced disease[34] and were observed with lumacaftor but not with tezacaftor.[36] Although LUM/IVA and TEZ/IVA showed significant benefits in patients homozygous for the F508del mutation, the clinical effects were somewhat variable and of insufficient magnitude, especially in patients with advanced lung disease.[37] Further LUM/IVA and TEZ/IVA combinations were ineffective in patients heterozygous for F508del with a minimal function mutation (one that produces no protein and/or does not demonstrate in vitro response to modulators).[20] This led to the development of next-generation correctors, targeting different CFTR sites to maximize the treatment effect in triple-combination therapy associating the next-generation corrector ELX with TEZ and IVA. TEZ was preferred to LUM due to its more favorable pharmacological profile, including lower CYP3A activation,[38] and its better safety profile with less pulmonary adverse effects.

The triple combination ELX/TEZ/IVA was first approved in 2020, for patients aged 12 and older, homozygous for the F508del mutation or with a F508del mutation associated with a minimal function (►**Table 1**).[15,17] Rapidly thereafter, approval was extended to patients with one F508del mutation associated with one gating, or residual function mutation (►**Table 1**).[16] Clinical trials evaluating the ELX/TEZ/IVA triple combination reported the greatest clinical improvements observed with CFTR modulators: F508del homozygous patients treated with ELX/TEZ/IVA showed rapid and significant improvements in lung function (absolute average increase by 10% in percent predicted forced expiratory volume in one second [ppFEV1]) in comparison to TEZ/IVA, and respiratory symptoms were also markedly reduced.[15] In patients carrying one F508del mutation, who were not eligible to receive CFTR modulator therapy, a 14% absolute increase in $ppFEV_1$ was observed, with a large improvement in symptoms.[16] The rate of pulmonary exacerbations was reduced by 60%,[16] and similar significant reductions rates were observed in the open-label study extension[39] and a randomized controlled study in F508del homozygotes.[40] In a real-world study conducted in patients with advanced lung disease, who were not eligible to clinical trials due to low lung function ($ppFEV_1 < 40$), Burgel et al reported that the results obtained in clinical trials could be extended to patients with more severe disease. In patients carrying at least one F508del mutation, $ppFEV_1$ was improved of +15.1 points and body weight increased by 4.2 kg on average, within 3 months after the initiation of ELX/TEZ/IVA.[41] The number of patients requiring long-term oxygen therapy, non-invasive ventilation, and/or enteral tube feeding decreased by 50, 30, and 50%, respectively.[41] Furthermore, a two-fold decrease in the number of LTx in pwCF between 2020 and the two previous years was found, suggesting that triple therapy has the potential to improve survival and delay the need for LTx.[41] These findings were confirmed by Martin et al in a study evaluating LTx eligibility criteria and changes in lung function, nutritional parameters, health care

resource utilization, and concurrent treatments over 12 months after the initiation of ELX/TEZ/IVA.[42] At baseline, 17 patients were waitlisted for transplantation, and 48 were considered for LTx within 3 months. At 1 month, $ppFEV_1$ had increased by +13.4 percentage points and remained stable throughout the 12-month observation period. After 1 year, two patients had been transplanted, two were still on the waiting list, and 61 no longer met transplantation criteria. Improvement in treatment burden decreased significantly, with an 86% decrease in the need for intravenous antibiotics, 59% for oxygen therapy, and 62% for non-invasive ventilation.[42]

The effectiveness of ELX/TEZ/IVA was also confirmed in the PROMISE study, including patients aged 12 years and older with at least one F508del mutation and starting ELX/TEZ/IVA for the first time, in one of the 56 U.S. CF Foundation Therapeutics Development Network sites.[43] At 6 months and compared with baseline, authors reported a 9.76 percentage point increase in $ppFEV_1$ and a body mass index (BMI) increase. Of note, 44.1% patients entered the study using TEZ/IVA or LUM/IVA and 6.7% were using IVA. Changes were larger in those naive to modulators but substantial in all groups, including those treated with IVA at baseline.[43]

Although initially developed in adolescents and adults 12 years and older, the use of CFTR modulator has been progressively extended to younger children and infants. IVA is now approved for infants as young as 4 months of age with gating and residual function mutations[44] and LUM/IVA and TEZ/IVA are approved for children homozygous for the F508del mutation (≥2 and 6 years old, respectively;[45–47] ►**Table 1**). Considering the major improvements obtained with ELX/TEZ/IVA in pwCF aged 12 and older, the safety and efficacy of ELX/TEZ/IVA were recently evaluated in a multicentric phase 3 open-label study including 6- to 11-year-old children homozygous for the F508del or carrying a F508del-minimal function mutation.[48] By 24 weeks of treatment, children treated with ELX/TEZ/IVA had improved $ppFEV_1$ and lung clearance index in both genotype cohorts. More recently, a randomized placebo-controlled trial evaluating the safety and efficacy of ELX/TEZ/IVA in children 6 to 11 years of age heterozygous for F508del and a minimal function mutation confirmed the findings of the open-label study: ELX/TEZ/IVA led to significant improvements in lung function and respiratory symptoms, and was generally safe and well tolerated.[49] Use of ELX/TEZ/IVA in pwCF carrying one F508del mutation combined to gating or residual function mutation is also supported by a recent trial demonstrating greater clinical improvement in patient treated with ELX/TEZ/IVA versus treatment with either IVA alone or TEZ/IVA.[18] In the United States, in vitro data have led to expansion of Food and Drug Administration (FDA) approvals to an increasing number of mutations and populations. The recent FDA approval of ELX/TEZ/IVA for patients ≥6 years and older with at least one copy of the F508del mutation or another in vitro modulator responsive mutation, has rapidly shifted other modulator utilization toward this HEMT. In the United States, ELX/TEZ/IVA is now approved for pwCF with one of 178 different mutations. To expand modulator therapy to an even greater number of patients, categorizing CFTR mutations according to in vitro responses to CFTR modulators is being explored.[50] In Europe, this strategy has not been validated to extend the access and approval. The ELX/TEZ/IVA combination is approved for pwCF aged 6 years and older and carrying at least on F508del mutation (►**Table 1**).

Extrapulmonary Effects of CFTR Modulators

The effects of CFTR modulators on respiratory symptoms, lung function, and pulmonary exacerbations have been well documented. However, CF is a multiorgan disease, and therefore assessing the effects of CFTR modulators beyond the respiratory system appears important. ►**Fig. 3** summarizes established and uncertain effects of HEMT in pwCF.

Exocrine Pancreatic Function

In patients carrying severe *CFTR* mutations, alteration of the exocrine pancreas function begins in utero and is usually described to be complete in early life.[51] In adolescents and adults treated with CFTR modulators, there is no evidence of reversal of exocrine pancreatic insufficiency. However, in younger children treated with IVA, fecal elastase-1 (FE-1) measurement was improved, suggesting the potential to reverse or delay pancreatic insufficiency in early life.[44,45,47] This effect appeared to be maintained through 84 weeks in children started on IVA between 2 and 5 years old.[47] Case reports suggested that similar findings may occur in children treated with IVA and LUM/IVA.[52–54] These results support the strategy of early-life starting HEMT to maximize clinical benefits. Patients with milder *CFTR* mutations and residual pancreatic function may experience recurrent pancreatitis. In a small retrospective study, Carrion and colleagues reported a reduction in the pancreatitis-related hospitalization rate and decreased opioid use in patients treated with IVA, suggesting that CFTR modulators may decrease episodes of pancreatitis among individuals with CF with residual pancreatic function.[55,56] A series of five patients with pancreatic insufficiency who developed acute pancreatitis following initiation of CFTR modulator therapy (IVA and LUM/IVA) has also been reported.[57] These data obtained in small series of cases will need to be confirmed in larger cohorts of patients.

Endocrine Pancreatic Function

The incidence of CF-related diabetes (CFRD) increases with age, and long-term complications of diabetes have become a growing concern with the increased survival observed in pwCF.[7] Currently, the benefit of CFTR modulators on CFRD remains uncertain. Cohorts of patients treated with IVA had lower rates of developing CFRD over the years when compared with patients not treated with IVA.[31] Improved insulin secretion and even resolution of CFRD with IVA have been described in small studies or case reports.[31,58,59] In an observational study involving 40 pwCF with glucose intolerance or newly diagnosed diabetes, Misgault et al reported improved glucose tolerance and regression of CFRD in a significant proportion of patients treated with LUM/IVA.[60]

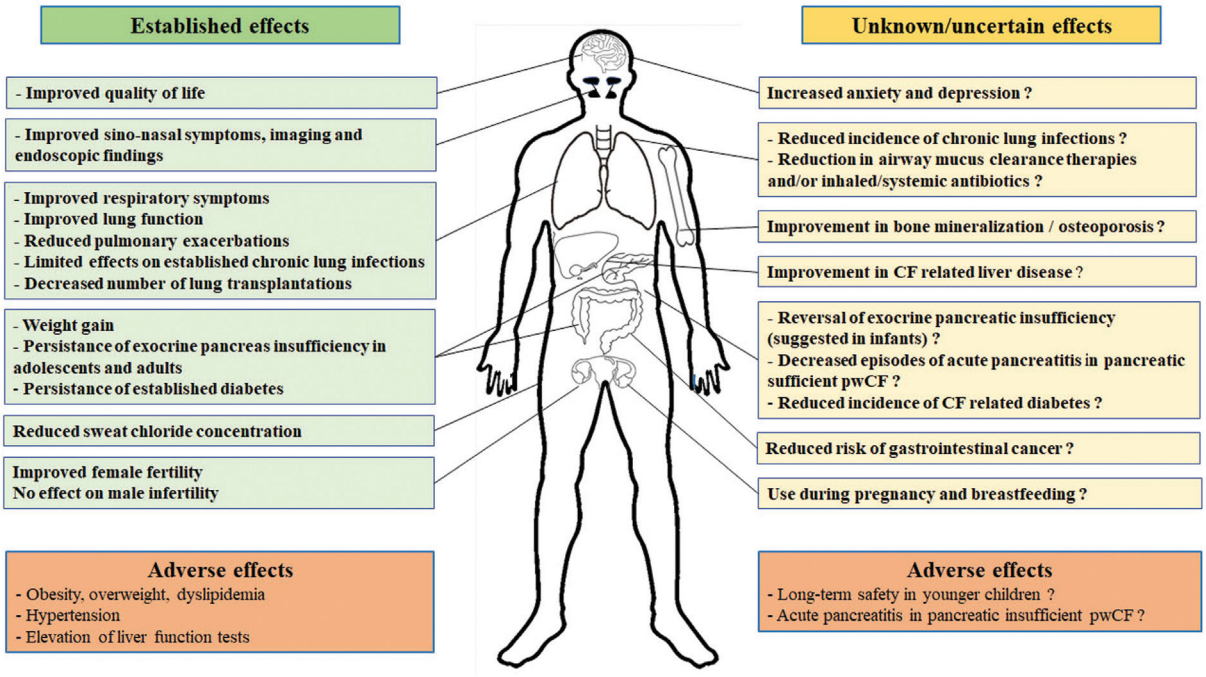

Fig. 3 Established, uncertain, and unknown effects of highly effective modulators on pulmonary and extrapulmonary cystic fibrosis features.

Improved glycemic status with ELX/TEZ/IVA has also been reported in small studies.[61–63] Whether HEMT can prevent the development of CFRD or improve glycemic control in established CFRD remains to be investigated. However, current clinical experience suggests that most patients with established diabetes and treated with insulin are not able to discontinue insulin after starting HEMT.

Sinonasal Disease

Sinus involvement in CF is characterized by almost universal presence of nasal polyps and/or chronic rhinosinusitis, both leading to significant symptom burden for pwCF. In those treated with IVA and ELX/TEZ/IVA, but not with LUM/IVA or TEZ/IVA, significant radiographic, symptomatic, and endoscopic improvements in sinus disease have been reported.[22,64–68]

Nutrition and Metabolism

Rapid and significant increase in BMI or weight has been reported with all approved modulators in both pediatric and adult pwCF. However, results obtained with LUM/IVA and TEZ/IVA were less marked compared with those obtained with IVA and ELX/TEZ/IVA.[12,13,15,16,48,69] The underlying mechanisms for weight gain related to IVA is likely multifactorial (reduced resting energy expenditure, decreased gut inflammation, and decreased fat). In adults with CF treated with IVA, weight gain and fat-free mass were observed in the first 6 months but subsequent gain in fat mass was described during follow-up.[70] An increasing number of pwCF identified as overweight or obese has been reported with unfavorable cardiovascular risk factors (median blood levels of cholesterol and systemic hypertension significantly higher in the overweighed than in normal or underweighted patients).[71] These results suggest that nutritional status and dietary recommendations should be modified and adapted in CF patients treated with modulators.[72,73]

Cystic Fibrosis–Related Liver Disease

The spectrum of CF-related liver disease (CFLD) is broad, ranging from mild liver function test (LFT) and imaging abnormalities to severe portal hypertension and cirrhosis. Data suggesting benefits from IVA and LUM/IVA on CFLD have been reported[74–76] but are limited and were not confirmed in larger studies. Ongoing studies are evaluating the impact of ELX/TEZ/IVA on CFLD in the RECOVER and PROMISE trials (identifier: NCT04602468 and NCT04038047).

Female Fertility

With HEMT, a dramatic increase in female fertility has been observed. In 2020 in the United States, >600 pregnancies were reported, compared with relatively stable rates of approximatively 200 pregnancies per year between 2000 and 2019.[77]

Pregnancies on modulator therapy with reassuring maternal and neonatal outcomes along with breastfeeding have been described.[78,79] However, these data are still preliminary and data from larger cohorts will be necessary to fully reassure the safety of HEMT during pregnancy. Evaluating the long-term effects on children exposed during pregnancy or breastfeeding also appears mandatory. Of note, case reports of improved health status of CF newborns born from CF mothers treated with ELX/TEZ/IVA during pregnancy or lactation have been published. Authors reported preserved pancreatic function, false-negative CF newborn

screening tests, and improved sweat chloride concentration.[80] These preliminary results suggest a theoretical role for prenatal treatment.

Adverse Effects

Serious AEs were reported in 10.5 to 24% of patients receiving IVA, which was similar to the rates of AEs in the placebo groups. The majority of these AEs were consistent with CF disease manifestations rather than with drug-related AEs (pulmonary exacerbations, cough, upper respiratory infections, nasal congestion, and chest tightness or diarrhea).[10,21,24–26] The rate of treatment discontinuation was lower in the IVA groups, ranging from 0 to 7.7%. Of note, a higher incidence of elevated LFT was reported in the pediatric studies than in adult ones.[47]

The incidence of AEs was comparable in the LUM/IVA and placebo groups, with a rate of serious AEs ranging from 15.4 to 45%. The most common AEs were pulmonary exacerbations, cough, headache, dyspnea, chest tightness, hemoptysis, and increased sputum production. Discontinuation rates were low (5.6–8.1%) in all three trials.[12,19,81] However, in the open-label extension study, dyspnea and chest tightness were reported more frequently, and the discontinuation rate was higher in the LUM/IVA group compared with the placebo group.[82] In real-world studies, respiratory AEs occurred in 51% of included patients and resulted in treatment discontinuation in 24%, which was markedly higher than 5% or fewer rates of discontinuation found in phase 3 clinical trials.[12,33] Burgel et al also reported a proportion of patients who discontinued LUM/IVA that was more than three times higher compared with phase 3 studies (18.2 vs. 5%), and reached 30% in patients with a $ppFEV_1$ <40.[34]

In clinical trials evaluating ELX/TEZ/IVA, the rate of AEs was comparable in the placebo and treatment groups, regardless of genotype or age,[15–18,48] and included cough, increased sputum production, nasopharyngitis, upper respiratory tract infections, oropharyngeal pain, and fever, with no acute bronchoconstriction episodes reported. The most frequent laboratory abnormalities were elevated liver enzymes and bilirubin. ELX/TEZ/IVA discontinuation was limited and ranged between 1.5 and 9.5%. In real-world setting, only mild adverse effects, which did not require treatment discontinuation, were reported.[41]

Impact of CFTR Modulators on Cystic Fibrosis Demographics

In the mid twentieth century, life expectancy of newborns with CF barely reached a year, with meconium ileus and malnutrition being the main causes of death.[83] Although CF remains associated with reduced survival, with lung disease being the major cause of morbidity and mortality,[84] significant improvement in survival has been achieved in the past decades, with a current median life expectancy over 50 years in many countries with well-established CF care and over 65 years of age in France.[4,85] This remarkable increase in life expectancy and quality of life can be attributed to multidisciplinary care in CF centers, neonatal screening, nutritional support, antibiotic therapy, intensive physiotherapy, mucoactive drugs, and treatment of CF-related complications.[6] Lung transplantation, which has become widely available in many countries over the past 30 years, has provided further opportunity to increase longevity in pwCF.[86] As a result, the demographic characteristics of the CF population have dramatically changed, and CF is no longer considered a strictly pediatric disease since adults (18 years and older) represent 50 to 60% of patients with CF.[1] Between 2010 and 2025, the overall number of pwCF was expected to have increased by approximately 50%, with a 20% increase in children with CF and 75% in adults.[87,88] However, these forecasts were made at a time when CFTR modulator therapies were not commercialized. While they were available only in few countries for a small number of pwCF 10 years ago, over 85% of pwCF have gained access to HEMTs in the past 2 years, with real-world data indicating they will likely further extend survival in the CF population.[41,42,89] Thus, the increase in the number of adults with CF is likely to continue in future years with aging of the CF population and novel emerging challenges.[90]

Perspective and Future Challenges

In conclusion, the care of pwCF has much improved over the past 80 years, and the introduction of highly effective CFTR modulators used in a continuously growing number of patients, and at a younger age, over the past 10 years is profoundly impacting the CF population and their caregivers. Initiation of HEMT dramatically slows but may not completely stop disease progression. Furthermore, the use of modulators in specific populations, including patients with liver cirrhosis and those with solid organ transplantation (lung and/or liver and/or kidney) still needs to be explored. Also, the timing of CFTR modulator initiation may have a significant impact on the degree of extrapulmonary response. Earlier intervention with CFTR modulator therapy before the establishment of extrapulmonary disease might be able to prevent the development of CF-related complications, such as pancreatic insufficiency. Finally, restoring CFTR function to all pwCF still remains a challenge since a small but significant proportion of patients (e.g., patients with nonsense mutations) are still not eligible to modulator therapy.[91] The access to modulators in multiple countries also remains a challenge, due to their high cost. The availability of CFTR modulators opens a new era for pwCF, but CF is not yet cured and multiple challenges will remain and emerge for the CF community.

Conflict of Interest
None declared.

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