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SPECIAL ARTICLE

Advances in the treatment of cystic fibrosis: CFTR modulators

Maria Dolores Pastor-Vivero[a,b,*], **Jordi Costa i Colomer**[c], **Carlos Martín de Vicente**[d], **Saioa Vicente-Santamaria**[e], **Ruth Garcia Romero**[f], **David González Jiménez**[g], **Carmen Luna Paredes**[h]

[a] *Sección de Neumología Pediátrica, Unidad Multidisciplinar de Fibrosis Quística, Hospital Universitario Cruces. Barakaldo. Bizkaia. Spain*
[b] *Instituto de Investigación Sanitaria Biobizkaia. Barakaldo. Bizkaia. Spain*
[c] *Servicio de Neumología Pediátrica y Unidad de Fibrosis Quística, Hospital Sant Joan de Déu, Esplugues de Llobregat. Barcelona, Spain*
[d] *Unidad de Neumología Pediátrica, Hospital Miguel Servet. Zaragoza. Spain*
[e] *Unidad de Fibrosis Quística, Gastroenterología, Hepatología y Nutrición Pediátrica, Hospital Universitario Ramón y Cajal. Madrid. Spain*
[f] *Unidad de Gastroenterología y Nutrición Pediátrica, Hospital Miguel Servet. Zaragoza. Spain*
[g] *Unidad de Fibrosis Quística, Area de Gestión Clínica de la Infancia y Adolescencia, Hospital Universitario Central de Asturias. Oviedo. Spain*
[h] *Sección de Neumología Pediátrica, Unidad Multidisciplinar de Fibrosis Quística, Hospital Universitario 12 de Octubre. Madrid. Spain*

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Abstract Cystic fibrosis is a severe genetic disease caused by variants in the *CFTR* gene. Although it is a multisystem disease, respiratory involvement is the main cause of morbidity and mortality. Cystic fibrosis transmembrane conductance regulator modulator (CFTRm) therapies have advanced the treatment of this disease by improving function of this protein. Ivacaftor, the first CFTRm, has been found to significantly improve lung function and quality of life in patients with certain gating variants. However, only a small percentage of patients in Spain are eligible for this treatment. Combinations of correctors and potentiators, such as lumacaftor-ivacaftor or tezacaftor-ivacaftor, have been developed for treatment of patients with the most frequent variant (F508del), although with limited benefits. Triple therapy with elexacaftor-tezacaftor-ivacaftor has been found to significantly improve respiratory, gastrointestinal and nutritional outcomes as well as quality of life, thus changing the management of CF in eligible patients. The impact of triple therapy is also reflected in an increase in life expectancy and a decrease in mortality and lung transplantation. As regards hepatic and pancreatic involvement, while CFTR modulators have exhibited promising effects, further research is required. The use of

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* Corresponding author.
E-mail address: mariadolores.pastorvivero@osakidetza.eus (M.D. Pastor-Vivero).

CFTR modulators has also shifted nutritional status trends in patients with CF, reducing the risk of undernutrition but increasing the risk of obesity. The use of these drugs for treatment of less frequent variants and for potential antenatal treatment is currently being investigated. Despite these advances, there is still a subset of patients who are ineligible for treatment with modulators or highly effective therapy.

PALABRAS CLAVE
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Avances en el tratamiento de la Fibrosis Quística: Los moduladores de la CFTR

Resumen La fibrosis quística es una enfermedad genética y grave causada por variantes en el gen CFTR. Aunque se trata de una enfermedad multisistémica, la afectación respiratoria es la que produce mayor morbimortalidad. Los moduladores de CFTR (CFTRm) han supuesto un avance terapéutico al mejorar la función de esta proteína. Ivacaftor, el primer CFTRm, mostró una mejora significativa tanto en la función pulmonar como en la calidad de vida en pacientes con algunas variantes gating. Sin embargo, solo un pequeño porcentaje de pacientes en España es elegible para su uso. Para pacientes la variante más frecuente (F508del), se desarrollaron combinaciones de correctores y potenciadores, como lumacaftor-ivacaftor y tezacaftor-ivacaftor, aunque con beneficios limitados. La triple terapia elexacaftor-tezacaftor-ivacaftor ha demostrado una mejora notable tanto en aspectos respiratorios, digestivos, nutricionales, así como en la calidad de vida, lo que ha cambiado el manejo de la FQ en aquellos en los que están indicados. El impacto también se refleja en un aumento de la esperanza de vida y una reducción de la mortalidad y el trasplante pulmonar. En el ámbito hepático y pancreático, aunque los CFTRm muestran efectos prometedores, se requiere mayor investigación. El tratamiento con CFTRm ha supuesto un cambio en el estado nutricional de los pacientes, reduciendo el riesgo de malnutrición, pero aumentando el de obesidad. Se está investigando su uso en otras variantes menos frecuentes y su potencial aplicación prenatal. A pesar de estos avances, aún existe un grupo de pacientes no aptos para el tratamiento con moduladores o terapias altamente eficaces.

Introduction

Cystic fibrosis (CF) is a severe genetic disease involving the epithelia of multiple organs. It is caused by variants in the *CFTR* gene, which encodes a chloride channel known as cystic fibrosis transmembrane conductance regulator (CFTR). Clinical manifestations, which may start in utero, progress throughout the lifespan. Respiratory disease is the leading cause of death in affected individuals, most of whom die prematurely. Cystic fibrosis transmembrane conductance regulator modulators (CFTRm) are small molecules that bind the defective CFTR protein, partially restoring its function. There are two types of modulators: potentiators and correctors.

In this article, we will present each of these drugs, how they work and the outcomes of their use.

CFTR modulators: what do we know from clinical trials?

Ivacaftor

Ivacaftor is a CFTR potentiator that acts by increasing the time that CFTR channels remain open, thereby improving ion transport through the apical membrane of epithelial cells. It was the first modulator authorized in the United States and Europe, in 2012, by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively. Early trials showed substantial efficacy in patients aged more than 12 years carrying the G551D variant,[1] with improvement in lung function parameters, a reduced incidence of exacerbations, improvement in respiratory symptoms assessed by means of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and, as a result of the increased channel function, a decrease in sweat chloride concentration (Table 1). Subsequent trials allowed expanding the approved uses of ivacaftor to other CFTR-gating variants and to younger patients.[2,3] However, in Spain, the proportion of patients with CF (pwCF) eligible for treatment with ivacaftor continues to be small, slightly over 1%, based on data from the 2022 annual report of the Spanish Cystic Fibrosis Registry.[4]

Dual combination CFTR modulator therapy

The most frequent *CFTR* variant is F508del. Correcting the malfunction of CFTR in patients with this variant requires a drug capable of improving the processing and transport

Table 1 Results of clinical trials of ivacaftor, lumacaftor-ivacaftor and tezacaftor-ivacaftor. Changes observed in different variables.

Modulator	Variant	Age	FEV_1 (%)	LCI	Reduction in RR of exacerbation	CFQ-R	Sweat chloride (mmol/L)	Weight (kg)	BMI (kg/m^2)
IVA vs placebo[a]	G551D	≥12 y	+10.6*	NA	55%*	+8.6*	−47.9*	+2.8*	NA
IVA vs placebo[a]	G551D	6−11 y	+12.5*	NA	NOD	+6.1*	−54.3*	+1.9*	+0.45*,[c]
LUM/IVA vs placebo[a,e]	F508del/F508del	≥12 y	+2.8*	NA	39%*	+2.2	NA	NA	+0.24*,[d]
LUM/IVA vs placebo[a]	F508del/F508del	6−11 y	+2.5*	−0.88*	NA	+5.4*	−24.8*	NA	+0.15[c]
TEZ/IVA vs placebo[a]	F508del/F508del	≥12 y	+4.0*	NA	35%*	+5.1	−10.1	NA	−0.04[c]
TEZ/IVA vs placebo[a]	F508del/RF	≥12 y	+6.8*	NA	54%*	+9.7*	−9.5	NA	+0.47*,[b,c]

Abbreviations: BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire-Revised (quality of life assessment); IVA, ivacaftor; LCI, lung clearance index; LUM, lumacaftor; NA, no data available; NOD, no observed difference; RF, residual function; RR, relative risk; TEZ, tezacaftor.

* Statistically significant.

[a] Difference between baseline and final values in relation to placebo group.

[b] Difference between baseline and final values in the study.

[c] BMI z score for age.

[d] BMI in kg/m^2.

[e] Pooled analysis of patients in TRAFFIC and TRANSPORT studies treated with lumacaftor 400 mg/12 h/ivacaftor 250 mg/12 h.

of this protein to the apical membrane of epithelial cells, such as lumacaftor or tezacaftor, which are CFTR correctors. The F508del variant also affects channel opening due to the changes in the regulatory domain of the CFTR protein, so it requires combination of a corrector with a potentiator. The results achieved with the lumacaftor-ivacaftor (LUM/IVA) and tezacaftor-ivacaftor (TEZ/IVA) combinations were favorable (Table 1),[5–9] so these combinations were approved for treatment of CF patients homozygous for F508del from age 1 year.

The TEZ/IVA exhibited advantages compared to LUM/IVA, such as fewer drug interactions and adverse effects, but neither combination achieved clinical benefits as robust as those of ivacaftor.[5–9]

Triple combination CFTR modulator therapy

Elexacaftor is the third CFTR corrector, and the addition of this new molecule to the TEZ/IVA combination (ETI: elexacaftor/tezacaftor/ivacaftor) has been found to achieve significant improvement in lung function and nutritional status, in addition to reductions in CFQ-R scores, the incidence of exacerbations and sweat chloride concentrations (Table 2) in pwCF carrying the F508del variant in at least one allele and aged more than 2 years,[10–13] the age from which its use is authorized.

The considerable efficacy of ETI in improving respiratory and nutritional outcomes and the high percentage of patients eligible for this treatment has radically changed the management of CF. On account of the benefits that they offer, ivacaftor and ETI are both referred to as ''highly effective modulator therapies''.

In late 2024, the vanzacaftor/tezacaftor/deutivacaftor (VTD) combination was approved in the United States for CF patients homozygous or heterozygous for F508del from age 6 years. This combination has proven non-inferior in efficacy compared to ETI,[14,15] with the advantage that it is administered only once a day, which could improve adherence to treatment.

Epidemiological changes after the introduction of CFTR modulators

Since the disease was first described, and following improvements in diagnosis, treatment, and follow-up in multidisciplinary units, the life expectancy of pwCF has progressively increased to such an extent that, today, adults make a greater percentage of the population with CF compared to pediatric patients.[4,16,17] The advent of CFTR modulators has increased the chances of modifying the course of disease in patients eligible for treatment.

Data from the Cystic Fibrosis Foundation Patient Registry show an exponential increase in the median predicted survival age, so that half of individuals born with CF in 2022 are expected to live to age 68.2 years.[16]

Year 2022 marked the tenth anniversary from the approval of ivacaftor. Studies with longer follow-up periods and of registry data have evinced long-lasting effects along with a decrease in mortality and lung transplantation (LTx) rates.[18]

Since the approval of ETI, the prevalence of affected individuals with advanced lung disease has decreased significantly in the United States,[16] Europe[17] and Spain,[4] and while LTx continues to be the last-resort treatment option, the percentage of patients who require it has also decreased drastically.[4,16,17]

The total number of deaths and the mortality rate have also decreased in the past decade (2012–2022) in the United States,[16] from 425 out of 27 804 individuals with CF to 230 out of 32 261 (from 1.5% to 0.71%), and in Europe,[17] from 338 out of 37 404 individuals with CF to 309 out of 54 406 (from 0.90% to 0.56%). The median age at death increased from 27 years in Europe and 27.4 in the United States in 2012 to 33 years in Europe and 36.6 in the United States in 2022.[16,17]

Table 2 Results of clinical trials of elexacaftor/tezacaftor/ivacaftor. Changes observed in different variables.

Modulator	Variant	Age	FEV_1 (%)	LCI	Reduction in RR of exacerbation	CFQ-R	Sweat chloride (mmol/L)	Weight (kg)	BMI
ETI vs placebo[b]	F508del/F508del F508del/MF	≥12 y	+11.0* +13.8*	NA	NA	+20.7* +25.7*	−39.6* −39.1*	NA	NA
ETI vs placebo[a]	F508del/MF	≥12 y	+13.8*	NA	62%*	+20.2*	−41.2*	NA	+1.04*[,d]
ETI vs placebo[b]	F508del/F508del F508del/MF	6−11 y	+11.2* +9.1*	−1.64* −1.72*	NA	+7* +6.9*	−70.4* −55.1*	NA	NA
ETI vs placebo[b]	F508del/F508del FF508del/MF	2−5 y	NA	−0.89* −0.82*	NA	NA	−70* −52.6*	NA	+0.1[c,e]

Abbreviations: BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire-Revised (quality of life assessment); ETI, elexacaftor/tezacaftor/ivacaftor; LCI, lung clearance index; MF, minimal function; NA, no data available; RR, relative risk.

* Statistically significant.

[a] Difference between baseline and final values in relation to placebo group.

[b] Difference between baseline and final values in the study.

[c] BMI z score for age.

[d] BMI in kg/m^2.

[e] Pooled analysis of F508del/F508del and F508del/MF groups.

Benefits of CFTR modulator therapy on respiratory health

Highly effective modulator therapies have brought significant improvement in many aspects associated with respiratory health in pwCF, which have also been corroborated by real-world studies. The latter, from as early as a few weeks from treatment initiation, have shown a decrease in chronic respiratory symptoms such as cough and mucus production, assessed by means of the CFQ-R, and improved lung function, assessed through the percent predicted forced expiratory volume ($ppFEV_1$), with a mean increase of 10%−13% in pwCF treated with ivacaftor as monotherapy[19] and 10%−15% in those treated with ETI,[20] or assessed with the Lung Clearance Index (LCI).[21]

The improvement in mucociliary clearance achieved by CFTRm therapy results in a decreased frequency of respiratory exacerbations requiring oral or intravenous antibiotherapy and fewer admissions a year due to respiratory causes. A reduction in bronchial colonization by *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) has been described in association with the reduction in airway inflammation and mucus viscosity.[22] Notwithstanding, chronic infection by *P aeruginosa* tend to persist in patients managed with modulator therapy, so studies in larger samples with longer follow-ups are required to determine the impact on the therapy burden associated with inhaled or systemic antibiotics in pwCF treated with CFTRm.[23]

Lastly, there has also been evidence of significant radiological improvement, for instance on lung computed tomography, with reductions in bronchial wall thickening, mucus plugging and hyperinflation,[20] or magnetic resonance imaging,[24] which has shown increased lung ventilation and perfusion and decreased mucus plugging and bronchiectasis.

With respect to sinonasal involvement, there is evidence of an improvement in chronic rhinosinusitis symptoms as well as radiological and endoscopic appearance in response to treatment.[25]

Impact of CFTR modulator therapy on hepatobiliary involvement

Cystic fibrosis hepato-biliary involvement (CFHBI) is common and encompasses a broad spectrum of manifestations. A cross-sectional study conducted by the working group on CF of the SEGHNP (Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition) estimated a prevalence of CFHBI of 20% (86% hepatic involvement without cirrhosis, 14% with cirrhosis).[26] The impact of modulator therapy on hepatobiliary involvement in pwCF is complex and not yet fully established.

The elevation of transaminase and bilirubin levels is a known adverse effect of CFTR modulators and can lead to temporary or definitive discontinuation of treatment. However, trials of triple therapy with novel molecules (VTD: vanzacaftor/tezacaftor/deutivacaftor) have not reported transaminase elevation among the most frequent adverse events.[14,15]

The evidence on the impact of modulator therapy in patients with advanced liver disease comes from obser-

vational studies, as advanced liver disease has been an exclusion criterion in clinical trials of CFTR modulators. In a case series published by Protich et al.,[27] the authors concluded that the use of ETI in patients with advanced liver disease improved pulmonary and nutritional outcomes without a negative impact on hepatic markers or outcomes.

The data published to date suggest that the use of CFTR modulators may be associated with changes in liver function, so close monitoring is recommended.

Pancreatic involvement and CFTR modulators

The degree of pancreatic involvement depends on CFTR function. Milder *CFTR* variants cause recurrent pancreatitis and severe variants cause exocrine pancreatic insufficiency (EPI) and CF-related diabetes. The mechanisms through which CFTR modulators improve exocrine pancreatic function are not fully understood, but it has been hypothesized that the improvement they achieve in the clearance of pancreatic acini (reduction in pancreatitis episodes) entails a recovery of pancreatic acinar function (improvement of EPI).[28]

- Pancreatitis and CFTRm

There is evidence of a reduction in the frequency of RP episodes in pwCF and pancreatic sufficiency treated with CFTR modulators. The published cases correspond to adult pwCF, most of them (59%) managed with ivacaftor as monotherapy. On the other hand, cases of pwCF with IPE who develop pancreatitis upon starting treatment with CFTR modulators have also been described, so pancreatitis should be included in the differential diagnosis of abdominal pain with onset after treatment initiation, even in patients with EPI.[28]

- Exocrine pancreatic insufficiency and CFTRm

Studies have suggested that CFTR modulators may result in the recovery of markers of pancreatic function. Pivotal trials of ivacaftor[2,3] found an increase in fecal elastase levels in children aged less than 6 years and suggested a limited potential for recovery from age 12 years for both ivacaftor and ETI, so early initiation of modulators may be crucial.[28]

The decision to reduce or cease pancreatic enzyme replacement therapy should not be based exclusively on fecal elastase levels, but also on patient symptoms, the amount of fat in stools and close monitoring of markers of nutrition.

Gastrointestinal changes and CFTR modulators

Cystic fibrosis also affects the gastrointestinal system, as the CFTR protein is expressed in the apical membrane of the enterocyte and mediates the secretion of chloride and bicarbonate, which is key in maintaining the fluidity and pH of the luminal contents. In addition to maintaining an adequate pH for nutrient digestion and absorption, bicarbonate is required for the normal solubility of intestinal mucus, that its decrease results in increased mucus viscosity, creating the ideal milieu for the colonization of bacteria and causing dysbiosis, dysmotility and secondary development of chronic bowel inflammation.[29]

Some of the more severe *CFTR* variants are associated with changes in the fecal microbiome composition. Higher levels of potentially harmful species, such as *Escherichia coli*, have been found in homozygous F508del patients and patients with severe disease, in addition to lower levels of beneficial species such as *Faecalibacterium prausnitzii*, *Bifidobacterium* and *Eubacterium limosum*.[29]

Treatment with ETI significantly improves gastrointestinal symptoms. The CFAbd-Score, a questionnaire specifically developed to assess them, evinced improvement with decreased scores for pain, gastroesophageal reflux, disorders of bowel movement, disorders of appetite and quality of life impairment at 24 weeks of ETI therapy.[30]

Recent studies have highlighted the impact of modulator therapy on the intestinal microbiota. Treatment with ivacaftor was associated with a decrease in intestinal inflammation and an increased abundance of beneficial bacteria, such as *Akkermansia*.[31]

Growth and nutritional status: changes in the approach to nutrition for patients with CF managed with CFTR modulators

Treatment with ETI is associated with increases in body mass index (BMI) in very age group, as it reduces the risk of undernutrition and increases the risk of overweight and obesity. In adults, the increase in fat mass seems to exceed the increase in lean mass, while in children the increase seems to be more evenly distributed between both compartments, giving rise to greater interindividual variability.[32] In consequence, the use of body composition tests and somatometric and functional assessments of nutritional status, such as bioelectrical impedance analysis, sonography or dynamometry, should be promoted for adequate monitoring of these changes.

The generalized recommendation of a hypercaloric diet (between 120% and 200% of the recommended dietary allowance) is obsolete, and nutritional support should be individualized, placing greater emphasis on the importance of a healthy diet from a very young age.

Other manifestations of cystic fibrosis and problems emerging with increasing life expectancy

Despite their hypothetical benefits, there is a dearth of data on the efficacy of modulators in improving bone health in the pediatric age group.

Results regarding the impact of CFTRm on disturbances of glucose metabolism are promising. Although most published clinical trials have been conducted in small samples, the current evidence suggests that ivacaftor[33] may improve insulin secretion and reduce the prevalence of CF-related diabetes, and that triple therapy with ETI may improve average glucose levels, glycemic variability and the time in range measured through continuous glucose monitoring.[34]

Although the effects of CFTRm have yet to be well established, glucose metabolism must be monitored closely

to adjust insulin requirements and prevent hypoglycemic episodes.

As the life expectancy of pwCF increases, they will face new medical challenges for which the evidence is scarce in this population, such as cardiovascular disease, malignancy or mental health disorders.[35] As pediatricians, we need to update follow-up protocols, inform families of these risks and, above all, encourage health promotion measures centered on healthy lifestyle habits.

Future challenges. Off-label access to CFTR modulators

CFTR modulators for patients with non-F508del variants

Access to ETI for the group of patients who do not carry the F508del variant is limited due to the lack of clinical data supporting its efficacy, except in the United States and some other countries where it is authorized in select circumstances.

A recent systematic review[36] evaluated real-world data and a placebo-controlled clinical trial (NCT05274269) in patients treated with ETI carrying rare non-F508del variants. In the case of some variants, N1303 K and G85E, there was consistent evidence of improvement in ppFEV$_1$ across individuals in different series, with a magnitude of response that was similar to that reported the F508del variant.

Prenatal use of CFTR modulators

Data on fetuses exposed in utero to CFTRm have started to be published in recent years, in some cases as a result of treatment of CF in the mother, in others of prenatal treatment of the fetus in a carrier mother on account of previous children with CF or prenatal diagnosis due to findings such as meconium ileus which, in some cases, has resolved after initiation of modulator therapy.[37] Other reports bring up the potential to preserve exocrine pancreatic function or fertility in male patients. The number of cases of CFTRm exposure in utero has been increasing in the past two years and introduces new therapeutic possibilities, but also challenges, such as the potential adverse effects of these drugs at such early stages of life[38] or of false negative results in newborn screening.[39] The monitoring of children whose mothers have received CFTRm during gestation must take this possibility into account, and performance of genetic testing should be considered, in addition to ophthalmological assessments and liver function tests, among others.

Other challenges. Mental health. Decreased adherence to treatment

CFTR modulators improve many clinical aspects and overall quality of life in patients with CF, but their increasingly widespread and prolonged use is revealing potential adverse effects on areas such as mental health, with manifestations like depression or anxiety symptoms, sleep disturbances or behavioral changes. The data are still scarce for the pediatric population, but warrant close surveillance, as these patients are still developing. In some countries, national protocols and consensus guidelines already include the use of the use of questionnaires to attempt to assess the potential neuropsychiatric impact of these drugs, even in the pediatric age group.

Despite the emphasis placed by multidisciplinary care teams in cystic fibrosis units on the advisability of maintaining all other treatments, especially nebulized therapies, numerous studies and real-world data already show that adherence decreases in a high percentage of patients treated with modulators, even among those with advanced lung disease.[40] Some studies that are still underway aim to assess the clinical impact of discontinuing specific nebulized therapies. We must undertake the challenge of educating the pediatric population on the actual consequences of the disease without adequate control and sustained adherence to recommended treatments.

Conclusion

CFTR modulators have revolutionized the treatment and management of patients with CF, given the substantial improvement that they experience, chiefly in respiratory, gastrointestinal and nutritional manifestations. However, access to these drugs is limited by eligibility based on the patients' genetics or age, so further research is required to make it possible for all patients to benefit from highly effective therapies.

Declaration of competing interest

M. Dolores Pastor Vivero reported participation as a paid speaker in events organized by Vertex Pharmaceuticals. She is also the principal investigator in clinical trials sponsored by Vertex. However, these ties have not influenced the work presented in this article.

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