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Cystic fibrosis transmembrane conductance regulator modulators and novel therapeutics for cystic fibrosis treatment

Moduladores de la conductancia de transmembrana de fibrosis quística y nuevos tratamientos para fibrosis quística

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ABSTRACT. Cystic fibrosis (CF) is a hereditary, autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. To date, more than 2,000 mutations or variants in this gene have been described. Historically, the treatment of CF focused on clinically managing the manifestations and complications resulting from CFTR protein dysfunction. The discovery of the gene and the mutations causing this disease has led to the development of drugs known as CFTR modulators, which restore and optimize the function of the defective protein. The objective of this publication is to conduct a review of these new medications and their impact on lung function, nutritional status, quality of life, and patient survival, serving as an example of personalized medicine.

Keywords: cystic fibrosis, cystic fibrosis transmembrane conductance regulator modulators, personalized medicine.

RESUMEN. La fibrosis quística es una enfermedad hereditaria, autosómica recesiva, causada por mutaciones en el gen de la proteína reguladora de conductancia de transmembrana de fibrosis quística (CFTR). A la fecha se han descrito más de 2,000 mutaciones o variantes en dicho gen. Históricamente el tratamiento de fibrosis quística estaba enfocado en el manejo clínico de las manifestaciones y complicaciones ocasionadas por la disfunción de dicha proteína. El descubrimiento del gen y de las mutaciones causantes de esta enfermedad ha permitido el desarrollo de fármacos conocidos como moduladores del CFTR que restauran y optimizan la función de la proteína defectuosa. El objetivo de esta publicación es llevar a cabo una revisión de estos nuevos medicamentos y su impacto sobre la función pulmonar, el estado nutricional, la calidad de vida y la supervivencia de los pacientes, constituyendo un ejemplo de medicina personalizada.

Palabras clave: fibrosis quística, moduladores de conductancia de transmembrana de fibrosis quística, medicina personalizada.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive hereditary disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein gene. The CFTR protein, a transmembrane ion channel regulated by cyclic *adenosine monophosphate (*AMP), facilitates ion transport, particularly chloride, across the apical edge of cell membranes in secretory epithelia. CF presents as a multisystemic disease primarily impacting the respiratory system, pancreas, gastrointestinal tract, reproductive system and sweat glands. CFTR dysfunction results in the production of thick, viscous secretions within affected organs.[1,2]

To date, over 2,000 mutations or variants have been identified within the CFTR protein gene. Among these, certain mutations are pathogenic, causing disease; while others exhibit variable clinical implications, and some remain of uncertain or unknown clinical significance.[3]

Mutations can induce diverse abnormalities in the CFTR protein, spanning from complete absence of synthesis,

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deficient protein folding and maturation, non-functional protein at the epithelial edge, early protein degradation, to reduced protein half-life, among other alterations.[4]

Based on resultant protein function, mutations are classified into six classes. Class I mutations result in a lack of CFTR protein synthesis, while class II mutations impair protein folding and trafficking to the epithelial edge. The most prevalent mutation worldwide is F508del, a class II mutation. Up to 80% of all patients have at least one copy of this variant.[5-7]

In class I and class II mutations, no protein is present at the epithelial edge. Class III mutations, or gating mutations, lead to the synthesis of non-functional CFTR protein at the epithelial edge. Class IV mutations produce a protein with decreased anionic conductance. Class V mutations exhibit reduced CFTR protein synthesis, while class VI mutations result in decreased protein stability, leading to decreased half-life and increased turnover. Notably, some mutations may give rise to multiple defects; for instance, the class II F508del mutation also produces class III and class V defects.

The severity of protein defects often correlates with clinical severity, although patient prognosis is influenced not solely by the genotype but also by environmental factors, socioeconomic status, sex, accessibility to treatment, among other variables.[8]

Historically, CF treatment focused on managing clinical manifestations and complications arising from CFTR protein dysfunction. Currently, novel therapeutics called CFTR modulators aim to restore and optimize defective protein function, halting or preventing disease progression by augmenting functional CFTR protein levels on cell surfaces or by enhancing protein activity.

CFTR MODULATORS

CFTR protein modulators are small molecules that bind to a site on the CFTR either prior or after processing. These modulators can be categorized into various classes such as potentiators, correctors, stabilizers, amplifiers, among others, each aimed at reinstating the functionality of the CFTR protein.[9]

CFTR Potentiators

Potentiators correct the activity of ion channels and allow for better chloride and bicarbonate transport through the CFTR. These medications are effective for class III mutations and class IV mutations.

Ivacaftor

VX-770 or Ivacaftor (Kalydeco®) was the first CFTR modulator approved by the United States Food and Drug Administration (FDA) in 2012. It is a potentiator as it increases the probability of the defective ion channel remaining open, allowing ions to pass more effectively.[10,11]

Ivacaftor is administered orally, along with fatty foods to increase its bioavailability. The recommended dosage varies according to age and weight and is outlined in *Table 1*.[10]

Peak plasma levels are reached in 4 hours, and its half-life is 12 hours. Ninety nine percent of the drug is bound to plasma proteins. It is metabolized by CYP3A to active metabolites, although of much lower potency, as well as to other inactive metabolites. It is eliminated by bile, with 87.7% of a dose eliminated as metabolites in feces and approximately 5% eliminated in urine as the original compound and/or its metabolites.[12,13]

Side effects

Mild to moderate elevation of aminotransferases (alanine aminotransferase and aspartate aminotransferase) is common in patients using this modulator.[14] Evaluation of liver function tests, particularly aminotransferases, is recommended in patients undergoing treatment with the drug. In cases where the elevation of transferases surpasses five times the upper limit, discontinuation of ivacaftor is recommended. Treatment may be reinstated following the normalization of these elevated levels. It may be necessary to adjust the dose and/or frequency of use.

Cases of non-congenital cataracts in pediatric patients treated with ivacaftor have also been reported. Routine ophthalmological evaluation is recommended at baseline and periodically thereafter.[13]

Teratogenicity

Research conducted in rodent models administering ivacaftor at doses up to five times the standard dosage has not demonstrated any adverse effects on fetal development. In 2021, a study assessing the influence of modulator

Table 1: Doses of ivacaftor for cystic fibrosis patients according to age and weight.

Age (month)	Dosage (packet BID)
1 to 2	One 5.8 mg
2 to 4	One 13.4 mg
4 to 6 (≥ 5 kg)	One 25 mg
6 months to 6 years	5 to 7 kg one 25 mg 7 to14 kg one 50 mg ≥ 14 kg one 75 mg
6 years or more	One 150 mg tablet BID

BID = *bis in die* (twice a day).

therapies during pregnancy and their subsequent effects on infants who were breastfed was published. The study included 46 CF patients who were taking triple modulator therapy (Trikafta®) upon confirmation of pregnancy, with six opting to discontinue treatment. Among the patients that continued the treatment, 31 adverse events were detected, with 28 unrelated to triple therapy. Of the remaining events, only one was linked to modulator use. These findings provide reassurance regarding the safety profile of modulator therapies in pregnant CF patients. Moreover, it is important to underscore the advantageous aspects of modulator therapy during pregnancy, which include enhanced nutritional status, reduced frequency of exacerbations, and overall improved health outcomes.[15] A study of pregnant women with CF using modulators during pregnancy and lactation is currently underway.[16]

Drug interactions

During treatment with ivacaftor, beverages and foods containing grapefruit should be avoided.[10] Azoles (ketoconazole, itraconazole, posaconazole, voriconazole) as well as some macrolides (telithromycin and clarithromycin) are potent inhibitors of the CYP3A4 isoenzyme, leading to a significant increase in ivacaftor plasma levels. If potent CYP3A4 inhibitors must be administered with ivacaftor, it is recommended to adjust the dosing regimen to 150 mg twice weekly.[12]

With moderate inhibitors (fluconazole and erythromycin), the dose should be reduced to 150 mg per day in patients over 12 years of age. Ivacaftor is not recommended for use in patients treated with potent CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, and phenytoin. If used concomitantly with benzodiazepines, caution should be exercised, and the possible adverse effects should be monitored. A similar situation occurs with the concomitant use of digoxin.[12]

Adverse reactions

In placebo-controlled studies, the most common adverse reactions in patients receiving ivacaftor were headache (22.9%), sore throat (20.5%), upper respiratory tract infection (22.9%), nasal congestion (20.5%), abdominal pain (15.7%), diarrhea (13.3%), dizziness (9.2%), cutaneous rash (14.5%), and increased aminotransferases (12.8%).[14,17]

Indications

Initially, ivacaftor was indicated for gating or class III mutations. However, its indication has since been expanded to include class IV mutations that exhibit residual function. It is indicated from the first month of life and for infants weighing 3 kg or more. This approval was largely based on *in vitro* data, as in vitro evaluation has proven predictive of clinical response.

CFTR correctors

Correctors bind to immature CFTR protein and assist in folding, processing, and trafficking the mutated protein to the cell membrane, thereby increasing the quantity of available and functional protein.[18] This type of medication has shown efficacy in specific class II mutations such as F508del.

In individuals homozygous for this mutation, the use of a potentiator (ivacaftor) alone is not sufficient to enhance CFTR function and provide clinical improvement.[19] Dysfunction caused by class II mutations, such as F508del, results in various defects in protein processing, including folding, trafficking to the epithelial edge, reduced channel opening, and shortened protein half-life, among others. Correcting all these molecular defects is necessary to restore CFTR function in F508del mutations.[20]

Lumacaftor

Lumacaftor (VX-809) is a first-generation CFTR corrector that improves stability in the first transmembrane domain and reduces the degradation of mutated protein in the endoplasmic reticulum.[21] In 2015, The FDA and the European Medicines Agency (EMA) authorized the use of lumacaftor in combination therapy with ivacaftor (Orkambi®) for homozygous F508del patients over 12 years of age.

Tezacaftor

Tezacaftor (VX-661) is a second-generation corrector that improves the trafficking of CFTR proteins to the surface of epithelial cells. Tezacaftor has some advantages over lumacaftor, such as fewer drug interactions and fewer adverse effects.[22,23] In 2018, clinical use of tezacaftor-ivacaftor (Symdeko®/Symkevi®) was approved for patients with CF who have at least one F508del mutation or mutations with residual function.

Triple combination therapies

Elexacaftor (VX-445) is a CFTR corrector and, when combined with tezacaftor, complements its action to improve protein processing and transport to the cell surface. The triple combination elexacaftor/tezacaftor/ivacaftor (ETI) is commercially known as Trikafta®/Kaftrio®. This triple combination increases the likelihood of defective CFTR protein channels remaining open, allowing chloride ions to pass more effectively. ETI was approved by the FDA in

2019 for patients with at least one F508del mutation. It is currently authorized from the age of two years onward. The dosage of triple therapy varies according to age and weight and is detailed in *Table 2*.[24]

EFFECTIVENESS OF MODULATORS

Ivacaftor

Since ivacaftor was the first modulator available and marketed, there is more information available regarding its efficacy and safety profiles.

Pulmonary function, as assessed by the percentage of predicted forced expiratory volume in one second (FEV1), has served as a primary endpoint in various studies assessing the effectiveness of novel medications in CF. For example, when compared to placebo, dornase alfa was associated with a 5.8% improvement in FEV1 at 24 weeks, and in studies with inhaled tobramycin compared to placebo, it was associated with a 12% improvement in FEV1 at 20 weeks.[25,26] Lung function has also been one of the parameters used to evaluate the effectiveness of CFTR modulators.

ENVISION and KONNECTION were phase III studies, randomized, double-blind, and placebo-controlled, in which the efficacy of ivacaftor in gating mutations was evaluated. These studies showed improvement in lung function, reduction in the frequency of exacerbations, and weight gain.[17,27]

In the study published by Ramsey *et al.*,[14] researchers demonstrated the impact of ivacaftor therapy on lung function, quality of life (CFQ-R), and nutritional status in patients over 12 years with at least one class III mutation. Patients were followed for 48 weeks and compared with a placebo group. In patients treated with ivacaftor, there was an increase of 10.6% in the predicted percentage of FEV1 compared to baseline, as opposed to patients in the placebo group ($p < 0.001$). It was also observed an improvement of 8.6 points in CFQ-R, an average weight gain of 2.7 kg, and a reduction in sweat chloride concentration of -48.1 mmol/L, with a lower proportion of adverse events with ivacaftor than with placebo (24 vs 42%).[14]

The efficacy of ivacaftor use was further corroborated through a long-term observational study involving patients receiving treatment in real-world clinical settings. This longitudinal study used data from the North American CF Registry, as well as data from the UK Registry. Patients from the North American registry who were receiving ivacaftor were included (635 patients) versus 1,874 controls and followed for 5 years; while, from the UK registry, 247 patients treated with ivacaftor were followed for four years and compared with 1,230 control patients.[28]

Patients treated from the North American Registry showed better-preserved lung function, with an average percentage change in predicted FEV1 of -0.7 versus -8.3% points in controls. Regarding the nutritional status, an average increase of +2.4 kg/m^2 in body mass index (BMI) in the treatment group versus +1.6 kg/m^2 in controls was observed. There was also a lower risk of pulmonary exacerbations and hospitalizations, lower prevalence of CF-related diabetes, and isolation of *Pseudomonas aeruginosa* in treated patients compared to the control group. Similar results were observed in the UK registry. These results demonstrate that the CFTR potentiator ivacaftor is a disease-modifying therapy in patients with CF.[28]

A clinical study with ivacaftor was conducted among CF patients in the UK and Ireland carrying the G551D mutation that presented with advanced disease, as indicated by inclusion criteria such as placement on the transplant waiting list and/or having a FEV1% less than 40%. Patients with the same clinical characteristics were included in the control group. In the treatment group, an improvement of 16.7% in the predicted percentage of FEV1, greater weight gain, and less use of intravenous antibiotics were observed. The differences with the control group were statistically significant.[29] While the predominant focus of clinical trials assessing CFTR modulators revolves around enhancements in pulmonary

Table 2: Recommended dosing of elexacaftor/tezacaftor/ivacaftor for cystic fibrosis patients according to age and weight.

Age	Morning dose	Evening dose
2 to < 6 years	< 14 kg 1 white and blue packet of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg ≥ 14 kg 1 white and orange packet of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	1 white and green packet of ivacaftor 59.5 mg 1 white and pink packet of ivacaftor 75 mg
6 to < 12 years	< 30 kg 2 light orange tablets of elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg ≥ 30 kg 2 orange tablets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	1 light blue tablet of ivacaftor 75 mg 1 light blue tablet of ivacaftor 150 mg
12 years and older	2 orange tablets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	1 light blue tablet of ivacaftor 150 mg

function, notable non-pulmonary benefits have also been documented. These include improvement in nutritional status, better glycemic control in patients with diabetes, amelioration of sinus disease, and improvement in hepatic steatosis, among other observed effects.[30-32]

Efficacy of combined therapy of ivacaftor with lumacaftor

Combined therapy with lumacaftor-ivacaftor produces clinically significant results on the predicted percentage of FEV1 (+2.6 to +4.0%, $p < 0.001$) as well as a decrease in pulmonary exacerbations (-30 to -39%, $p < 0.001$) in individuals with homozygous F508del mutations. However, these results were not as significant as those seen with ivacaftor for individuals with gating mutations.[33]

Combined therapy of ivacaftor with tezacaftor

In the EVOLVE study, where the combination of tezacaftor-ivacafor was used in homozygous F508del patients, an improvement in the predicted percentage of FEV1 of +4.0% ($p < 0.001$) and a decrease in pulmonary exacerbations (-35%, $p < 0.005$) were observed when compared to placebo.[23]

In individuals heterozygous for F508del and a residual function mutation, tezacaftor-ivacaftor improved the predicted percentage of FEV1 (+6.8%, $p < 0.001$) when compared to placebo and to ivacaftor alone (+2.1%, $p < 0.001$).[34] However, both lumacaftor and tezacaftor exhibit limited efficacy as modulators, resulting in minimal improvement in lung function, nutritional status, and sweat chloride levels among F508del patients when compared to the notable impact of ivacaftor on gating mutations and conductance mutations.[33,34]

Triple combination elexacaftor, tezacaftor, and ivacaftor (ETI)

Clinical trials have shown that triple therapy is highly effective in patients with at least one F508del mutation.[35,36] A phase III, randomized, double-blind study evaluated the effect of triple therapy in homozygous F508del patients aged 12 years or older.[36] During the initial four-week period, all participants were administered the combination therapy of tezacaftor/ivacaftor, following which they were subjected to randomization at a ratio of 1:1. One group continued with the triple therapy regimen (elexacaftor/tezacaftor/ivacaftor), while the other group received an additional four weeks of tezacaftor/ivacaftor. This study assessed the therapeutic impact on pulmonary function indicated by the percentage of predicted FEV1, along with changes in sweat chloride levels, and the respiratory domain of the CFQ-R. The group of patients on triple therapy showed an improvement in the predicted percentage of FEV1 (10.0 with a 95% confidence interval (CI) of 7.4-12.6, $p < 0.0001$). The sweat chloride concentration showed a reduction of 45.1 mmol/L (95% CI 50.1-40.1, $p < 0.0001$) when compared to the group that received tezacaftor-ivacaftor only. The treatment was well tolerated, with mild or moderate adverse events.[36]

Research by Middleton *et al.* examined the efficacy of triple therapy in heterozygous CF patients with a F508del mutation and another minimal function mutation for 24 weeks. This study observed an improvement in the predicted percentage of FEV1 of +14.3% at 24 weeks and an improvement in the respiratory domain scores of the CFQ-R of +20.2. At the same time, a 63% reduction in pulmonary exacerbations was detected. There was an increase in BMI of +1.04 kg/m^2, and all these changes were statistically significant.[35]

He *et al.* published a meta-analysis in January 2024 including studies that evaluated the efficacy and safety profiles of triple therapy in CF patients. Six studies with a total of 1,125 patients were included. The meta-analysis revealed that triple therapy significantly improves lung function measured by the predicted percentage of FEV1 by 10.29% (95% CI 6.44-14.14, $p < 0.00001$). Additionally, there was a substantial reduction in sweat chloride concentration by 40.30 mmol/L (95% CI -49.85 – -30.74, $p < 0.00001$), and an improvement of 15.59 points in the respiratory domain of the CFQ-R (95% CI 9.25-19.94, $p < 0.00001$), compared to placebo.

The incidence of adverse events in the triple therapy group was slightly higher than in the placebo group or groups treated only with ivacaftor or ivacaftor-tezacaftor, although not statistically significant. Adverse events found included odynophagia, cough, nasopharyngitis, headache, increased expectoration, pulmonary exacerbations, and upper respiratory tract infections. The meta-analysis concludes that the findings suggest that the triple ETI therapy is an effective treatment in CF patients, although long-term safety monitoring should continue.[37]

It is important to underscore that CF patients undergoing treatment with CFTR modulators still require additional maintenance medications to treat systemic manifestations of the disease. Published studies demonstrate the clinical efficacy of modulators in CF patients, as their use leads to substantial improvements in quality of life, lung function, nutritional status, and reduction of particularly bothersome symptoms such as cough and digestive symptoms. There are also significant reductions in healthcare resource utilization, hospitalizations, pulmonary exacerbations, and emergency room visits.[38]

Nevertheless, the elevated cost associated with these medications poses a significant challenge to accessibility, particularly in low- and middle-income countries such as Mexico.[39]

Conflict of interests: the author declare no interest conflicts.

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