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CLINICAL CASE

Tritherapy with cystic fibrosis transmembrane conductance regulator protein modulators in cystic fibrosis

Triterapia con moduladores de la proteína de conductancia de transmembrana en fibrosis quística

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What do we know about the subject matter of this study?

The Transmembrane Conductance Protein modulator triple therapy (Elexacaftor-Tezacaftor-Ivacaftor), recently approved in the United States and Europe, has been shown to improve lung function and quality of life in patients with Cystic Fibrosis as young as 6 years of age.

What does this study contribute to what is already known?

This one-year clinical follow-up study demonstrates the improvement in the quality of life, nutritional status, and pulmonary function of what we believe is the first Chilean pediatric patient with Cystic Fibrosis to have access to Elexacaftor-Tezacaftor-Ivacaftor triple therapy.

Abstract

Recent studies have shown that therapy with Cystic fibrosis transmembrane conductance regulator (CFTR) modulators in Cystic Fibrosis (CF) patients with Elexacaftor-Tezacaftor-Ivacaftor (ETI) decreases exacerbations and improves lung function and quality of life. **Objective:** to report the clinical response in the first patient in our setting treated with ETI. **Clinical Case**: 14-year-old female patient with severe cystic fibrosis phenotype, heterozygous for the Phe508del mutation (Phe508del/1078delT), with moderate pulmonary involvement and pancreatic insufficiency (PI). The patient started ETI therapy after the disease entered a phase of clinical and pulmonary function deterioration. From the second visit (45 days) until the end of the follow-up (365 days), the patient experienced a significant improvement in the quality-of-life domains measured by the CFQ-R 14+ questionnaire. In the pulmonary function study at 45 and 365 days, FVC increased by 21% and 22%, FEV1 by 20% and 27%, and FEF 25-75 by 23% and 37%, respectively. Nutritional assessment parameters in the first six months of follow-up showed an increase in wBMI from 1.6 to 5.6 k. No adverse effects were observed. **Conclusion:** treatment with ETI in our CF patient showed a remarkable improvement in quality of life, pulmonary function, and nutritional status.

Keywords:
Cystic Fibrosis;
Modulators;
Transmembrane Conductance Protein;
Triple Therapy

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Introduction

Cystic Fibrosis (CF) is the most common hereditary disorder with a poor prognosis in whites and affects more than 100,000 people worldwide. It is an autosomal recessive disease with multisystem involvement, caused by mutations of the transmembrane conductance protein regulator gene, known as CFTR[1]. More than 2000 different CFTR mutations have been reported, with Phe508del being the most common worldwide. CFTR mutations have been classified into classes I to VII, according to the cellular mechanism involved in the failure of their production[2]. In Chile, estimates have been made considering the racial mix of the population, and studies of variants (CFTR mutations) and neonatal screening have shown an incidence of 1/8000 live newborns, predicting about 30 new cases per year[3]. It has been reported that the Phe508del mutation is the most frequent in our sphere with 30.3% of the alleles studied, followed in a much smaller proportion by R334W with 3.3% and G542X with 2.4%[4].

The usual treatment of CF includes antibiotics, mucolytics, pancreatic enzymes, nutritional supplementation, kinesiotherapy, and comprehensive management in multidisciplinary centers, which has allowed for prolonging the survival and quality of life of patients. However, most of these therapies are aimed at the symptoms and not at the disease itself.

In recent years, with the advancement of precision medicine, therapies have been developed to ameliorate specific CFTR defects and were termed "CFTR modulators". Modulators are divided into *correctors*, which improve trafficking of the defective CFTR to the cell surface, *enhancers*, which increase the probability of opening the chlorine channel bound to the previously closed CFTR, *amplifiers*, which increase CFTR synthesis, and *stabilizers*, which maintain CFTR in the correct position on the cell surface[5,6].

In 2019, two studies were published simultaneously of combination therapy with three CFTR modulators, which is likely to change the course of the disease in the future. These studies were conducted in CF patients older than 12 years, homozygous 7 and heterozygous 8 for the Phe508del variant, who received the combination of Elexacaftor (corrector), Tezacaftor (corrector), and Ivacaftor (enhancer), managing to demonstrate a decrease in exacerbations and beneficial effects on lung function and quality of life.

Based on this evidence, the US Food and Drug Administration (FDA) authorized the combination of Elexacaftor, Tezacaftor, and Ivacaftor (ETI), designating it as a first-line drug in rare diseases and estimating that almost 90% of the CF population could benefit from this therapy[9]. The ETI combination is commercially known as Trikafta® in the United States and Kaftrio® in Europe. Figure 1 details its mechanism of action[10,11].

Recently, the FDA and the European Medicines Agency (EMA) have extended the age of approval to children with CF between 6 and 11 years, considering a phase 3 study, conducted over a 24-week period, which evaluated the safety and efficacy of the ETI scheme for children in this age range with at least one PheF508del mutation. The study showed that the drug was generally efficacious, well tolerated, and with a good safety profile[12]. The objective of this report is to present the results of the first 12-month follow-up of what we believe is the first Chilean pediatric patient to have access to this innovative therapy.

Clinical Case

A 14-year-old female patient with severe phenotype CF, heterozygous for the PheF508del mutation (Phe508del/1078delT, class I and II variants, respectively), with pulmonary involvement and pancreatic insufficiency. She was diagnosed at 3 months of life, due to the association of respiratory symptoms, persistent diarrhea, and poor weight gain, through the sweat electrolytes test, with a Chlorine level of 88 meq/l (normal value < 30meq/l). Pancreatic insufficiency led her to chronic malnutrition very early, so at 7 months of life, a gastrostomy tube was placed, which she has maintained until today.

She presented numerous endobronchial infections requiring oral and intravenous antibiotic treatment, being hospitalized on 15 occasions for periods of 2 weeks up to 85 days. Most of these infections were due to multi-sensitive *Staphylococcus aureus*, which became chronic, and intermittent *Pseudomonas aeruginosa*, which was detected on two occasions. At 12 years of age, the glucose tolerance test confirmed the diagnosis of CF-related Diabetes Mellitus, as a complication of her pancreatic damage.

Her baseline respiratory treatment consisted of respiratory kinesiotherapy three times a day, followed by nebulization of dornase-α once a day and 7% hypertonic NaCl solution twice a day. Nutritional and digestive treatment included pancreatic enzymes (Zenpep®) before each feeding, vitamins A, D, E, and K, lansoprazole, hypercaloric feeding by mouth, and gastrostomy. The bone density scan showed a density within the low normal range and diabetes was maintained on treatment with ultra-rapid-acting insulin.

Pulmonary damage was moderate to severe, expressed in pulmonary function with FEV1 at 66% of predicted, and the chest CT scan showed diffuse, cylindrical, and cystic bronchiectasis in all lung

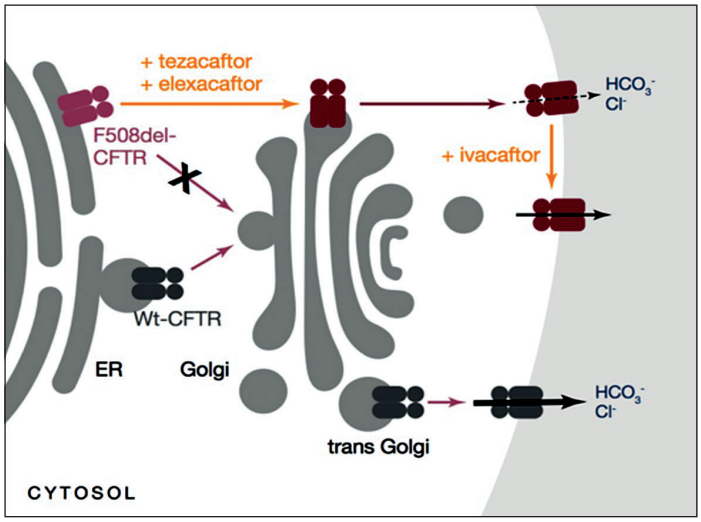

Figure 1. Tezacaftor + Elexacaftor + Ivacaftor (Trikata®). The combination of correctors Tezacaftor + Elexacaftor acts in a complementary way, modifying CFTR assembly, processing and traffic defects. The Ivacaftor enhancer drives the opening of the CFTR channel. The figure is freely accessible and distributed under the terms of the Creative Commons Attribution License CC-BY 4.0, which permits unrestricted use, distribution, and reproduction in any medium (Ref[10,11]).

segments, fibrosis, and diffuse mucoid impactions. Pulmonary deterioration intensified, and the patient presented persistent bronchorrhea and progressive drop in FEV1 so bronchoalveolar lavage (BAL) was performed at the level of the RUL, whose culture only showed multi-sensitive *Staphylococcus aureus*; endobronchial infection by other bacterial agents was ruled out, as well as non-tuberculous bacilli and fungi. Despite antibiotic management, kinesiologic support, adequate nutrition, good diabetic control, dornase- α, and hypertonic saline solution, pulmonary function did not improve.

The patient's parents opted to initiate treatment with CFTR modulators. As advised by our multidisciplinary team, the parents purchased from the United States the ETI triple therapy (Trikafta®), which was initiated without discontinuing her baseline treatment. The drug was administered in two daily doses: 2 fixed-dose tablets of Elexacaftor 100mg, Tezacaftor 50mg, and Ivacaftor 75mg in the morning and twelve hours later 1 tablet of Ivacaftor 150mg. The tablets were administered with a hypercaloric diet and pancreatic enzymes to maximize their efficacy.

It was decided to monitor the response to ETI triple therapy by measuring the quality of life, pulmonary function, and nutritional status. This was performed in five clinical assessments: on the day of initiation of therapy, which we named day 0 or baseline, and then at 45, 90, 180, and 365 days after initiation of therapy. The evaluations were carried out with the informed consent of the parents and the assent of the patient.

To measure quality of life, the self-administered and validated Spanish version of the Cystic Fibrosis Questionnaire-Revised (CFQ-R 14+) in its version for adolescents over 14 years of age and adults was used. During the five evaluations, the patient completed the survey smoothly and in approximately 15 minutes each time. Table 1 shows the scores evolution of the different domains of quality of life at follow-up.

Pulmonary function was measured using the Vyntus™ v-176430 Spirometer (Vyaire®, USA) according to the recommendations of international standards[14,15]. In spirometry, forced vital capacity was measured in liters and percentage of predicted (FVC L, FVC %), forced expiratory volume in 1 second in liters and percentage of predicted (FEV_1 L, FEV_1%), and forced expiratory flow at 25%-75% of FVC also in liters and percentage of predicted (FEF25-75 L, FEF 25%-75%), for which Quanjer's multi-ethnic reference values were used[16]. The patient could perform baseline spirometry without difficulty in all five evaluations. The three pulmonary function parameters analyzed showed percentage improvements compared with the predicted values of the second visit. The evolution of FVC% was 74% (baseline), 95% (45 days), 95% (90 days), 94% (180 days), and 96% (365 days); FEV_1% was 69% (baseline), 89% (45 days), 96% (90 days), 95% (180 days), and 96% (365 days); and FEF 25%-75% was 53% (baseline), 76% (45 days), 90% (90 days), 80 (180 days), and 90% (365 days). The values of these three parameters measured in liters showed a similar trend (Table 2).

The patient was weighed and measured on a SECA model 769 digital scale with measuring rod. The nutritional status was calculated by measuring the BMI percentile (wBMI) at each evaluation, according to WHO curves[17]. From the initial evaluation to the end of the 12-month follow-up period, the patient gained 1.8k and increased her wBMI by 2.8. Table 3 shows the evolution of these parameters in the follow-up period.

During the follow-up period, the patient did not present exacerbations, hospitalizations, or unscheduled medical consultations, remaining on her usual therapy plus ETI triple therapy during the 12 months. Adherence to treatment was adequate and no adverse effects related to triple therapy were detected. Liver function was monitored periodically and remained normal, and abdominal ultrasound scans were performed, ruling out liver involvement. There were no dermatological manifestations or symptoms suggestive of visual alterations during follow-up, corroborated by an ophthalmologic evaluation before starting triple therapy and at the end of the follow-up.

Table 1. Evolution of the dimensions of the CFQ-R 14+ quality of life questionnaire in 12 months of ETI triple therapy

Dimensions	ETI day 0	ETI day 45	ETI day 90	ETI day 180	ETI day 365
Physical capacity	4.5%	66.7%	91.7%	100%	100%
Vitality	25%	83.3%	91.7%	100%	100%
Emotional functioning	60%	80%	80%	93.3%	100%
Eating problems	66.7%	55.6%	100%	55.6%	88.9%
Treatment burden	44.4%	55.6%	66.7%	77.8%	77.8%
Health perception	33.3%%	55.6%	100%	88.9%	88.9%
Social functioning	0%	0%	0%	55.6%	66.7%
Body image	66.7%	88.9%	88.9%	88.9%	100%
Activity limitation	41.7%	66.7%	75%	91.7%	100%
Weigth problems	66.7%	66.7%	100%	66.7%	66.7%
Respiratory symtoms	83.3%	72.2%	88.9%	100%	100%
Digestive symtoms	77.8%	88.9%	77.8%	77.8%	88.9%

ETI: Elexacaftor +Tezacaftor + Ivacaftor triple theraphy. The CFQ-R 14+ has 50 questions, structured in 12 domains. The questionnaire has 4 response alternatives for each question, which are integrated into the corresponding domain, obtaining a percentage score for each domain that fluctuates between 0 (lowest score) to 100 (highest score).

Table 2. Evolution of lung function in 12 months of ETI triple therapy.

	Basal	LLN	ETI Day 45	LLN	ETI Day 90	LLN	ETI Day 180	LLN	ETI Day 365	LLN
FVC L	2.18	2.38	2.77	2.35	2.82	2.39	2.81	2.41	2.89	2.41
FEV_1 L	1.83	2.14	2.33	2.11	2.57	2.16	2.55	2.17	2.62	2.17
FEF_{25-75} L	1.78	2.24	2.56	2.23	3.06	2.26	2.74	2.28	3.11	2.28

ETI: Elexacaftor +Tezacaftor + Ivacaftor triple theraphy, FVC L: forced vital capacity in liters, FEV1: forced expiratory volume for 1 second in liters, FEF 25-75: forced expiratory flow at 25–75% of FVC in liters, LLN: Lowed limit of normal according to multi-ethnic reference values for gender, age and height (Ref. 16).

Table 3. Evolution of nutritional status in 12 months of ETI triple therapy

	ETI Day 0	ETI Day 45	ETI Day 90	ETI Day 180	ETI Day 365
Weigth in kg	43.2	45.6	45.1	44.8	45
wBMI	41.3	59.4	50.9	46.9	44.1

ETI: Elexacaftor + Tezacaftor + Ivacaftor triple theraphy, wBMI: body mass index percentile.

Discussion

During the follow-up, the patient presented favorable changes in quality of life, pulmonary function, and nutritional status. In the second evaluation, performed 45 days after starting ETI therapy, important changes were already noted in the domains of physical capacity, vitality, emotional functioning, health perception, activity limitation, and body image, which were maintained during the 12 months. The improvement in the domains of perceived treatment burden and respiratory symptoms was more gradual but constant until the end of the follow-up. These findings are in line with that reported in the study of patients with heterozygous mutation for the ΔF508, who received the ETI combination and reported 20 percentage points higher in quality of life measured with the CFQ-R, than those who received placebo between 4 and 24 weeks of treatment[8].

Regarding the degree of social functioning domain, there was a significant increase in the last two visits, which corresponded to the final phase of follow-up. The questions in this domain are related to the patient's autonomy, such as whether she spent time outside the house, went out in the evenings, or shared with friends, activities that the patient could not perform in the initial follow-up period due to the restriction measures and reduced capacity caused by the COVID-19 quarantine.

The changes observed with therapy in the domains of eating problems, weight problems, and digestive symptoms were variable and not so relevant. In relation to digestive and exocrine pancreatic function, the evidence with CFTR modulators is scarce, limited to studies performed with Ivacaftor or the Ivacaftor-Lumacaftor combination, which have shown slight improvement in gastroesophageal reflux, decreased intestinal inflammation, changes in intestinal microbiota, and increased fecal elastase, but with a low number of patients[18]. A European multicenter study was recently published in eight centers distributed in Germany and the United Kingdom that measured the response of digestive symptoms to triple therapy with a specific questionnaire for this purpose in CF patients aged 12 years or more. The patients in Germany achieved better symptom control than those in the United Kingdom, differences that were attributed to the type of diet in each country, the older age, and therefore greater proportion of pancreatic insufficiency in the patients in the United Kingdom[19].

The values of FEV_1 L, FVC L, and FEF25-75 L before the start of the ETI therapy were below the lower limits of normality[16], however, at 45 days of therapy, all values normalized, remaining high until the end of follow-up. The same occurred with FEV_1%, FVC%, and FEF 25-75% with respect to those predicted, which increased by 20 percentage points on average at 45 days, remaining stable until the end of follow-up. This response was similar and even better to the follow-up of patients with heterozygous mutation for the ΔF508, treated with ETI, who showed 13.8 percentage points of improvement at 4 weeks and 14.3 points at 24 weeks compared with the group receiving placebo[8].

In addition, there was an improvement in nutritional parameters, highlighting the increase in weight by 1.6k and 5.6 wBMI during the first 6 months, corroborating what was previously reported in patients with heterozygous mutation for the ΔF508 treated with ETI for 6 months, who reported 1.04 more wBMI than those who received placebo[8]. However, in the second half of the follow-up (fourth and fifth visits), weight remained stationary and wBMI dropped by 2.8 points, which could be explained by a response plateau due to pancreatic insufficiency and/or diabetes since, in this period, the patient did not decrease nutritional intake, did not increase her growth, nor did she increase energy expenditure, according to the evaluations recorded by her nutritionist and physical trainer.

A recent systematic review concluded that the effect of CFTR modulation therapy on anthropometric parameters depends on the genetic mutation and the type of modulator therapy used, but further research is required to understand the long-term clinical impact of these drugs on nutritional status, including body composition and the role of dietary intake[20]. In adolescents with CF, monitoring of body composition and skeletal muscle mass preservation is essential, as it has been shown that increases in lean mass correlate better with increases in FEV_1 than increases in BMI or fat mass and is now recognized as one of the best parameters for predicting long-term lung function[21].

The patient did not present the adverse effects associated with therapy such as dermatological manifestations, liver function alterations, digestive symptoms, and cataracts. A recent meta-analysis concluded that CFTR modulators are safe in the pediatric population, with no higher incidence of adverse effects than placebo-treated controls; however, the number of pediatric patients was small, the studies were heterogeneous, and follow-up was no longer than 6 months[22].

To date, there are no recommendations regarding the duration of triple therapy, but it probably should not be less than 6 months as demonstrated by efficacy and safety studies in children and adults[23]. We are aware of only one study conducted in CF adult patients older than 20 years with homozygous mutation for the ΔF508 that has recently completed an annual follow-up with good efficacy and safety profile[24]. Considering the historical perspective of the therapies that have been incorporated into the treatment of CF in pediatrics and the great benefit demonstrated so far by the ETI therapy, it is not surprising to think that the duration in children and adolescents could be long-term or even permanent if the good efficacy and safety rates are maintained.

The recent international authorization of the triple therapy combination with Elexacaftor, Tezacaftor, and Ivacaftor for patients with one or 2 Phe508del mutations will change the course and way of treating CF in the near future. The remarkable clinical response of the patient presented is just one example of what many patients with the disease in our country could experience when this therapy is incorporated into the CF therapeutic arsenal.

The high cost of triple therapy (250,000 dollars per year) is a major barrier to access and its equitable distribution at a global level, and it is currently estimated that only 12% of CF patients have managed to receive it, most of them from developed countries[25]. We believe that each country is responsible for guarantying

compliance with justice in medicine, a basic moral principle of medical ethics that includes the equitable distribution of resources and costs in health care.

This new era in CF treatment involves important future challenges, such as searching for CFTR modulators in populations with rarer genotypes, especially for class I variants, evaluating the safety of long-term therapy, considering the reduction of conventional therapy we were used to, evaluate the impact of modulator use in pregnancy and lactation, avoid excessive weight gain that could also affect lung function, prescribe CFTR modulators to treat extrapulmonary problems, or ethical dilemmas such as making the decision not to perform lung transplantation in terminally ill patients who experience significant clinical improvement with modulators[26-28].

Conclusions

The ETI therapy administered to the patient achieved early and sustained improvement in quality of life as measured by the CFQ-R 14+ questionnaire, mainly in the domains of physical capacity, vitality, emotional functioning, health perception, activity limitation, and body image. Pulmonary function measured by FEV_1, FVC, and FEF 25-75 rapidly normalized and remained so until the end of follow-up. Although to a lesser extent, there was also evidence of improvement in nutritional status as measured by weight gain in kilograms and BMI. The medium-term response in these follow-up variables demonstrates the efficacy of the ETI therapy in patients with cystic fibrosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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