Use of CFTR Modulators for Cystic Fibrosis in a Patient with Liver Transplant and ESRD on Hemodialysis

Nefrologo in corsia

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ABSTRACT
Cystic fibrosis is an autosomal recessive disorder caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The most recent therapeutic approach to cystic fibrosis aims to correct structural and functional abnormalities of CFTR protein.
CFTR modulators including ivacaftor-tezacaftor-elexacaftor are used in patients with F508del mutation, with clinical improvement. To date, there are no experiences of CFTR modulator therapy in cystic fibrosis patients with organ transplantation and severe renal impairment.
We report the case of a patient diagnosed with cystic fibrosis with F508del mutation, who underwent liver transplantation at the age of 19 and started hemodialysis at the age of 24 due to end-stage renal disease secondary to membranous glomerulonephritis. She was treated with Kaftrio (ivacaftor-tezacaftor-elexacaftor) with clinical benefits on appetite, improvement of body mass index, and reduction of pulmonary exacerbations. A reduction of dosage to 75% of the standard dose was required due to alterations of the liver function.
Conclusions. Use of CFTR modulators in patient with cystic fibrosis, liver transplant and end-stage renal disease could be considered safe but a clinical and laboratoristic monitoring of hepatic function is needed.

KEYWORDS: CFTR modulators, cystic fibrosis, ESRD, liver transplant

Introduction

Cystic fibrosis (CF) is an inherited disease caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, expressed on the epithelial cells of many organs, including respiratory tract, pancreas, liver, intestine, reproductive tract.

The main clinical manifestations include chronic productive cough, difficulty in breathing, intolerance to exercise, pancreatic insufficiency, intestinal malabsorption, meconium ileus at birth.

The main burden to quality of life and the major cause of mortality in CF is progressive lung disease secondary to chronic airway obstruction that predisposes to recurrent pulmonary infection.

Classical treatment of CF is focused on the consequences of CFTR dysfunction and it includes respiratory physiotherapy, muco-active agents, aggressive antibiotic therapy, pancreatic enzyme replacement, high-calorie and high-fat diet. The newest therapy approach to CF aims to correct structural and functional abnormalities of CFTR protein using CFTR modulators.

To date, there is no experience of CFTR modulators use in patients with end-stage renal disease (ESRD) and in patients undergone organ transplantation. This report describes the case of a 25-year-old woman with cystic fibrosis, liver transplantation, and end-stage renal disease on dialysis. The patient was previously evaluated negatively for lung and kidney transplant due to poor general conditions but after treatment with Kaftrio (ivacaftor/tezacaftor/elexacaftor) she improved her general status and quality of life. The clinical improvement secondary to therapy with Kaftrio has allowed inclusion on the kidney transplant waiting list, with significant amelioration of the compliance and psychological status of the patient.

Case report

A 25-year-old female was diagnosed with CF in infancy, with CF genetic analysis demonstrating the presence of homozygous F508del mutation. She had mild CF lung disease with previous pulmonary aspergillosis infection, pancreatic insufficiency, and diabetes mellitus type 1.

Her medical history included also CF-related hepatopathy treated with portosystemic shunt at age 19 which required liver transplantation one year later due to refractory ascites, portal hypertensive gastropathy, and esophageal varices; generalized seizure treated with lacosamide; end-stage renal disease on dialysis from the age of 24 secondary to membranous glomerulonephritis associated with diabetic nephropathy (diagnosed by kidney biopsy at age 17); hypertensive cardiopathy with dilation of cardiac rooms; generalized seizure.

She suffered from frequent pulmonary infectious exacerbations during the years with loss of quality of life. In November 2021 she was evaluated by the Transplant Center for combined lung and kidney transplant. Her parameters were: height 155 cm, weight 33 kg, BMI 13,74 kg/m^2. She performed cardiac catheterism that revealed pulmonary pre-capillar hypertension with elevated cardiac index at rest and normal atrial pressure. After collegial evaluation, she was suspended from organ transplant waiting list due to her poor general conditions, extreme weakness, serious malnutrition and labile psychoemotional compensation that has limited therapeutic adherence in the past.

The patient was therefore addressed to a nutritional and physiotherapeutic program to improve general conditions. Due to the gravity of the clinical picture and the absence of more efficient therapeutic alternative to CFTR modulators to treat cystic fibrosis, in December 2021 the CF care team together with the nephrology team decided to pursue off-label use of ivacaftor-tezacaftor-elexacaftor (Kaftrio). The patient began treatment with Kaftrio administered by mouth as 1

combination tablet of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg in the morning. After two weeks the dose was increased to 2 tablets every day.

For safety issues, she received routine hepatic function monitoring. She had hepatic function testing prior to initiation of Kaftrio that was within normal limits (aspartate aminotransferase [[AST]] 9 U/L, alanine aminotransferase [[ALT]] 5 U/L, gamma-glutamiltranspeptidase [[gGT]] 7 U/L). The hepatic function panel was repeated every two weeks after initiation and it showed an increase in hepatic enzymes levels (GOT 41 U/L, GPT 73 U/L, gGT 116 U/L) after 45 days of treatment. The reduction of the daily dose to 1 tablet alternated to 2 tablets every other day resulted in an improvement of hepatic function.

However, after 9 months from initiation of Kaftrio, the patient was admitted to the hospital due to acute hepatitis with hyperbilirubinemia up to 4.8 mg/dL (direct 4.7 mg/dL) and acute increase of hepatic enzyme levels (GOT 61 U/L, GPT 76 U/L, gGT 356 U/L, ALP 554 U/L). Serum tacrolimus levels were stable to previous measurements. Treatment with Kaftrio was temporarily suspended and the patient underwent liver biopsy. Histological analysis showed aspects of slight hepatitis compatible with toxic/pharmacological etiology, focal aspects of biliary and endothelial damage compatible with rejection (rejection activity index, RAI 3); moderate siderosis more suggestive of secondary etiology, vascular changes referable to slight alteration of the microcirculation. The patient was treated with two boluses of metilprednisolone 500 mg and subsequent decalage of steroid therapy. She was discharged with stable hepatic enzyme levels (GOT 103 U/L, GPT 69 U/L, gGT 468 U/L, ALP 603 U/L).

In December 2022, after a pulmonary exacerbation with acute respiratory insufficiency treated with antibiotics and considering the stability of hepatic function, the patient restarted therapy with a reduced dose of Kaftrio of 1 tablet twice a week, increased to 1 tablet thrice a week after one month.

She did not report any other adverse reactions after the initiation of Kaftrio, with exception for worsening of hypertension. Table 1 provides a summary of patient's home medications.

Acetilsalicilic acid 100 mg	1 tablet daily
Amitriptiline 40 mg/mL	3 drops daily
Beclometason/formoterol 100 mcg/6 mcg	2 puffs daily
Carbonate calcium 1 g	1 tablet thrice a day
Cholecalcifferol 10.000 IU/1 mL	10 drops per week
Doxazosin 2 mg	1 tablet twice a day
Elexacaftor/tezaxaftor/ivacaftor 100 mg/50 mg/75 mg	1 tablet thrice a week
Hydroxyzine 25 mg	1 tablet daily
Lacidipine 4 mg	1 tablet daily
Lansoprazolo 30 mg	1 tablet daily
Nebivolol 5 mg	1 tablet daily
Pancrealipase	125.000 IU daily
Prednisolone	12.5 mg daily
Pregabalin 25 mg	1 tablet daily
Rapid-acting insulin	Accu-check insight microinfusor
Salbutamol 100 mcg/puff	2 puffs daily
Sevelamer 800 mg	3 tablets thrice a day
Sodium zirconium cyclosilicate 5 g	1 sachet daily
Tacrolimus 2 mg	1 tablet twice a day
Ursodeoxycholic acid 450 mg	1 tablet daily

Table 1. Patient's home medications.

It was observed a progressive weight increase to 39.5 kg (BMI 16.44 kg/m^2) in March 2023. The patient reported improvement of general status, started working again and experienced only two episodes of pulmonary infection (on May and August 2022), over 12 months, less than previous infectious rate of one episode every two months. Worsening of hypertension was recorded and consequent anti-hypertensive treatment was prescribed. Psychiatric assessment revealed a better compliance to therapy, psychological suitability and motivation to transplant. Considering the positive benefits on overall clinical condition, a new transplant evaluation assessed the patient as suitable for kidney transplant only. The combined kidney and lung transplant option was excluded due to the improvement of respiratory status after treatment with CFTR modulators, which did not require lung transplantation, considering the high risk of surgery associated to sarcopenia.

Discussion

Cystic fibrosis is the most common life-shortening autosomal recessive disorder among Caucasian people with a prevalence of 1 in 2000 at birth [1]. It is caused by mutations on chromosome 7 (7q31) in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an anion channel conducting chloride (Cl−) across the apical membranes of exocrine epithelial cells [2]. NaCl loss through the sweat gland is a hallmark of cystic fibrosis and the sweat test is the gold standard to diagnose CF. In genetic analysis, F508del is the most common mutation observed in the majority of CF patients. F508del impairs the stability and folding of the CFTR protein, thus leading to mistrafficking and premature degradation, which drastically reduces the quantity of CFTR protein at the apical surface of epithelial cells. This results in dysregulation of epithelial fluid secretion with intense production of viscous secretion in respiratory airways, pancreatic gland, biliary tract, intestine and reproductive tract [2, 3].

Although CF is a multiorgan disease and greatly variable in clinical expression, the major cause of morbidity and mortality is progressive respiratory failure caused by chronic airway obstruction that predisposes to bronchiectasis and chronic pulmonary infection [4].

The hyperviscose mucus produced in the respiratory tract limits ciliary activity and its clearance mechanism. Impairment of these natural defense mechanisms ultimately results in facilitating the infection and chronic bacterial colonization of the lung, typically with microorganisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* [5]. Other clinical manifestations of CF consist of exocrine pancreatic insufficiency, diabetes, portal hypertension, hepatic cirrhosis, sinus infections, greasy stools, gastro-esophageal reflux disease, infertility [6]. Patients with CF have frequently growth failure due to malabsorbtion issues, reduced appetite and increased energy needs.

While CF was previously considered a lethal disease in infancy and childhood, nowadays the median life expectancy has reached over 40 years of age, as a consequence of the early diagnosis through neonatal screening, recognition of mild forms and more effective therapies (including antibiotics, lung transplant, CFTR modulators). As in the general population, comorbid conditions become more common with advancing age and awareness of renal complications increases. Although CFTR is ubiquitous and is located in the proximal and distal tubules of the nephrons, its exact role and effect in CF related kidney disease is unknown. Patients with CF are at higher risk for marked metabolic alkalosis and electrolyte disorder in CF is termed Pseudo-Bartter Syndrome. Urolithiasis is common, secondary to hypercalciuria, hyperuricosuria, and hyperoxaluria. Secondary kidney amyloidosis may occur as a result of chronic infection and inflammation. Patients with CF are at higher risk for acute kidney injury (AKI) due to dehydration from salt loss syndrome and treatment with nephrotoxic antibiotics such as aminoglycosides [7]. The development of chronic kidney disease requires

nephrologic follow-up and end-stage renal disease is treated with renal replacement therapy, including hemodialysis, peritoneal dialysis, and kidney transplant. Kidney transplant is the most optimal renal replacement therapy for the majority of patients, which need to meet certain criteria to be accepted onto the transplant waiting list. The presence of chronic health conditions may limit the eligibility of the patient to the transplant and specialized evaluations are needed.

In the presented case, the patient was referred to the Transplant Center for a combined lung and kidney transplant evaluation due to severe respiratory insufficiency secondary to cystic fibrosis and end-stage renal disease. The patient was not accepted onto the transplant waiting list due to her poor general status and serious malnutrition. CFTR modulator therapies are designed to correct the malfunctioning protein made by the mutated CFTR gene and they have revolutionised CF care. The improved CFTR function results in increased lung function (improved forces expiratory volume in one second, FEV1), decreased acute pulmonary exacerbations, improved growth, and quality of life [8]. Kaftrio is a triple combination therapy (IVA/TEZ/ELX) and it is effective for patients with cystic fibrosis who have at least one F508del mutation in the CFTR gene [9, 10]. Elexacaftor and tezacaftor increase the amount of CFTR ion channels on the cell surfaces, facilitating the processing and trafficking of the CFTR, while ivacaftor potentiate the open probability of the CFTR channel, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. Kaftrio is supplied as two separate products packaged together: ivacaftor/tezacaftor/elexacaftor in a fixed-dose combination for morning administration and ivacaftor for evening administration [11]. *In vitro* studies showed that elexacaftor, tezacaftor, and ivacaftor are all metabolized by CYP3A. Exposure to elexacaftor, tezacaftor, and ivacaftor may be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors [11]. Kaftrio binds primarily to albumin, with a protein binding ratio of approximately 99%. To date, there was no experience of use of CFTR modulator therapy in patients with severe renal impairment or ESRD who have undergone organ transplantation. In our specific case, benefits were expected to outweigh the risks and frequent monitoring of hepatic function was set. In our patient Kaftrio is used with caution and at a reduced dose of one tablet of ivacaftor/tezacaftor/elexacaftor three times a week, with no evening ivacaftor dose. Moreover, considering the potential interaction between Kaftrio and Tacrolimus (which exposure may increase), appropriate monitoring of blood concentrations of FK 506 are recommended.

Conclusions

To our knowledge, this is the first report of beneficial treatment of cystic fibrosis with Kaftrio in a patient with liver transplantation and ESRD in hemodialysis. Even though studies on larger case series are required to confirm the benefits, the availability of new therapies that are able to improve the clinical and nutritional status of extremely fragile patients, who otherwise would have no hope of kidney transplantation due to the severe comorbidities, opens up new perspectives. Also, the psychological aspect related to being placed in a transplant program has an important role in the improvement of compliance and quality of life. Lastly, collaboration among kidney centers, cystic fibrosis care centers and kidney transplantation centers is essential to optimize outcomes of patients.

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