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CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR MODULATOR THERAPY PERSPECTIVE: FINDINGS IN CLINICAL OUTCOMES IN A SERIES OF PEDIATRIC PATIENTS

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Abstract: *Cystic Fibrosis (CF) is the most frequent autosomal recessive disorder in Caucasians and has reduced life expectancy. It is caused by the mutations in the CF transmembrane conductance regulator (CFTR) gene which results in impairment of production, expression and trafficking of the CFTR protein. CF has a multifaceted clinical representation with respiratory involvement as a main cause of morbidity and mortality. Multidisciplinary approach, care in specialized centers, early diagnosis through neonatal screening and development of symptomatic treatments improved survival in the last decades. CFTR modulators were developed based on the discovery of the CF gene in 1989 and improvement of genetic testing and have changed the perspective of a debilitating disease. These therapies, acting more upstream in the pathogenic cascade, overcome the underlying dysfunctions caused by CFTR mutations, having the ability to enhance or restore the resulting functional effects. CFTR modulator therapies are highly effective treatments for cystic fibrosis patients as shown in many clinical trials and real life analysis so far. Improvement of quality of life, lung function and pulmonary exacerbation rates are indisputable targets when evaluating efficacy and efficiency of medical interventions in such a disease as CF., and they have been substantially changed in the era of modulators. We analyzed a small group of patients that were initiated on Kaftrio as per indicated protocol. Al significant clinical and functional aspects were improved, demonstrating the disease changing potential of this therapy. We did not observe threatening side effects, no patients were stopped from the medication. CFTR modulators are a beginning of a new era in CF, a perspective for improvement and effectiveness of precision medicine in CF patients.*

Key words: *Cystic Fibrosis, CFTR, modulators, life expectancy, improvement*

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1. Introduction

Cystic fibrosis (CF) is an autosomal-recessive genetic disorder, affecting both copies of the gene encoding the CF transmembrane conductance regulator (CFTR), [1] discovered in 1989 [2]. CFTR is a protein that transports anions like chloride and bicarbonate, through the epithelial cell membrane [3]. Mutation in the CFTR gene on chromosome 7 can cause abnormalities, starting with defects in protein folding, till to total absence of the protein [4]. There are more that 2000 variants of the CFTR gene, but only around 350 were listed as disease causing [5] and are grouped into 6 classes based on their effect [3].

This malfunctions leads to an ion imbalance and dehydration of the epithelial surface [3]. This changes cause an impairment of mucociliary clearance and problems with the host immune system, both leading to higher susceptibility to severe chronic respiratory infections [6].

The disease is multisystemic and affects all organs that may express CFTR, but most frequently the respiratory system, due to a thick, mucous secretion leading to chronic bacterial infections and fungal colonization. This causes obstructive lung disease with airway edema and mucous plugging and bronchiectasis [7]. The abnormal secretion is also found in other organs like the pancreas, (leading to malabsorption and CF-related diabetes [4], liver, digestive tract, reproductive tract and skin [5].

90 % of patients have pancreatic insufficiency and multisystemic disease, with major problems in the lungs.

Since the first description of disease in 1938, after development of sweat testing as diagnostic tool and specialized CF centers, many therapies were introduced, such as inhaled hypertonic saline, antibiotics and recombinant DNase to help improve airway clearance. Pancreatic enzymes substitution therapy was developed to improve malabsorption, oral or systemic antibiotics to reduce pulmonary exacerbation rates[3].

All treatments, as well as centralized specialized care, improved survival and life expectancy. Till recent years, medication was mostly symptomatic, until the discovery of molecules that could target the gene mutations (modulator therapy).
Modulators are formed of small molecules that are able to modify CFTR function [8] and include activators, potentiators and correctors [8]. The activators are improving the levels of cAMP which is a cellular signal needed for stimulating the CFTR activity [8]. Potentiators increase ion transport facilitating opening of channels and correctors increase ion transport by correcting misfolding errors[5]. The first molecule approved was Ivacaftor, but it was beneficial only for class III mutations. Around 90% of CF patients have p.Phe508del mutation, found on at least one allele, which is a class II mutation [9]. The need of improving the function of CFTR class II mutations led to discovery of new and improved molecules and the possibility of combining them, as it happens in Kaftrio: ivacaftor/ tezacaftor/ elexacaftor (Table 1).

	Class I	Class II	Class III	Class IV	Class V	Class VI
Molecular Defect	Synthesis	Processing	Gating	Conduc-tance	mRNA Stability	Protein Stability
Defect Results	No mature CFTR protein	CFTR degradation	Channel opening defect	Reduced Cl conduc-tance	Reduced synthesis of CFTR	Decreased CFTR stability
Mutation Exemples	G542X	F508del	G551D	R117H	A455E	Rescued F508del
	R553X	N1303K	V530F	R334W	c.1680-886A>G	Q1412X
	W1282X	G85E	S549R	S1235R	c.2657+5G>A	
Modulator Therapy	NONE	Corrector + Potentiator	Potentia-tor	Potentia-tor	NONE	NONE

2. Methods

We retrospectively analyzed a group of 10 CF patients (p1-p10) before and after initiation of Kaftrio treatment, as part of their national evaluation protocol, in the Regional Cystic Fibrosis Center, in the Clinical Emergency Children's Hospital.

3 patients were analyzed at 12 months, 6 patients at 9 months and 1 patient at 3 months from initiation.

We illustrated baseline demographic, clinical and biologic characteristics of patients (Table 2).

Table 2

Demographic, clinical and laboratory findings at initiation

Characteristics	
Gender	
Male	6
Female	4
CFTR mutation(delF508)	
Homozygous	8
Heterozygous	2
Colonization	
Pseudomonas	6
MRSA	5
Stafilococcus	6

There were 6 male patients and 4 female patients. All patients, except one, started with growth failure. All patients had at least one delF508 copy, 8 patients being homozygous and 2, heterozygous. We also analyzed chronic lung colonization.

Our study demonstrated an increase of BMI score in 7 patients out of 10.

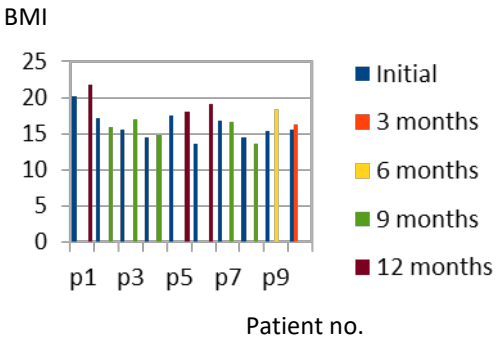

Fig. 1. *Outcome of BMI during study period*

We analyzed the outcome of lung function based on the results of the spirometry: force vital capacity (FVC) and forced expiratory volume in one second (FEV1). All patients showed an improvement of the lung function with a

medium increase of more than 15**%** of FVC and of more than 20**%** of FEV1.

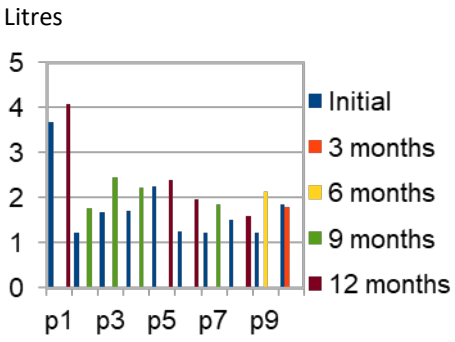

Fig. 2. *Outcome of FVC during study*

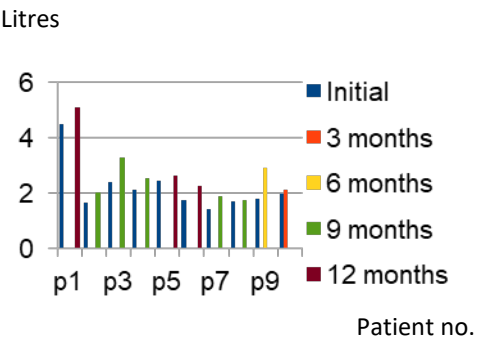

Fig. 3. *Outcome of FEV1 during study period*

During the treatment period, none of the patients had any pulmonary exacerbation, respiratory symptoms decreased substantially and all of them reported less cough and an overall improved quality of life. They were more active, had increased energy, good appetite and were more engaged in daily activities.

We analyzed sputum cultures and did not find substantial changes, being colonized with already known pathogens. More so, due to decrease of sputum production, in some patients, cultures were negative. In patients that started treatment with more severe lung disease, sputum cultures remained intermittently positive, despite clear radiologic improvement, explaining reduction of mucus impactation and less mucus production.

We highlighted chest Xrays changes in some patients, with improvement of bronchiectasis and bronchial thickening in one of our 14 year old patient.

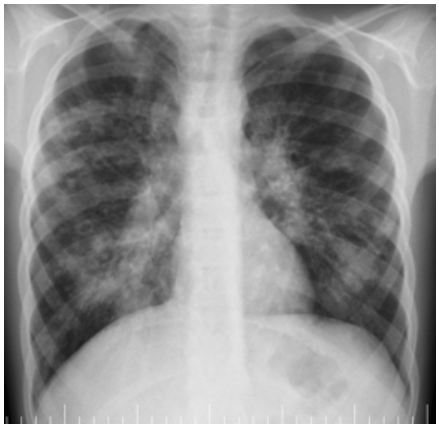

Fig. 4. *Chest X-ray at treatment initiation of patient*

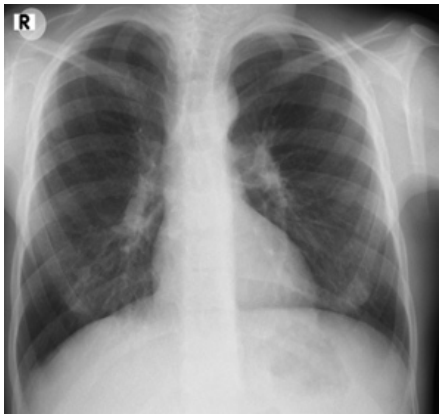

Fig. 5. *Chest X-ray at 6 months after treatment initiation of patient 9*

3. Discussions

The new modulator therapies, targeting the genetic defect of cystic fibrosis, have already beenshown that improve many aspects of the disease in larger groups of patients in Europe and USA.

The major followed up aspects were pulmonary exacerbations (PEx), lung function, nutrition and quality of life. Many studies demonstrated overall improvements [10].

Lung function was and still is a major marker of survival in CF. The clinical trials that led to approval of Kaftrio had remarkable results with an improvement of more than 10% of FVC and FEV1, as we also showed in our small series of patients. This has been already shown in larger studies in adults and children that have been done so far [5].

Some studies also demonstrated a possibility of eradication of lung pathogens after completion of longer periods of treatment. Some of our patients still had positive sputum cultures, mainly with *Pseudomonas aeruginosa.*

One of the most important aspects of treatment effects was decrease of pulmonary exacerbations (PEx), that meant that patients did not need anymore hospitalizations for intravenous antibiotics. This has also been shown in our case series, no patient was admitted during the treatment period with Kaftrio for PEx.

Nutrition is one of the aspects that led nowadays to scientific discussions regarding overweight in some patients and risk of development of metabolic syndrome. Nutritional interventions are important and probably will change the lifestyle of CF patients that are treated with CFTR modulators. In some countries where treatment was already affordable for a longer period, there are reports of patients that stopped pancreatic enzyme replacement therapy.

Regarding side effects, in some studies, authors reported side effects like migraines, „brain fog", sound sensitivity [10], abdominal pain, diarrhea, elevated liver enzymes [5]. None of the patients in our case series presented with serious or persistent side effects that could lead to stopping the treatment. Some patients experienced disturbed sleep, that was improved when taking a smaller dose.

In patients that due to a reason had to take smaller doses as recommended in the protocol, we observed the reversal of initial symptoms, as more cough, and sputum production.

4. Conclusions

CFTR modulator therapies are highly effective treatments for cystic fibrosis patients as shown in many trials and also in real life analysis that have been done so far. Improvement of quality of life, lung function and pulmonary exacerbation rates are indisputable targets when evaluating efficacy and efficiency of medical interventions in such a disease as CF, and they have been substantially changed in the era of modulators.

Management of CF as known already, targeting a multisystemic disease that has reached improved life expectancy in the last 30 years, has not to be abandoned, even effects of CFTR modulators are remarkable.

Regular evaluation, multidisciplinary approach, analyze of each aspects of the multifaceted outcome of every patient is still important. Care in tertiary hospitals and specialized centers is still the core of

improvements in all life aspects of CF patients.

Questions regarding side effects, early initiation of therapy and acknowledging disease changing strategies are in focus of scientists and caregivers.

Our small study has shown beneficial effects in all aspects that have been targeted in the evaluation protocol, as it was shown in clinical trials that led to the approval of these medications.

Even we analyzed a small case series of patients with some having serious problems and deficiencies when initiated on Kaftrio, observed positive effects on their outcomes, make us believe that there is a perspective for continuous improvement and with a game changing effect.

CF may no longer be a disease that has a reduced life expectancy, as long term results already have been shown to be positive.

Treatment protocols and medical approach may be changing in the near future. As well, children that could be treated early in life may not develop the disease that we knew before.

For sure, CFTR modulators are a new dawn for CF and show a lot of promises and changes for patients' life and disease outcomes.

Much more, CFTR modulators can be the representation of the beginning of a new era for CF patients, with a „new" disease.

Based on the results that have already been seen in larger scale interventions, the perspective for CF looks well today.

Identifying barriers and future directions in order to optimize treatment adherence, finding solutions for equitable access to these therapies and expanding the pipeline of novel molecules, may result in improvement and effectiveness of precision medicine for CF patients.

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