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THE USE OF CYSTIC FIBROSIS CONDUCTANCE REGULATOR MODULATORS IN PATIENTS WITH RARE MUTATION

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BACKGROUND AND IMPORTANCE

Cystic Fibrosis (CF) is a monogenic and multi-organ disease that induces different types of conditions like lungs infections, meconium ileus, pancreatitis. This condition is related to mutations in Cystic Fibrosis Transmembrane Regulator (CFTR), the gene encoding the epithelial ion channel that normally trasports chloride and bicarbonate (**Figure 1**). Therapeutic strategies deeply changed when Ivacaftor and the combination therapy Ivacaftor/Tezacaftor/Elexacaftor (ETI) were marketed in 2021. At this moment the ETI therapy is licensed to treat CF's patients >6 years with at leats one F508del mutation, the most common one. However, patients with rare CFTR's mutations, don't have access to this therapy and they use this medicines in an off-label way.

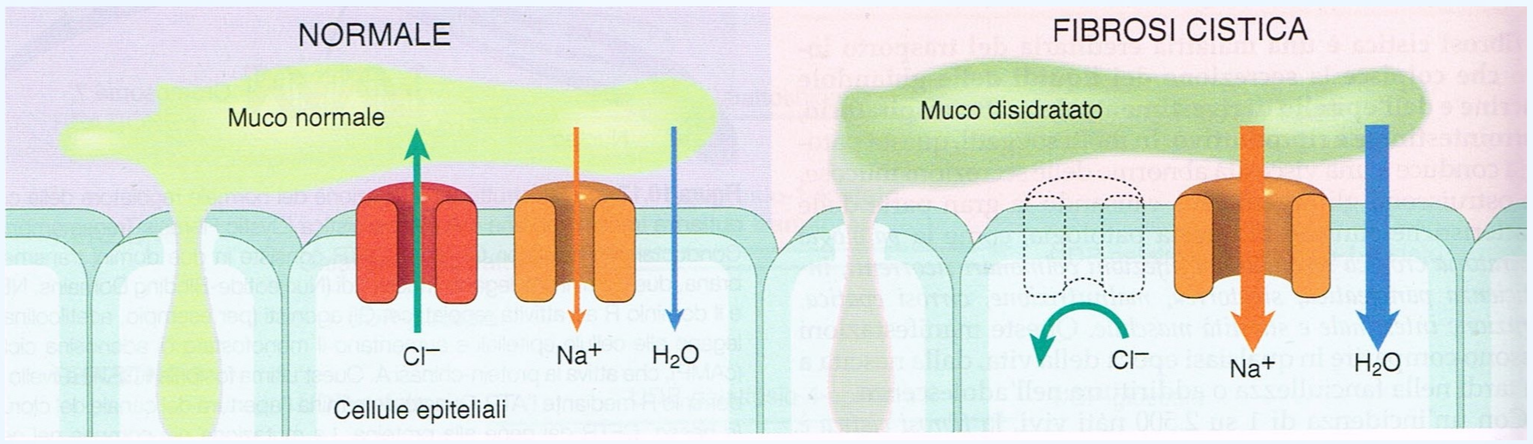

Figure 1

AIM AND OBJECTIVES

With our work we report the use of the combination therapy Ivacaftor-ETI in two young patients with rare CFTR's mutations: the N1303K/2183AA>G and the W1282X7N1303K.

MATERIAL AND METHODS

Starting from the off-label authorizations from January-2015 to June-2022 by our Hospital Committee (composed with a Clinician, a Pharmacologist and a Hospital Pharmacyst) in accord to Law 94/98, we identified patients that required off-label CFTR's modulators' combination therapy due to their CFTR's rare mutations and in vitro response to ETI therapy. For these patients we analyzed: age at the beginning of the therapy, gender, type of mutation, clinical manifestations, period of therapy, Adverse Drug Reactions (ADRs) notified as it shows in **Table 1.**

Patient's identification	Age at the beginning of the therapy	Gender	Type of mutations	Clinical manifestations	Period of therapy	Adverse Drug Reaction
P1	19	F	N1303K/2183AA>G	Lung's infections, low BMI	3 cycles of 28 dyas for each cycle	No ADRs are notified.

Table 1

RESULTS

Only in 2022 two patients were authorized to use off-label CFTR modulators' combination therapy due to their rare CFTR's mutations. The first patient (that we identified like P1) was a female, she has 20 years and se has the W1282X/N1303K mutation; her clinical history showed meconium ileus, serious pneumopaty and she often required antibiot therapy due to her lungs' infections. The second patient (that we identified like P2) was a female, she has 19 years and she has N1303K/2183AA>G mutation; her clinical history showed pancreatic and lung insufficiency, BMI <14, infections induced by multidrug resistant Pseudomonas and Mycobacterium Abscessus, D hypovitaminosis.

At first the Hospital Committee authorized 3 cycles of therapy for P1 and 4 cycles (28 days for each cycle) for P2. Both of them were authorizd to prolonge their therapy due to their clinical efficacy. No ADRs related to the Ivacaftor-ETI therapy were notified.

CONCLUSION AND RELEVANCE

CFTR modulators are small molecules that directly impact and achive the function of the CFTR channel. They give long-term improvements in clinical outcomes and we hope more research on their efficacy in patients with rare CFTR's mutations.

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