**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 transports 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 least one F508del mutation, the most common one. However, patients with rare CFTR’s mutations, don’t have access to this therapy and they use medicines in an off-label way.

**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 W1286T7N1302K.

**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 Pharmacist) 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.

<table>
<thead>
<tr>
<th>Patient’s identification</th>
<th>Age at the beginning of the therapy</th>
<th>Gender</th>
<th>Type of mutations</th>
<th>Clinical manifestations</th>
<th>Period of therapy</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>19</td>
<td>F</td>
<td>N1303K/2183AA&gt; G</td>
<td>Lung’s infections, low BMI</td>
<td>3 cycles of 26 days for each cycle</td>
<td>No ADRs are notified</td>
</tr>
</tbody>
</table>

**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 she has the W1286T7N1302K mutation; her clinical history showed meconium ileus, serious pneumopathy and she often required antibiotic 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 authorized to prolong 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 activate 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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