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Efficacy and safety of CFTR modulators in patients with interstitial lung disease caused by ABCA3 transporter deficiency.

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Introduction


- ABCA3 transporter deficiency leads to severe interstitial lung disease (ILD).
- The mode of inheritance of ABCA3 variants is autosomal recessive.
- Treatments are limited and lung transplantation is the only option in terminal stages.
- Cystic fibrosis is caused by CFTR mutation, and result in impaired cystic fibrosis transmembrane conductance regulator (CFTR) function.
- CFTR modulators have revolutionized the management of cystic fibrosis.
- Homology between ABCA3 and CFTR (aka ABCA7) suggests that CFTR modulators could be a therapeutic option for ABCA3.
- *In vitro* study showed that ivacaftor and genistein restored the loss of ABCA3 activity caused by some ABCA3 non-null pathogenic variants (1).

Objective :


To assess the safety and efficacy of CFTR modulators in patients with ABCA3 deficiency.


Methods


- Three patients with severe ILD caused by ABCA3 non-null pathogenic variants received a compassionate use of CFTR modulators

 Patient 1 (P1) : 30 years old women, received Elexacaftor-Tezacaftor-Ivacaftor (ETI).

 Patient 2 (P2) : 22 years old men, received ETI.

 Patient 3 (P3) : 4 years old child, received Lumacaftor-Ivacaftor.

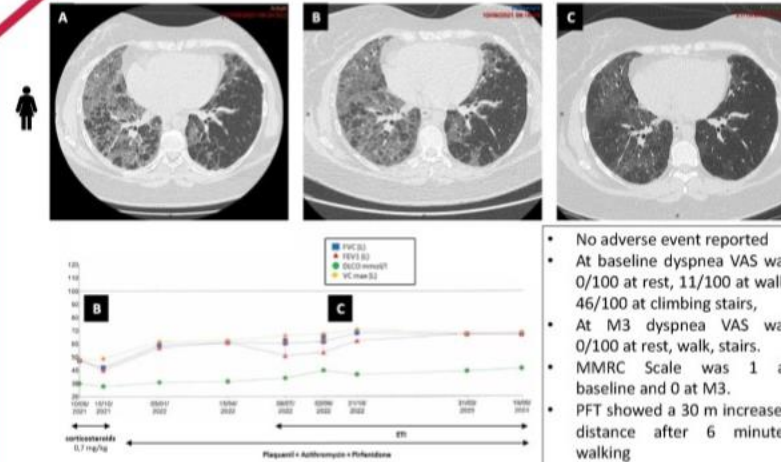
 We assessed pulmonary functional test (PFT), Chest CT scans, and dyspnea visual analogy scale (VAS) to evaluate our patients.

 Patients were evaluated at weeks 6 and 12 (3 months) *.

* Patient 3 only received 3 weeks of Lumacaftor-Ivacaftor after he developed an adenovirus infection and was admitted in ICU.

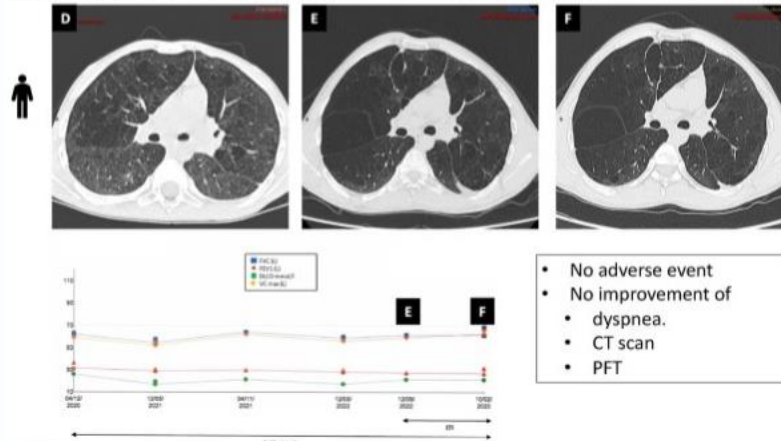
Results

P1 was diagnosed at the age of 30 with compound heterozygous ABCA3 missense pathogenic variants (A).



- No adverse event reported
- At baseline dyspnea VAS was 0/100 at rest, 11/100 at walk, 46/100 at climbing stairs,
- At M3 dyspnea VAS was 0/100 at rest, walk, stairs.
- MMRC Scale was 1 at baseline and 0 at M3.
- PFT showed a 30 m increased distance after 6 minutes walking

P2 was diagnosed after neonatal respiratory failure for ABCA3 homozygous mutation



- No adverse event
- No improvement of dyspnea.
- CT scan
- PFT

Main findings

- One patient with ILD secondary to ABCA3 mutation showed improvement with Elexacaftor-Tezacaftor-Ivacaftor (ETI) (may be related to Azithromycin/Hydroxychloroquine)
- Two others patients received ETI without any objective improvement.
- No adverse effect was reported for our 3 patients.
- It is worth doing a prospective clinical trial with Azithromycin, Hydroxychloroquine, or ETI for ILD associated with ABCA3 variants.

Conclusion

- In this short-term proof-of-concept pilot study, ETI was safe, and showed promising results for ILD adult patients caused by ABCA3 mutations.
- These results support the need for a multicenter prospective international trial.

