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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.

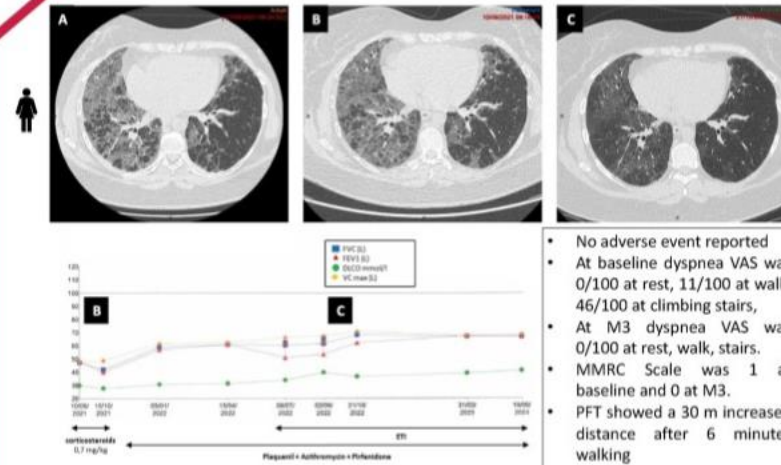
📋 We assessed pulmonary functional test (PFT), Chest CT scans, and dyspnea visual analogy scale (VAS) to evaluate our patients.

📅 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.

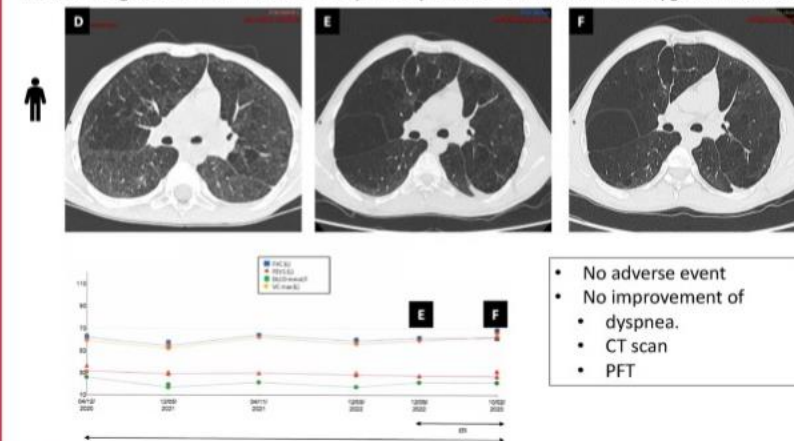
Results

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.

