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

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To the Editor:

Pulmonary surfactant is essential to reduce alveolar surface tension. Ultra-rare pathogenic variants in surfactant related genes (SRGs) result in severe interstitial lung disease (ILD) in children and adults. Among SRGs, *ABCA3* encodes for the ATP-binding cassette (ABCA3), an intra-cellular surfactant transporter [1]. Bi-allelic pathogenic variants in *ABCA3* are responsible for ILD ranging from fatal neonatal respiratory distress to adult-onset lung fibrosis [2].

Some benefit has been reported with prednisone, azithromycin or hydroxychloroquine, but evidence is lacking in adults [3, 4]. A recent series reported a comparable risk of death in adult patients with SRG variants and those with idiopathic pulmonary fibrosis [5]. Lung transplantation remains the only curative measure [6].

In contrast, the prognosis of cystic fibrosis (CF) was revolutionised by the discovery of CF transmembrane conductance regulator (CFTR) modulators [7, 8]. CFTR, also known as ABCC7 presents homologies with ABCA3. CFTR modulators might improve ABCA3 function. An *in vitro* study confirmed that ivacaftor and genistein partially restored ABCA3 activity in certain *ABCA3* pathogenic variants [9]. Based on these findings, we provided compassionate prescription of CFTR modulators to three adult patients with severe ILD caused by *ABCA3* pathogenic variants.

A 30-year-old non-smoking woman was referred for the diagnosis of an ILD. She reported shortness of breath for several years without prior evaluation. Biological tests were normal. A chest computed tomography (CT) scan showed diffuse ground glass opacities (GGOs) associated with interlobular lines (figure 1a). Bronchoalveolar lavage was clear and revealed 1000 cells·μL^{-1} with 60% neutrophils, 20% macrophages, 19% eosinophils and 1% lymphocytes without hemosiderin-laden macrophages. Pulmonary functional tests (PFTs) showed a total lung capacity (TLC) of 2.85 L (51% of predicted value), forced vital capacity (FVC) of 2.07 L (52%), and a diffusing capacity of the lung for carbon monoxide (D_{LCO}) of 26%. Treatment was initiated with prednisone 60 mg·day^{-1} alongside oxygen therapy without any improvement after 1 month (figure 1b). Next generation sequencing identified two compound heterozygous *ABCA3* missense variants: c.4237G>A, p.(Gly1413Ser) and c.4444C>T p.(Arg1482Trp), classified as likely pathogenic (allelic frequency 1/31408 and not reported in gnomAD and conserved amino acid). Pirfenidone, hydroxychloroquine and azithromycin were added while prednisone was tapered to 10 mg·day^{-1}. The patient was also referred for pre-lung transplant assessment. After a dedicated multidisciplinary discussion, and a specific approval from the patient and the French health insurance for a 6-month period of treatment, we initiated compassionate treatment with elexacaftor/tezacaftor/ivacaftor (ETI) at the recommended CF dosage.

After 3 months of treatment, the patient reported significant improvement in dyspnoea and cough. Dyspnoea improved from 46/100 to 0/100 while climbing stairs, and her modified Medical Research Council score improved from 1 to 0. TLC increased by 130 mL, FVC by 240 mL, D_{LCO} by 8%, 6-min distance by 40 m and maximal oxygen uptake from 13 to 18·mL·min^{-1}·kg^{-1}. *CFTR* sequencing results were normal. The normal chloride sweat test remained unchanged. The chest CT scan showed a dramatic decrease in GGO. The improvement was maintained at 6 months and ETI treatment was discontinued due

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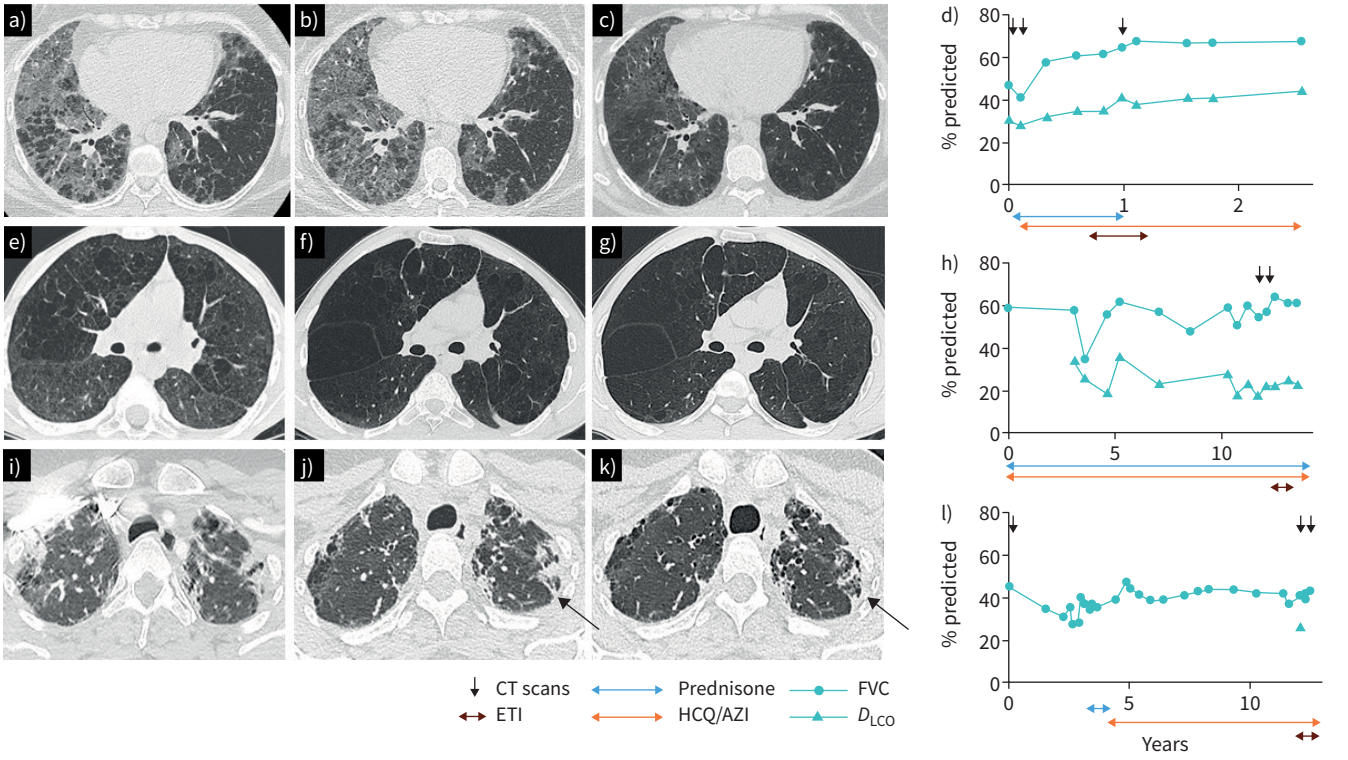

FIGURE 1 Evolution of CT scan and PFT before and after elexacaftor/tezacaftor/ivacaftor (ETI). Case 1, a) CT scan at diagnosis; b) after prednisone; c) after 3 months of ETI; d) evolution of PFT beginning from diagnosis. Case 2, e) CT scan in 2007 at the age of 8; f) before ETI; g) after 3 months of ETI; h) evolution of PFT beginning from 2010 at the age of 11. CT scan showed improvement of condensation (arrow) after ETI. Case 3, I)) CT scan at diagnosis; j) before ETI; k) after 6 months of ETI; l) evolution of PFT beginning from diagnosis. CT: computed tomography; PFT: pulmonary function test; FVC: forced vital capacity, HCQ: hydroxychloroquine; AZI: azithromycin D_{LCO}: diffusing capacity of the lungs for carbon monoxide.

to a lack of funding. No adverse events were observed. Hydroxychloroquine and azithromycin were maintained with patient stability at 24 months.

A previously reported 22-year-old non-smoking man was diagnosed at birth, after neonatal respiratory failure, with ILD caused by an *ABCA3* homozygous missense pathogenic variant c.757G>C p.(Asp253His) [10, 11]. He was initially managed with oxygen therapy, prednisone pulses and a daily dose of 5 mg. Azithromycin 250 mg three times a week from age 6 years led to dramatic respiratory improvement and stability into adulthood. Chest CT scan (figure 1f) showed extensive hypo-attenuating zones, evoking emphysema and cysts and a limited area of GGO in the right lower lobe. PFTs showed a TLC of 7.35 L (101%), FVC of 2.94 L (55%), forced expiratory volume in 1 s (FEV_1) of 1.32 L (29%) and D_{LCO} of 19%. ETI treatment was initiated for 6 months. After 3 months of treatment, dyspnoea and PFTs were improved, with TLC increasing to 7.97 L (109%), FVC to 3.3 L (61%), FEV_1 to 1.2 L (27%) and D_{LCO} to 21%. The chloride sweat test went from 56 mmol·L^{-1} to 47 mmol·L^{-1} after 3 months of ETI. *CFTR* sequencing was normal. Improvement was maintained at 6 months and persisted 3 months after treatment discontinuation. GGO seemed to regress on CT scan. Treatment was well tolerated.

A previously reported 48-year-old non-smoking woman was diagnosed at the age of 35 with ILD and at the age of 40 with *ABCA3* homozygous missense variants p.Ala1027Pro (c.3079G>C) and p.Gly974Asp (c.2921_2922delinsAC) as a result of uniparental disomy [12].

Initial PFTs showed TLC at 2.42 L (56%) and D_{LCO} of 15%. The patient showed clinical and progressive progression during the first 4 years (figure 1l). She then received pulses and oral prednisone for 6 months without improvement and was referred for lung transplantation. She then received hydroxychloroquine (400 mg·day^{-1}) with clinical, functional and radiological improvements at 6 months and stabilisation for 6 years but eventually presented clinical, functional and radiological progression. A compassionate ETI treatment was initiated despite normal *CFTR* sequencing and chloride sweat test (12 mmol·L^{-1}). After

3 months of treatment, dyspnoea and PFTs were improved, including a 100 mL increase in FVC and improvement was confirmed on CT scan and PFT at 6 months. The treatment was well-tolerated.

This report highlights the potential benefit of CFTR modulators in ILD caused by *ABCA3* pathogenic variants. Three patients showed objective improvement in symptoms and PFTs. Chest imaging improved in two patients.

ILD management in patients with *ABCA3* variants remains challenging, with limited therapeutic options and variable outcomes. The subgroup of the Dutch cohort and some case reports suggest that *ABCA3* variants carriers may have a better prognosis [11, 13]. In children, treatment currently relies on expert opinion and usually includes prednisolone, hydroxychloroquine and azithromycin though supportive strong evidence is lacking.

In this series, the respective role of ETI or any drug combination remains to be determined. Whether the ETI efficacy is related to any specific *ABCA3* genotype is unknown. *In vitro* studies showed that ivacaftor and ciclosporin are promising candidates to target ABCA3 activity, but their effectiveness may vary depending on the variants [9, 14]. *In vitro* effect of ETI on the variants identified in our patients was not assessed, and *in vitro* tests could not be performed [9, 14]. These case series have several other limitations: short follow-up, early drug discontinuation and limited number of patients.

Given the advanced disease presented by patients 2 and 3, the limited improvement with ETI was not unexpected. These data could support ETI use at an earlier stage of the disease. CFTR modulators were also tested in a child with end-stage ABCA3 deficiency, without any potentially conclusive data. A boy presented with severe ILD from birth due to an homozygous *ABCA3* pathogenic variant c.3518C>G, p.(Thr1173Arg) despite prednisone, azithromycin and hydroxychloroquine. He received a compassionate treatment with lumacaftor/ivacaftor at the age of 4 years. The parents reported improvement in cough, but he required non-invasive ventilation because of adenovirus infection at day 21, leading to treatment discontinuation. He died at age 6 years in the absence of a compatible lung donor.

ETI has revolutionised the management of patients with severe CF carrying a wide range of *CFTR* variants, with few adverse events [15]. ILD secondary to SRGs are rare respiratory diseases but this case series illustrates the potential therapeutic benefit of genetic testing in young patients with cryptogenic ILD, as patients with *ABCA3* variants could benefit from CFTR-targeting drugs. Further prospective studies are needed to assess the objective benefit of ETI in addition to a better genotype/phenotype analysis and functional tests for *ABCA3* variants to better target patients who could benefit from ETI.

Mathilde Le Brun [1,2], Nadia Nathan [3,4,5], Camille Louvrier [3,4,5,6], Marie Legendre [5,6], Severine Feuillet[7], Justine Frija-Masson [8], Mwetty Onanga[1], Lise Morer[9,10], Marie-Pierre Debray [10,11], Isabelle Fajac[10,12], Pierre-Régis Burgel [10,13], Sylvain Marchand-Adam [14], Bruno Crestani [1,2] and Raphaël Borie [1,2]

[1]Service de Pneumologie A, Hôpital Bichat, Assistance Publique–Hôpitaux de Paris (APHP), Paris, France. [2]Université Paris Cité, Inserm, PHERE, Paris, France. [3]Sorbonne Université, APHP, Pediatric Pulmonology, Department and Reference Center for Rare Lung Diseases RespiRare, Armand Trousseau Hospital, Paris, France. [4]Département de Génétique Médicale, APHP, Hôpital Armand-Trousseau, Paris, France. [5]Inserm UMR_S933, Laboratory of Childhood Genetic Diseases, Sorbonne Université, Paris, France. [6]UF de Génétique moléculaire, Sorbonne Université, APHP, Hôpital Armand-Trousseau, Paris, France. [7]Service de Pneumologie Cancérologie thoracique – hôpital Marie Lannelongue, Le Plessis-Robinson. [8]Université de Paris, NeuroDiderot, Inserm U1141 APHP, Hôpital Bichat, Explorations Fonctionnelles et Centre du Sommeil – Département de Physiologie Clinique, Paris, France. [9]Service de Pneumologie B Hôpital Bichat, APHP, Paris, France. [10]Université Paris Cité, Inserm, Paris, France. [11]Service de Radiologie Hôpital Bichat, APHP, Paris, France. [12]Service de Physiologie-Explorations fonctionnelles Hôpital Cochin, APHP, Paris, France. [13]Université Paris Cité, Inserm,Université Paris Cité, Paris, France. [14]Service de Pneumologie, Hopital de Tours, Tours, France.

Corresponding author: Raphael Borie (raphael.borie@aphp.fr)

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