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Case Report

Elexacaftor-Tezacaftor-Ivacaftor in 2 cystic fibrosis adults homozygous for M1101K with end-stage lung disease

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ABSTRACT

Elexacaftor-tezacaftor-ivacaftor (ETI) therapy is shown to improve the health of individuals with cystic fibrosis (CF) who have the F508del variant. There are *in vitro* studies showing benefit with ETI for select rare CF variants. Limited data exists on the use of ETI in individuals with rare CF variants, particularly in those with advanced lung disease. We present 2 cases of CF individuals homozygous for the rare M1101K variant with end-stage lung disease who demonstrated sustained improvements in lung function, pulmonary exacerbation frequency, respiratory symptoms, and body mass index after 6 months of ETI treatment – similar to that expected with F508del.

1. Introduction

Cystic Fibrosis (CF) is a progressive life-limiting disease of autosomal recessive inheritance, affecting approximately 105,000 individuals diagnosed with CF worldwide [1]. The basis for CF is from an abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein that regulates chloride and bicarbonate transport in epithelial cells [2]. Dysfunctional CFTR protein results in viscous and sticky mucus affecting many organs, most notably in the airways, gastrointestinal tract, pancreas and sweat glands, which cause impaired organ function that leads to morbidity and mortality in people with CF (pwCF) [2]. CFTR dysfunction is grouped into 6 classes based on the effect of the mutation on the CFTR protein production, trafficking, function, and stability [2,3]. CFTR modulators are small molecule therapies designed to restore the activity of mutant CFTR [2]. Clinical trials have demonstrated that the CFTR modulator elexacaftor-tezacaftor-ivacaftor (ETI) is effective in improving lung function, pulmonary exacerbation frequency, sweat chloride concentration, nutrition status and quality of life for pwCF with F508del, the most common CFTR variant worldwide [4,5]. Limited data is available for the clinical use of pwCF with non-F508del variants. However, pre-clinical studies examining the efficacy of ETI on non-F508del CFTR variants have shown *in vitro* benefit in selected CFTR variants, including c.3302T > A (M1101K) [6,7].

M1101K is a rare class II variant, found in 0.2% of CF patients registered in CFTR2 worldwide registry [8]. However, in Canada, M1101K is found in 1.7% of individuals with CF [9]. In particular, rates of M1101K in the Prairie provinces of Canada are dispropor-

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ETI, elexacaftor-tezacaftor-ivacaftor; GAD-7, Generalized Anxiety Disorder 7-item; IV, intravenous; lpm, liters per minute; mmHg, millimeters of mercury; PHQ-9, Patient Health Questionnaire 9; $ppFEV_1$, percentage predicted forced expiratory volume in 1 second; pwCF, people with cystic fibrosis[1].

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tionally enriched because of the high prevalence of Hutterite colonies [10,11]. As such, the incidence of CF is 1:313 live births in these communities [12] compared to the national rate of 1:3850 [9].

Use of ETI in pwCF with M1101K is rarely reported. Whereas, approval for ETI use in those with M1101K is present in the United States [13], the majority of countries including Canada [14] have neither approval nor funding mechanisms for ETI use in non-F508del variants, and the lack of supporting clinical data is a barrier. Herein, we describe 2 cases of individuals homozygous for M1101K with end-stage lung disease who had marked clinical improvement following initiation of ETI through an Exceptional Drug Therapy funding program.

2. Case 1

ETI was started in a 28-year-old man with CF (genotype M1101K/M1101K) in December 2022. His past medical history included asthma, allergic bronchopulmonary aspergillosis, chronic pulmonary infection with *Pseudomonas aeruginosa,* intermittent respiratory cultures of methicillin-sensitive *Staphylococcus aureus* and *small colony variant S. aureus*, pancreatic sufficiency, CF-related diabetes, chronic abdominal pain, and osteopenia. Baseline percentage predicted forced expiratory volume in 1 second ($ppFEV_1$) 2 years prior to ETI initiation was 22%. In the 12 months preceding ETI initiation, there was progressive decline in lung health with development of chronic hypoxia, hypercapnia and pulmonary hypertension, new acquisition of methicillin-resistant *S. aureus*, and 5 CF pulmonary exacerbation hospitalizations. Two weeks prior to ETI initiation, $ppFEV_1$ was 10% and there was a weight loss of 10% in the preceding month despite over 6 weeks of intravenous (IV) antibiotics. Arterial blood gas showed the partial pressure of carbon dioxide was 59 mm of mercury (mmHg), and partial pressure of oxygen was 50 mmHg, and he was on supplemental oxygen at 4 L per minute (lpm). Echocardiogram showed severely elevated pulmonary artery systolic pressure at 78 mmHg and mildly dilated right ventricle.

ETI was started as an outpatient on a reduced dose and escalated to the full dose by Day 7. Within the first week of ETI use, there was rapid improvement in sputum production, cough and dyspnea, there was a reduction in supplemental oxygen from 4 lpm to 1 lpm, and IV antibiotics were discontinued. Six weeks after ETI initiation, $ppFEV_1$ was 21%. At 6 months after ETI initiation, hypercapnia resolved. Depression and anxiety scores were measured by the Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) Scale, respectively. PHQ-9 score at baseline was 23 and after 6 months on ETI was 0. Baseline and 6-month post-ETI start GAD-7 scores were 18 and 2, respectively. No adverse effects were noted on initiation nor during the first 6 months of ETI therapy. There were sustained improvements in clinical status and sweat chloride comparing baseline to 6 months after ETI initiation (Table 1).

3. Case 2

This is a 35-year-old female with CF (genotype M1101K/M1101K) who started ETI in September 2022. Her past medical history includes end-stage lung disease, chronic pulmonary infection with *P. aeruginosa*, chronic pulmonary infection with *Pseudallescheria boydii* complex (and to a lower degree *Aspergillus fumigatus*) requiring interventional bronchoscopy for debridement of mycetoma, hemoptysis, pancreatic sufficiency with repeated episodes of pancreatitis, depression and prior episodes of distal intestinal obstruction syndrome. Baseline $ppFEV_1$ 2 years prior to ETI initiation was 46%. In the 12 months preceding ETI therapy, there was a progressive decline in lung health with development of chronic hypoxia requiring supplemental home oxygen, 6 CF pulmonary exacerbations treated with oral/IV antibiotics and a decrease in baseline $ppFEV_1$ to 27%. After starting ETI, there was a rapid decrease in sputum production, cough and dyspnea and cessation of episodes of hemoptysis. Her $ppFEV_1$ increased to 33% at 7 weeks and peaked at 38% at 6-months post initiation. This improvement in sputum production, cough and dyspnea has persisted with ongoing ETI therapy. There was a sustained improvement in overall health and sweat chloride after 6 months of ETI therapy (Table 1). No adverse effects were noted from initiation of ETI in this patient.

Table 1
Clinical characteristics before and after modulator therapy.

Clinical characteristics	Case 1		Case 2	
	Baseline	After 6 months on ETI	Baseline	After 6 months on ETI
FEV_1, L	0.44	0.84	0.85	1.19
FEV_1, % predicted	10	21	27	38
FVC, L	1.68	2.62	1.81	2.34
FVC, % predicted	34	53	48	62
Sweat chloride, mmol/L	86	34	92	30
BMI, kg/m^2	16	22.2	22.2	23.8
Number of CF pulmonary exacerbations	5 in 12 months prior to ETI start	0	6 in 12 months prior to ETI start	1
Days in hospital for CF pulmonary exacerbations	49 in 12 months prior to ETI start	0	33 in 12 months prior to ETI start	0
Days of IV antibiotics for CF pulmonary exacerbations	149 in 12 months prior to ETI start	0	33 in 12 months prior to ETI start	0

Abbreviations: ETI = elexacaftor-tezacaftor-ivacaftor; FEV_1 = forced expiratory volume in 1 second; FVC = Forced Vital Capacity; BMI = body mass index; CF = Cystic Fibrosis; IV = intravenous.

4. Discussion

To our knowledge, our cases are the first to demonstrate sustained clinical improvements with ETI therapy for pwCF and the rare M1101K variant for pulmonary and extra-pulmonary CF manifestations. Moreover, these cases demonstrate safety in initiating ETI for individuals with M1101K variant and end-stage lung disease. In both cases, $ppFEV_1$ improved after 1 month of ETI therapy, and they were sustained after 6 months with respect to $ppFEV_1$, pulmonary exacerbation rates and respiratory symptoms. There were associated improvements in nutrition as measured through body mass index (BMI), anxiety and depression. There were no reported adverse effects during ETI initiation nor with continued use during the observation period.

Those changes observed herein with the M1101K variant in our cases are similar clinical improvements compared with pwCF with F508del variant on ETI therapy. Our cases demonstrated increased $ppFEV_1$ after the first month of ETI therapy and maintained $ppFEV_1$ in the subsequent 6 months, with an absolute increase in $ppFEV_1$ at 11% for both cases, despite advanced lung disease at baseline. The rapid improvement that is sustained over time with reduction in pulmonary exacerbation rate in our cases is similar to results from clinical trials of ETI use in pwCF with F508del [5]. Similar improvements were shown in studies in pwCF with F508del with advanced lung disease on ETI [15,16]. A single center retrospective study of ETI therapy in pwCF with F508del variant and advanced lung disease with baseline median $ppFEV_1$ 27.5% showed median $ppFEV_1$ increase of 10.5% at 6 months [16]. In the nutrition domain, BMI increased from 19.1 to 22.8 kg/m^2 after ETI therapy. Our cases similarly showed an increase in BMI to the normal weight category.

One case of a pwCF and M1101K with baseline $ppFEV_1$ 37% showed improved $ppFEV_1$ and weight 4–6 weeks after treatment with ETI [18]. Our cases demonstrate that pulmonary and extra-pulmonary improvements from a much lower baseline $ppFEV_1$ are still achievable, and such improvements are sustained over 6 months.

In vitro studies using nasal epithelial cell cultures from pwCF homozygous for M1101K showed that ETI improved CFTR function [6,7]. Moreover, these improvements were superior to the CFTR function rescue by ETI in F508del homozygous nasal epithelial cell cultures [6]. Sweat chloride, a biomarker of CFTR function, can be used to assess the efficacy of treatments that influence CFTR function [17]. Our cases exhibited a reduction in sweat chloride to near normal CFTR function after ETI use, from baseline values within the CF diagnostic range [19]. The decrease in sweat chloride from baseline after ETI start in our cases exceeds the sweat chloride reduction reported in clinical trials of ETI in pwCF and F508del variant [4,5]. Our cases demonstrate improvement in CFTR function with ETI therapy, consistent with the *in vitro* data of CFTR function rescue.

More than 700 CFTR variants have been associated with CF [8]. The distribution of these alleles is often concentrated in specific communities [20]. Within Canada, those in Hutterite communities are disproportionally affected by CF and the M1101K homozygous genotype has been found in 39% of those with CF in this population [11]. Evaluation of the clinical effects for rare CFTR variants such as M1101K is challenging due to the paucity of cases available for enrollment in large-scale studies. Our cases not only demonstrate therapeutic benefit of ETI in individuals with non-F508del variants, but also provide supporting data in the worldwide efforts to access ETI for individuals who would benefit from this therapy.

5. Conclusion

We report 2 cases of pwCF with the rare M1101K variant who have improvements in lung function, pulmonary exacerbation frequency, respiratory symptoms and BMI following 6 months of ETI CFTR modulator therapy. CFTR function as measured by sweat chloride achieved near-normal values with ETI in our cases. These cases show sustained clinical efficacy in a rare but important Canadian variant, whose efficacy was previously shown in *in vitro* studies and a short-term study. Pulmonary and extra-pulmonary clinical improvements may still be safely achieved with ETI in end-stage lung disease.

Declaration of competing interest

WML and MDP are site investigators for Vertex Pharmaceuticals clinical trials. PMD, AL and CS declare no competing interests associated with this manuscript.

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