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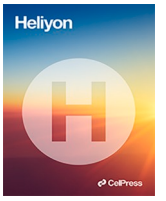

Case report

Response to Elexacaftor/Tezacaftor/Ivacaftor in people with cystic fibrosis with the N1303K mutation: Case report and review of the literature

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A B S T R A C T

Cystic fibrosis (CF) is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Thousands of CFTR mutations have been identified, but only a fraction are known to cause CF, with the most common being the prototypical class II CFTR mutation F508del. Elexacaftor-Tezacaftor-Ivacaftor (ETI) is a CFTR modulator that significantly increases ppFEV1 and reduces exacerbation frequencies. It is indicated for people with CF (pwCF) 2 years or older with at least one copy of F508del or one copy of the other 177 CFTR mutations that are responsive to ETI based on clinical or *in vitro* data. N1303K is the second most common class II mutation in the U.S. but is not yet FDA-approved for CFTR modulator therapy. However, N1303K is very similar to the F508del mutation and reveals variable *in vitro* responses to ETI.

Theratyping provides an opportunity to consider ETI therapy for pwCF with mutations currently not approved by the FDA. We describe the case of an adult CF patient with W1282X and N1303K CFTR mutations and advanced CF lung disease (ACFLD) and declining lung function in which ETI was started after theratyping of nasal cells showed a meaningful response to ETI (current enhanced to over 10% of WT CFTR). The patient experienced clinical improvement with a 5% improvement in ppFEV1 and 10% increase in weight. However, there was no change in sweat chloride and the increase in ppFEV1 was less than what has been described for ACFLD patients with more typical ETI-amenable mutations. However, the response was in line with a few other cases described in the literature. This suggests a partial functional CFTR rescue like first-generation modulators for F508del. Thus, pwCF with N1303K CFTR variant could be considered for ETI eligibility.

1. Introduction

Cystic fibrosis (CF) is a recessive genetic disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR mutations can be classified into 6 main classes according to their cellular phenotypes, characterized by no protein production (class I), protein folding (class II), channel gating (class III), channel conductance (class IV), protein quantity (class

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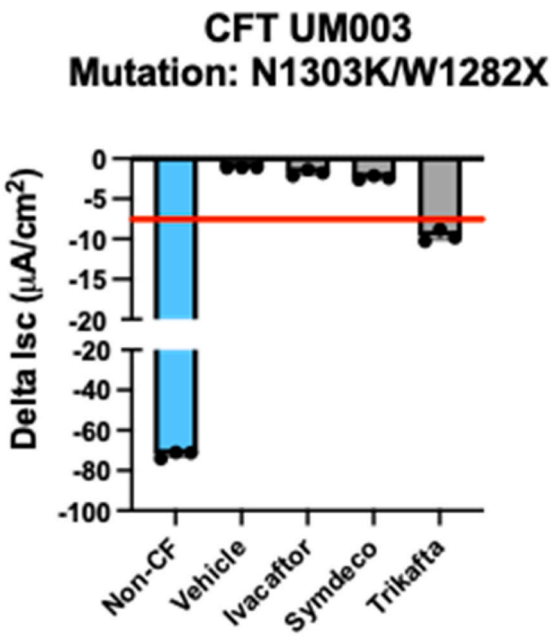
A.



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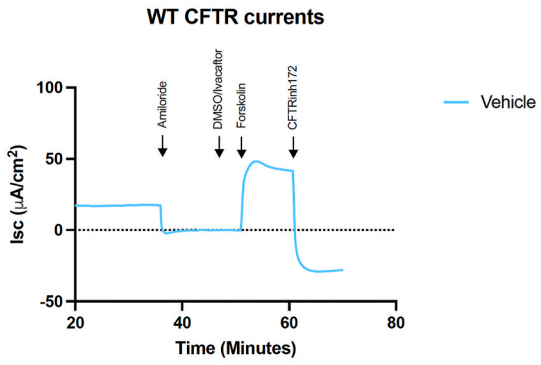

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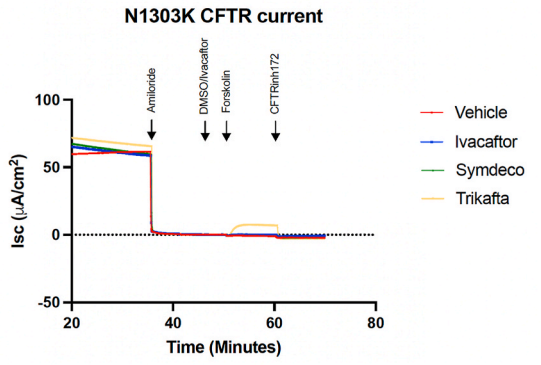

(caption on next page)

Fig. 1. Theratyping results A. CFTR activity measured by short-circuit current (delta-I_{sc}) upon addition of the CFTR inhibitor CFTRinh172 (Y-axis). Non-CF cells and the different modulators tested (X-axis). The red line represents 10% of normal WT CFTR activity. A delta I_{sc} above the red line represents a CFTR function recovery reliable enough to lead to milder manifestations. This figure shows improvement in the current through the nasal cells with ETI (Trikafta^{R}) but not with the other modulators tested. B and C. Representative tracing from Ussing chamber measurements. B. WT CFTR current (I_{sc}) at different time points when exposed to amiloride, DMSO/Ivacaftor, forskolin, and CFTRinhibitor172. C. N1303K CFTR current (I_{sc}) at different time points when exposed to amiloride, DMSO/Ivacaftor, forskolin, and CFTRinhibitor172. Each color line represents the current of N1303K CFTR cells treated with a different modulator (Ivacaftor, Symdeco, and Trikafta). There is an increase in the current in the N1303K CFTR only with Trikafta. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

V), and peripheral stability (class VI) defects. Two CFTR mutations are required to have the disease. The most common CFTR mutation is F508del, a class II mutation. Although more than 2000 CFTR mutations have been identified and a significant fraction are known to cause CF [1], their overall theratyping (i.e., matching their conductance responsiveness to modulators) remains incomplete.

CFTR modulators are specialized therapies that can enhance or restore the functional expression of CFTR mutants. Multiple defects (misfolding and lack of normal gating) can be addressed by CFTR modulators. There are different types of CFTR modulators, potentiators, and correctors, but only a few are approved for clinical use in pwCF with specific CFTR mutations. Potentiators improve CFTR protein by augmenting channel gating (associated with class III and IV mutations) and correctors improve the processing of a mutant CFTR to increase the quantity of CFTR protein at the cell membrane (associated with class II mutations). Both work independently or together to modify the CFTR protein and improve chloride transport [13]. The currently FDA-approved modulators are Ivacaftor (Vx770) which is a potentiator, Lumacaftor (Vx809) a corrector, Tezacaftor (Vx661) a corrector, and Elexacaftor (Vx445) a corrector with some potentiator activities.

Mostly used today is the second-generation CFTR modulator combination of Elexacaftor-Tezacaftor-Ivacaftor (ETI). It significantly increases ppFEV1 and reduces sweat chloride and exacerbation frequencies in pwCF (including children) and pwCF with advanced CF lung disease (ACFLD) with at least one copy of F508del or one copy of the other 177 CFTR mutations that are responsive to ETI based on clinical or *in vitro* data [2,3]. For those pwCF with CFTR variants that do not qualify for CFTR modulator treatment, no therapies to repair or restore CFTR are yet approved. These mutations include rare mutations not yet studied in clinical trials such as N1303K, or mutations whose biological features prevent the use of CFTR modulators, i.e. premature stop mutations producing truncated unstable mRNA and a lack of full-length CFTR proteins, such as W1282X.

Among the rare CFTR mutations that are not yet FDA-approved for CFTR modulator therapy, the N1303K class II mutation is the most common. This mutation shows variable *in vitro* responses to ETI [4], and there are very few reports of pwCF with N1303K that responded clinically to ETI. Out of a total of 11 pwCF reported, there was only one adult with ACFLD included [5–7]. Here we report another case of an adult patient with ACFLD with two non-F508del mutations, W1282X and N1303K, where ETI was started after confirming CFTR function recovery in nasal cells by theratyping.

2. Case presentation

We describe the case of a 44-year-old female with CF due to the mutations W1282X and N1303K, and ACFLD with a baseline lung function of ppFEV1 27%. She had pancreatic insufficiency, CF-related diabetes, and a low BMI (BMI 18). Due to her declining lung function over the prior year after a severe exacerbation, theratyping of the patient's nasal cells (human nasal epithelial cells, HNE cells) was done.

Theratyping is a method of testing modulators on laboratory or patient-derived cells. It has the potential to characterize complex CFTR variants, assess modulator responsiveness of rare/unique CFTR mutations, and even provide optimization in the modulator regimen by comparing modulator responses [8].

Nasal cells were obtained by nasal brushings and sent to the lab. Upon arrival at the lab, the brushes were rotated a few times into the media before being discarded. The tube was spun for 5 minutes at 400×*g* at 4 °C. The supernatant was removed, and the cell pellet was resuspended in 2 mL PneumaCult™-Ex Plus media and seeded as passage 0 (P0) into one well of a 6-well plate coated with collagen I. Additional antibiotics were added. The media was changed the next day and subsequently, every other day until the cells were confluent. A second expansion as P1 followed into a 10 cm dish coated with collagen I, in PneumaCult™-Ex Plus media. Upon confluency, the cells were transferred to Transwell inserts coated with collagen IV, as P2 and cultured submerged for 5 days. Air-liquid interface was created at that time and the media was switched to PneumaCult™-ALI media. The cells were apical washed using DPBS and the media changed in the basolateral compartment every other day for 2–3 weeks until ciliary beating and mucus transport could be observed in the microscope. The day before CFTR current measurements, cells were washed and media replaced with the following treatments: one control with DMSO (0.1%); one with 1 μM ivacaftor; one with 1 μM ivacaftor plus 5 μM tezacaftor; and one with 1 μM ivacaftor, 5 μM tezacaftor, and 1 μM elexacaftor. CFTR current measurements were done in Ussing chambers and CFTR currents were recorded in the presence of acute DMSO (0.1%) or ivacaftor (5 μM). The experiments were carried out in triplicates.

In this case, theratyping of the nasal cells showed that current was enhanced to over 10% of WT CFTR (Fig. 1) which represents the ≥10% CFTR recovery that has been considered reliable to lead to milder clinical manifestations [9]. In 2022, due to the patient's clinical deterioration, our team decided to pursue off-label use of ETI. The patient began treatment with ETI (Elexacaftor 200mg -Tezacaftor 100mg-Ivacaftor 150mg in the morning and Ivacaftor 150mg orally at nighttime) in April 2022. Three months after the patient came back to the clinic and reported significant improvement in respiratory symptoms, with decreased cough overall, especially at night. She was now able to sleep better at night, wake up rested, and had more energy during the day. She had less chest tightness and less sputum, was less short of breath, and able to exercise more. Her lung function increased by 5% of ppFEV1 (27%–

32%; Table 1). She had more appetite, gained weight 3.6kg (from 44.5kg to 48.1kg) and her BMI increased from 18.8 to 20.1. After ten months, the clinical improvement was maintained: her lung function was 33% ppFEV1, her weight was 48.0kg, her BMI remained at 20.0, and required less insulin to control her CF-related diabetes. She did not grow methicillin-resistant staphylococcus aureus (MRSA) in the sputum for 10 months but continued to grow methicillin-susceptible staphylococcus aureus and Pseudomonas. She had only one exacerbation after which she recovered faster than usual.

For safety monitoring, the patient continued with her quarterly CF clinic visits, and liver function tests were checked every three months. The transaminases did not significantly change, the alkaline phosphatase decreased, and the total bilirubin increased to 1.7mg/dl but after ten months decreased to 0.9mg/dl. She did report some memory problems, but it was unclear if it was related to ETI or to a recent COVID infection. There were no other adverse effects.

Despite this benefit in her symptoms, lung function, and quality of life, her sweat chloride concentration two months after ETI initiation showed no significant reduction (108–99mmol/L, and 102 to 101mmol/L).

3. Discussion

The patient's CFTR mutations (W1282X and N1303K) are classified as class I and II variants respectively and none is approved for CFTR modulator therapy.

W1282X is a common nonsense mutation that leads to a truncated transcript that is susceptible to nonsense-mediated mRNA decay (NMD) and produces a shorter CFTR protein that is unstable and lacks normal channel activity. Some studies have shown that modulator treatment increases the activity of the truncated CFTR protein, but these results could not be replicated in HNE cells with W1282X mutation because of its decreased abundance due to NMD of nonsense transcripts [10]. This substantial decay needs to be addressed before efforts aimed at augmenting CFTR protein function can be effective. Laselva et al. provided in-vitro evidence that the functional defects incurred by W1282X have the potential to be effectively repaired pharmacologically with a combination of small molecules (NMD inhibitor SMG1i with two new correctors developed by Galapagos/AbbVie, AC1, and AC2-2) [11]. Response to ETI is not expected for W1282X.

N1303K is the fifth most common CFTR variant in pwCF in the U.S. and the second most common class II mutation after F508del [12]. It belongs to the same class as the F508del variant but is not approved for CFTR modulator therapy as it did not meet the criteria for *in vitro* responsiveness, an increase in the CFTR chloride transport of at least 10% of normal over baseline following ETI administration in Fisher Rat Thyroids (FRT) Cells expressing mutant CFTR [3].

The F508del variant is the most common CFTR mutation and is the prototypical class II CFTR mutation that leads to defective CFTR protein folding that markedly responds to CFTR correctors. The N1303K variant is a mutation that disrupts CFTR delivery to, and stability at the plasma membrane, and functions as a regulated chloride channel, which is associated with a severe disease phenotype [13]. Its mutation in the nucleotide-binding domain 2 (NBD2) is like F508del in NBD1 but has different structural and functional effects on the final assembly of the CFTR when compared to F508del [20], and has a severe gating defect, similar to G551D [14]. Its unique characteristics (i.e. in response to temperature rescue, conformation, and NBD2 processing) indicate that individualized strategies may be needed to restore its function [15].

Substantial CFTR rescue of rare misprocessing mutations confined to membrane-spanning domain (MSD)1, MSD2, NBD1, and NBD2 of CFTR, has been seen in airway epithelia, suggesting an allosteric correction mechanism and the possible application of ETI for patients with rare CFTR misfolding mutants like N1303K [15]. It is likely that mutations that are resistant to single corrector treatment will be susceptible to correction with a combination of different types of correctors, for example, a type I combined with a type II or III corrector. Type I correctors stabilize the NBD1-CL1–4 interface (i.e., VX661-Tezacaftor, C3, C18), type II correctors restore NBD2 or its

Table 1
Summary of patient characteristics before and after ETI.

	Year before ETI	3 months after ETI	10 moths after ETI
Symptoms	Persistent productive cough with thick mucus. Dyspnea on exertion with limitation of physical activities. Low energy. Took a long time to recover from any exacerbation.	Decreased cough, decreased amount of sputum production, thinner mucous. Able to do more physical activities. More energy. Recover faster from exacerbations.	Continues with minimal cough and sputum production. More energy.
BMI (kg/m2)	18.8	20.3	20.0
Weight (kg)	44.5	48.1	48.0
ppFEV1 (%)	27	32	33
Microbiology	Pseudomonas Aeruginosa, Methicillin resistant Staph aureus, Aspergillus sp.	Methicillin sensitive Staph aureus	*Pseudomonas aeruginosa*
Sweat chloride (mmol/L)			
Right arm	108	99	
Left arm	102	101	
Liver function test			
AST (U/L)	21	18	22
ALT (U/L)	25	30	34
Alk phos (U/L)	232	152	145
Bilirubin total (mg/dl)	1.1	1.7	0.9
A1C	6.0	5.5	5.7

interfaces (i.e. C4a), and type III correctors assist assembly of MSD1 and MSD2 (possibly VX445-Elexacaftor) [16 preprint]. As well, there is some evidence supporting the use of combination potentiator therapy.

Despite N1303K being reported initially as refractory to Ivacaftor/Lumacaftor/Tezacaftor *in vitro*, variable responses to ETI have been reported on functional rescue in cell lines and human bronchial epithelial (HBE) cells [17,18]. *In vitro* studies demonstrated that VX-445 (Elexacaftor) combined with type I correctors as VX-661 (Tezacaftor) corrected homozygous N1303K-CFTR to 22% of the WT I_{sc} in the presence of chronic VX-770 (Ivacaftor) exposure [19]. This degree of CFTR activity correction would likely be associated with a therapeutic benefit despite being below the ~62% of the mean WT-CFTR I_{sc} correction achieved by ETI in F508del homozygous HNE cells [19]. Also, other not-yet-approved small-molecule corrector combinations (C3+C4 and C4+C18) has been shown to influence the CFTR protein band B and C maturation in HEK 293 cell lines expressing N1303K [20]. In a transfected FRT cell model, VX-770 (Ivacaftor) enhanced N1303K-CFTR-dependent current and this response was further increased by C3 combined with a co-potentiator, suggesting that a co-potentiator and corrector combination could be a therapeutic option for N1303K [21]. In FRT cells N1303K appeared to respond functionally in fluorescent-based membrane potential (FMP) to MCG151 (a newly developed F508del-CFTR corrector), to VX661 (tezacaftor), and to both combined. However, this rescue of CFTR processing was not confirmed by Western blot in CFBE (cystic fibrosis bronchial epithelial) cells expressing N1303K [22].

In vivo, there have been two case reports in children with CF N1303K heterozygous who received ETI treatment with evidence of functional response. The first one was an 11-year-old patient with CF caused by N1303K and E193X who started ETI treatment, and despite clinical improvement, the sweat chloride was only marginally reduced (108mmol/L to 95mmol/L) [5]. The second was a 15-year-old patient with CF caused by N1303K and Q493X initially treated with Tezacaftor-Ivacaftor and then with ETI resulting in clinical improvement and clinical stability despite almost no change in sweat chloride (113mmol/L to 111mmol/L) [6].

Most recently, Sadras et al. reported a case series of 8 pwCF with N1303K variant (2 homozygous and 6 heterozygous N1303K/nonsense or frameshift mutation, 5 adults and 3 children) [7]. The patients were treated off-label with ETI and had a good clinical response. Most patients had ETI responses evaluated *in vitro* with intestinal organoids. Overall patients had a mean increase in ppFEV1 of 18.4%, higher than the mean ppFEV1 reported for pwCF homozygous or heterozygous for F508del in the pivotal ETI studies [13], a mean BMI increase of 0.79kg/$m^{2,}$ and a mean lung clearance index (LCI) decrease of 3.6 points. All this with only a partial response in nasal potential difference (NPD) without a significant change in sweat chloride.

In our case, theratyping of human nasal cells gave this patient an opportunity to consider ETI therapy. Our patient is the second adult with ACFLD with the N1303K variant that has been reported receiving ETI. At ten months, she had a good clinical response to ETI with an increase in ppFEV1 of 6%, and an increase in BMI of 1.2 (weight increase of 3.5 kg), which are more modest than the 15% absolute increase in ppFEV1 and the 4 kg gain reported for patients with ACFLD with eligible mutations for ETI in observational studies [23].

This patient did not grow MRSA in subsequent cultures but continued to grow Pseudomonas. Previous reports have shown how CFTR modulators affect the CF airway microbiology by improving airway clearance, reducing the requirement for antibiotics, and in some cases, through direct antimicrobial effects. Additionally, Ivacaftor and ETI have direct antimicrobial activities against *Staphylococcus aureus* but not against *Pseudomonas aeruginosa* [24,25].

In line with previous case reports of patients with N1303K variants treated with ETI, this patient had clinical improvement despite no significant changes in sweat chloride (108 mM–99 mM), suggesting functional rescue of CFTR at least in the lung, and supporting an indirect relationship between the clinical response and the CFTR functional rescue.

The limitation of this study is that it is retrospective and clinical improvement was mainly characterized qualitatively rather than quantitatively.

4. Conclusion

Theratyping should be used to consider ETI therapy for pwCF with ineligible mutations. ETI produced a clinically significant response in this patient with N1303K. Collectively, there are now 11 pwCF (5 children and 6 adults) including 2 adults with ACFLD carrying the N1303K mutation treated with ETI who showed significant symptomatic and clinical benefits despite minimal CFTR functional response outside the airways (minimal change in sweat chloride), confirming *in vitro* data of N1303K responses to ETI. Given this mounting evidence of clinical improvement and functional CFTR rescue by ETI in this patient population, pwCF with the N1303K mutation could be considered for ETI eligibility.

Patients perspective

The cystic fibrosis label has been in my life since I was one year old. Although, admittedly, I only started to really take care of myself and my lung function when I was about 30 years old. Exacerbated when I became very sick right before the pandemic began, and I was having difficulty maintaining the weight, never mind gaining it. Trikafta has helped me regain the weight without much effort; it has helped reduce my phlegm, which is a game changer in my life in general but also when it comes to getting sick (I have been able to stay healthy), and lastly, it has helped me reduce my A1C.

Ethics statement

Informed consent was obtained from the patient and is available upon request.

Data availability statement

Data is included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Maria G. Tupayachi Ortiz: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Nathalie Baumlin:** Investigation, Writing – review & editing. **Makoto Yoshida:** Investigation, Writing – review & editing. **Matthias Salathe:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Mathias A. Salathe and Nathalie Baumlin report financial support was provided by National Heart Lung and Blood Institute.

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