Treatment effects of CFTR modulators on people with cystic fibrosis carrying the Q359K/T360K variant

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To the Editor:

The identification of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and cystic fibrosis (CF)-causing variants has led to the development of therapies to correct the basic cellular defect that causes the condition. CFTR modulators (CFTRm) are among such therapies, which either correct protein misfolding (correctors) or restore cell surface channel activity (potentiators) [1, 2].

The Q359K/T360K CFTR variant is described in Jewish CF patients of Georgian descent [3]. According to the CFTR2 database, this variant is CF-causing, described in only 15 people with CF (pwCF) [4]. In a published cohort of nine pwCF, the Q359K/T360K variant has been associated with minimal CFTR function [3]. Structural three-dimensional CFTR models suggest the Q359K/T360K variant may interfere with CFTR transmembrane chloride conductance, and as such patients may potentially benefit from potentiators which improve CFTR conductance [3]. Whether correctors have an additive effect on this variant has not been conclusively demonstrated. Ramalho *et al.* [5] described the responsiveness of intestinal organoids derived from a pwCF homozygous for the Q359K/T360K variant to the corrector/potentiator combination lumacaftor/ivacaftor (LI). The treatment of the patient with LI also resulted in a significant clinical response [5]. A recent paper showed responsiveness of this variant in Fisher Rat Thyroid cells (<10% baseline CFTR function, increased to 10–30% of wild-type function after ETI) [6].

To date, no CFTRm is approved for the treatment of the Q359K/T360K variant, and pwCF carrying it have endured a therapeutic need remaining unmet. Here we describe the clinical experience of four pwCF carrying the Q359K/T360K variant treated with tezacaftor/ivacaftor (TI) or elexacaftor/tezacaftor/ivacaftor (ETI).

A 39-year-old female (patient 1), homozygous for the Q359K/T360K variant, was diagnosed with CF at the age of 3 months due to pancreatic insufficiency. She has severe bronchiectasis, with moderately reduced pulmonary function, with forced expiratory volume in 1 s (FEV_1) being 58%, and chronic infection with resistant *Pseudomonas aeruginosa*. In the year prior to commencing treatment with CFTRm, she experienced four pulmonary exacerbations treated with IV antibiotics. She has fatty liver and multiple pancreatic cysts.

Following discussions with her CF care team regarding the prospect of response to CFTRm, the patient commenced treatment with TI for 1 month on July 2022, and then switched to ETI for an additional 2 months. The patient experienced substantial improvement in lung function and weight gain, with significant reductions in sweat chloride concentrations. All parameters further improved after switching to ETI (FEV_1 improved from 58% to 72% to 81%, weight increased from 61.2 to 67 to 72.3 Kg, and sweat chloride concentration decreased from 98 to 48 to 28 $meq \cdot L^{-1}$ respectively after TI and ETI, figure 1a). There were no pulmonary exacerbations during the 6 months after commencing ETI. Based on these results, the health maintenance organisation approved ETI treatment for this patient.

A 21-year-old female (patient 2), heterozygous for the Q359K/T360K and N1303K variants, was diagnosed at age 14 months due to pancreatic insufficiency. Her lung function was preserved (FEV_1 % pred=103), but she intermittently cultured *P. aeruginosa*. She also had chronic colonisation of *Mycobacterium abscessus* without radiological or clinical evidence of disease. A year prior to commencing

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pwCF carrying the Q359K/T360K variant may have significant clinical benefit from treatment with ETI that may exceed improvements observed with TI treatment. These data support routine clinical use of ETI in this rare patient group. https://bit.ly/45DjFw9

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a)

Patient	Sex	First variant	Second variant	Pancreatic status	Age at CFTRm start	CFRD	CFLD	PA	Other infections	CFTRm treatment	FEV_1 % pred			Weight kg			Sweat chloride mEq·L^{-1}		
											Before	After	Change	Before	After	Change	Before	After	Change
1	F	Q359K/T360K	Q359K/T360K	Insufficient	39	No	Fatty liver	Yes	No	TI	58	72	+14	61.2	67	+5.8	98	48	−50
										ETI	72	81	+9	67	72.3	+5.3	48	28	−20
2	F	Q359K/T360K	N1303K	Insufficient	21	No	No	Yes	*M. abscessus*	ETI	103	107	+4	55.7	58	+2.3	106	23	−83
3	M	Q359K/T360K	Q359K/T360K	Insufficient	31	Yes	No	Yes	No	TI	87	99	+12	71	74.5	+3.5	113	55	−58
4	F	Q359K/T360K	2789+5G >A	Sufficient	46	No	No	Yes	No	Ivacaftor switched to TI	35	38	+3	57.8	61.4	+3.6	97	56	−41

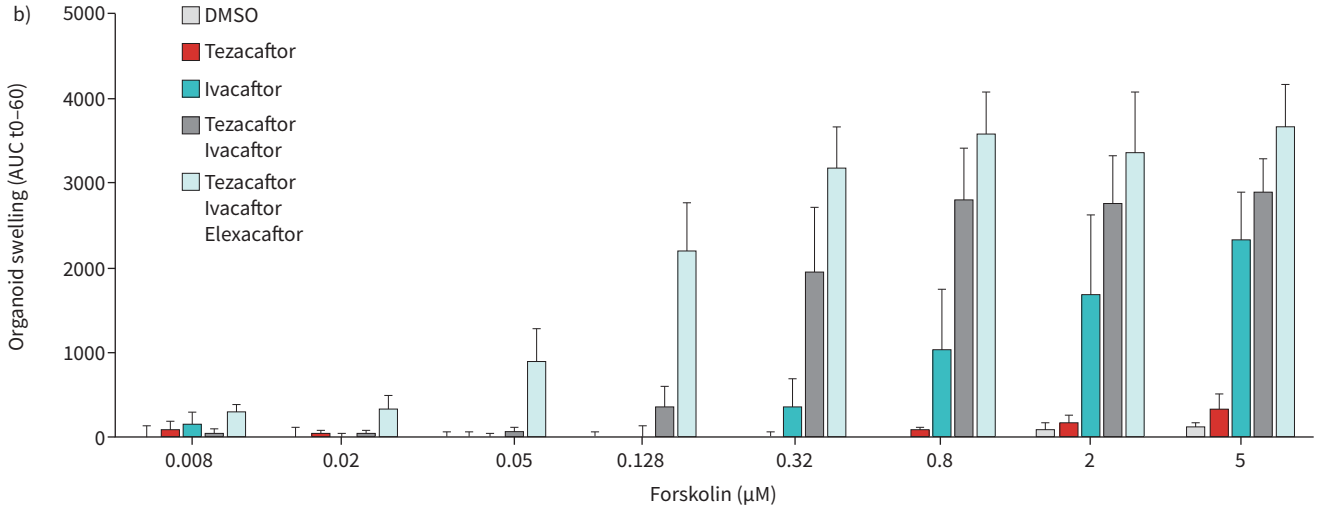

FIGURE 1 a) Baseline characteristics and clinical data before and after starting treatment with CFTR modulators. b) Patient number 3's intestinal organoid response to CFTRm. Forskolin induced swelling (FIS) assay on the organoids obtained from the biopsies of a CF subject (genotype Q359K_T360K/Q359K_T360K). Organoids were incubated over night with tezacaftor 3 μM with and without elexacaftor 3 μM and stimulation was done after 24 h with forskolin (range concentrations from 0.008 to 5 μM) alone or in combination with ivacaftor 3 μM during 1 h. For each individual experiment, each condition was tested in duplicate. Four independent (individual) experiments (n=4) were performed on different days. Values plotted correspond to the average of AUC (area under the curve) calculated from plots representing the mean percentage (%) of organoid swelling from t0 to t60 (60 min−1 h) and standard deviation (SD) of the three independent experiments. Note highest response to ETI. CFTRm: Cystic Fibrosis Transmembrane Regulator modulators; CFRD: CF-related diabetes; CFLD: CF liver disease; F: female; M: male; PA: Chronic infection with *Pseudomonas aeruginosa*; FEV_1: forced expiratory volume in 1 s; TI: tezacaftor/ivacaftor; ETI: elexacaftor/tezacaftor/ivacaftor; *M. abscessus*: *Mycobacterium abscessus.*

ETI, she experienced several pulmonary exacerbations requiring parenteral treatment, and then had a subsequent exacerbation that was treated orally.

The patient commenced treatment with ETI in April 2021, which led to an improvement in sweat chloride, weight, and lung function (figure 1a) as well as symptomatic improvement, with no pulmonary exacerbations during the first 6 months of treatment.

A 31-year-old male (patient 3), homozygous for the Q359 K/T360 K variant, was diagnosed with CF at the age of 14 due to haemoptysis. He has significant upper lobe predominant bronchiectasis, with preserved pulmonary function (FEV_1 % pred=87), and chronic infection with multi-drug resistant *P. aeruginosa*. He is pancreatic insufficient and has CF-related diabetes. In the year prior to commencing TI, he experienced one pulmonary exacerbation.

Within the scope of a research project (Katholieke Universiteit Leuven, Belgium, Ethics Committee approval S56329), a clear response to CFTRm in intestinal organoids grown from the patient's rectal biopsy was demonstrated. Initially the test was done with I, T and TI and higher responses were observed with TI (figure 1b). Based on these results, the patient commenced treatment with TI in August 2020.

He reported reduced cough and sputum production, and had improved lung function, sweat chloride, and weight gain (figure 1a), with no pulmonary exacerbations. Later, when ETI was available, it was also tested in the organoids from this patient, and there was a slight increase in CFTR rescue when ETI was used compared to TI (figure 1b).

A 46-year-old female (patient 4) heterozygous for the Q359K/T360K and 2789+5G->A variants, was diagnosed with CF at age 33 years due to widespread bronchiectasis. She is pancreatic sufficient, has severely reduced pulmonary function (FEV_1 % pred=35) and chronic infection with multi-drug resistant *P. aeruginosa*.

She commenced ivacaftor in 2018 and switched to TI in March 2019, after its approval for pwCF with splice variants. She experienced improvements in lung function, sweat chloride, and nutrition (figure 1a). She continued to complain of respiratory symptoms, remaining on chronic oral antibiotics.

To our knowledge, this is the first report of the clinical benefits of treatment with TI/ETI in pwCF who carry the Q359K/T360K variant. Four pwCF, compound heterozygous or homozygous for Q359K/T360K, demonstrated an improvement in pulmonary exacerbation frequency (in three of four patients), lung function, and weight. A reduction in sweat chloride concentration, which is the most proximal measurement of CFTR function, to normal-borderline values (<60 $mEq \cdot L^{-1}$) was seen in all patients.

Two of the patients included in our report (patients 1 and 3) were homozygous for the Q359K/T360K variant. Both patients showed clinical improvement on TI, with patient 1 showing an even greater response when switched to ETI. This is in line with the previous finding that elexacaftor has both correction and potentiation effects on CFTR that may be synergistic with ivacaftor's CFTR potentiation [7]. Based on clinical data from patient #1 and the organoid analysis data, patient #3 may also benefit from the change from TI to ETI.

One of the patients included in our study (patient 2) was a compound heterozygote to Q359K/T360K and N1303K and showed a dramatic response to ETI. Improvements may be due in part to the response of the N1303K variant as has been previously demonstrated [8]. In contradiction with the findings of Sadras *et al*. [9] of modest sweat chloride response in N1303K patients, patient #2 had a significant decrease in sweat chloride to normal values, which we hypothesize is mediated by the response of the Q359K/T360K variant to ETI.

Patient 4 was a compound heterozygote for Q359K/T360K and 2789+5G->A, which is a splice variant. Both variants should potentially benefit from potentiators such as ivacaftor.

Our report has several limitations. The small number of patients is obviously a limitation dictated by the rarity of this *CFTR* variant. We did not systematically monitor adherence to CFTRm, but we assume good adherence due to the novelty and potential improvements that the CFTRm allow for this rare *CFTR* variant. We did not collect *in vitro* data in 3D intestinal organoids and 2D nasal epithelial cultures from these pwCF to show a response in CFTR channel activity to CFTRm, although one patient's response was substantiated by intestinal organoid assays. Moreover, to our knowledge, this is the first "real life" report of clinical outcomes in patients with this rare variant.

In conclusion, this clinical report suggests that pwCF carrying the Q359K/T360K variant may have significant clinical benefit from treatment with ETI that may exceed improvements observed with TI treatment. Our results support routine clinical use of ETI in this rare patient group based on the significant reduction in sweat chloride concentrations and the substantial clinical improvements. A larger study that includes patient-derived intestinal organoids and human nasal epithelial cells derived from patients treated with ETI would be required to validate a correlation between *in vitro* data and the improved clinical results observed in pwCF carrying the Q359K/T360K allele.

Karin Yaacoby-Bianu[1,2,8], Moshe Heching[3,4,8], Mordechai R. Kramer[3,4], Einat Shmueli[5], Dario Prais[4,5], François Vermeulen[6], Anabela S. Ramalho[6], Raya Cohen[2,7], Galit Livnat[1,2,8] and Michal Shteinberg[2,7,8]

[1]Pediatric Pulmonology Unit and CF Center, Carmel Medical Center, Haifa, Israel. [2]B. Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel. [3]Pulmonology Institute and CF Center, Rabin Medical Center, Petah Tiqva, Israel. [4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. [5]Pediatric Pulmonology Institute and CF Center, Schneider Children's

Medical Center, Petah Tiqva, Israel. [6]CF Research Lab, Woman and Child Unit, Department of Development and Regeneration, KU Leuven, Leuven, Belgium. [7]Pulmonology Institute and CF Center, Carmel Medical Center, Haifa, Israel. [8]These authors contributed equally.

Corresponding author: Michal Shteinberg (michalsh@technion.ac.il)

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Data availability: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors. All participants have verbally assured their consent to the publication that describes their age, sex, country of residence, CFTR variants and clinical baseline characteristics with response to CFTR modulators.

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