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Early View

Editorial

Gathering real-world compassionate data to expand eligibility to elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with N1303K or other rare *CFTR* variants: a viewpoint

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Running title: ETI in N1303K with no F508del

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Take home message (253 signs, max 256 signs): The off-label use of elexacaftor-tezacaftor-ivacaftor (ETI) in 35 people with cystic fibrosis with the N1303K variant but not F508del was associated with increased lung function, which combined with *ex-vivo* data, demonstrate that N1303K responds to ETI.

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Introduction

Elexacaftor-tezacaftor-ivacaftor (ETI) was approved in 2019 by the United States Food and Drug Administration (FDA) and in 2020 by the European Medicines Agency (EMA) for people with cystic fibrosis (pwCF). It is a combination of small molecules that bind to the defective cystic fibrosis transmembrane conductance regulator (CFTR) protein, thus allowing the rescue of CFTR structure and function (1). Pivotal studies in pwCF carrying at least one F508del variant (the most common) have shown that treatment with ETI induced a significant decrease in sweat chloride concentrations, an increase in percent predicted forced expiratory volume in one second ($ppFEV_1$) and weight gain, all of which occurred within the first month after treatment initiation (2, 3). A decrease in respiratory symptoms (especially chronic cough and sputum) was also observed within two weeks and reductions in the frequency of pulmonary exacerbations were further reported (4-6). Real-world studies have also suggested that ETI is associated with increased survival without lung transplantation (7-10). ETI has thus established a new standard of care in pwCF carrying at least one F508del variant. However, F508del is present in 40 to 90% of pwCF (11) and many pwCF are still not eligible for ETI. Current evidence suggests that a fair proportion of pwCF with no F508del variant could benefit from ETI. Vertex Pharmaceuticals, has developed an *in vitro* model in Fischer Rat Thyroid (FRT) cells transfected with *CFTR* variants (12). Data obtained using ETI exposure in FRT cells have led the FDA, but not the EMA, to expand the approval of ETI for 177 rare variants.

The Asn1303Lys variant, also known as N1303K, is the third most common *CFTR* variant in Europe (11) and is found in 2-4% of pwCF (11, 13-15). N1303K is not part of the list of 177 rare variants approved by FDA for the use of ETI (16) as it was not found to respond to ETI in FRT cells (17). However, a seminal case report described a response to ETI in a patient with N1303K and E193X (a stop codon variant resulting in no CFTR protein) (18). Two independent studies reported data from small case series and showed effectiveness of ETI in pwCF carrying

at least one N1303K variant (19, 20). As CF is bi-allelic condition, the most convincing evidence to determine the effects of ETI on the N1303K variant would be obtained by analyzing its effects in pwCF homozygous for N1303K and in those carrying a second variant that produces no CFTR protein (e.g., a stop codon), predicting the absence of response to ETI of this second variant. However, the sample size in individual studies of pwCF with N1303K and no F508del was too small to perform meaningful subgroup analyses.

The objective of this study was to determine whether ETI can induce a clinical response in pwCF carrying a N1303K variant by (A) reviewing all published cases of ETI in pwCF with at least one N1303K (but no F508del and none of the 177 rare variants approved for ETI) variant and (B) analyzing data from new (previously unpublished) cases that benefited from treatment through the French Compassionate program (19, 21). An individual data analysis regrouping all published and unpublished cases was conducted in order to examine the effects of ETI on $ppFEV_1$ and sweat chloride concentrations in this N1303K population.

Methods

The French compassionate program began in May 2022, and was limited to pwCF with no F508del variant, aged 12 years and older, and with advanced lung disease (19). On June 1st, 2023, an extended program was launched for all pwCF with no F508del, aged 6 years and older. Eligible pwCF are granted access to ETI for an individual trial. Responders are allowed to continue receiving ETI after the 4-6 weeks trial period. Response to ETI is evaluated by a centralized adjudication committee as described previously (19). For this study, all pwCF with at least one N1303K variant who received ETI through the French Compassionate program and had been evaluated by August 13th, 2023, were included. In accordance with French law, written consent was not required, and the study was approved by the Institutional Review Board of the *Société de Pneumologie de Langue Française* (#2020–003). Data were combined with those of published cases (18, 22, 23) and case series (20) treated with ETI outside of France.

Data are shown as median [interquartile range, IQR], mean (95% confidence interval, CI) or n (%). Data on sweat chloride concentrations, $ppFEV_1$ and body weight before initiation and with ETI were compared using the non-parametric Wilcoxon's signed rank test. Results were considered statistically significant when $P<0.05$. All analyses were performed using GraphPad Prism 9.4.1 (Graphpad Software LLC).

Results

Data analysis included 35 cases of pwCF with at least one N1303K variant and no F508del who received off-label ETI. Data were obtained from previously published reports from the French Compassionate program (n=10) (19, 21), from the Israeli study by Sadras et al. (n=8) (20) and from three case reports (18, 22, 23). Unpublished data (as per August 13th, 2023) obtained from 14 pwCF that enrolled in the French Compassionate program was also included. The individual characteristics of these 35 pwCF (16 females, 19 males) are provided in **Table 1**. Data was recorded at different time points (e.g., 4 to 6 weeks in French patients and in two case reports (22, 23), 8 weeks in Israeli cases, 10 months in one case report (18). Because previous studies have shown that the effects of ETI on sweat chloride concentrations and $ppFEV_1$ generally occur within the first few weeks after initiation of ETI and remain stable thereafter (4, 24), collating these data obtained at different time points was considered acceptable.

Median [IQR] age at ETI initiation was 23 [15; 31] years (range, 8-62). Eleven pwCF were homozygous for the N1303K variant, 14 were compound heterozygous with a stop codon variant, and 10 patients were compound heterozygous with another *CFTR* variant (see Table 1 and legend to Figure 1). Median [IQR] sweat chloride concentrations were 107.0 [99.5; 112.5] mmol/l (n=33; missing in 2 cases) and median $ppFEV_1$ was 49.5 [38.3; 70.5] (n=34; missing in 1 patient for whom $ppFEV_1$ was not reproducible due to young age).

ETI was associated with clinically-significant improvement in all 35 patients, leading to the decision of continuing treatment. Changes in sweat chloride concentrations and in $ppFEV_1$ following initiation of ETI are shown in **Figure 1**.

Sweat chloride concentrations saw an overall (N1303K/any) median [IQR] decrease of 9.0 [3.5; 21] mmol/l (n=33; $P<0.001$; missing in 2). They decreased by 10.0 [4.5; 31] mmol/l in N1303K/N1303K pwCF (n=9; $P=0.0039$; missing in 2), by 6.5 [2.8; 12.3] mmol/l (n=14; $P=0.0024$) in those with N1303K/stop codon, and by 13.5 [0.8; 22.0] mmol/l (n=10; $P=0.09$) in those with N1303K/other. All sweat chloride concentrations performed in ETI treated subjects (n=34) remained over 60 mmol/l, the diagnostic threshold for CF (25). A decrease by ≥20 mmol/l in sweat chloride concentrations occurred in 9/34 (26.5%) with N1303K/any, in 4/9 (44.4%) with N1303K/N1303K and in 2/14 (14.3%) with N1303K/stop codon.

The median [IQR] increase in $ppFEV_1$ was 17.0 [10.0; 25.0]% in all pwCF (N1303K/any; n=34; $P<0.0001$; missing in 1), corresponding to a mean (95%CI) increase by 18.5 (14.2; 22.9)%. The median [IQR] increase was 11.0 [10.0; 23.0] % in N1303K/N1303K cases (n=11; $P=0.001$) and by 16.5 [9.0; 23.0] % in those with N1303K/stop codon (n=14; $P=0.0001$) and by 21.0 [12.0; 31.0]% in those with N1303K/other (n=9; $P=0.004$). An increase in $ppFEV_1 \geq 10\%$ under ETI was found in 79% (n=27 of 34) of the N1303K/any, 82% (9/11) in the N1303K/N1303K group and 71% (10/14) of the N1303K/stop codon group.

In the 24 pwCF from the French Compassionate Program, weight had increased by a median 2.0 [1.0; 3.5] kg ($P<0.0001$) by 4 to 6 weeks after ETI initiation. Significant increase in body weight and/or body mass index were also reported in other studies, but combined analysis was not possible due to differences in data reporting.

Discussion

This study presents combined individual data describing the clinical response to ETI in 35 pwCF with at least one N1303K variant (and no F508del and none of the 177 rare variant FDA-approved for ETI) who are not currently eligible to receive ETI anywhere in the world. ETI initiation was associated with a marked reduction in clinical symptoms, an increase in body weight and a major increase in ppFEV$_1$, which was also found in those pwCF with N1303K/N1303K and in N1303K/stop codon. These latter data provide unequivocal evidence that ETI is effective in N1303K carriers. The median decrease in sweat chloride concentrations that occurred in N1303K pwCF was however small and was approximately four times less compared to the reduction observed in pwCF with at least one F508del variant (3, 24). Laselva et al. reported that ETI induced no improvement in N1303K CFTR protein processing despite a relative improvement in functional rescue in cultured nasal epithelial cells, suggesting a mechanisms of action that differs from that of ETI rescue for F508del (26). This could explain, at least partially, the limited reduction in sweat chloride concentrations observed in the clinical setting. This data suggests that sweat chloride decrease is not a robust marker of clinical effectiveness in pwCF with N1303K. It further suggests that the evaluation of ETI effectiveness in individual patients should rely on a combination of clinical findings (e.g., patient symptoms, requirement for other therapies) and multiple biomarkers (e.g., sweat chloride, FEV$_1$, imaging) rather than only on a single biomarker.

One of the next frontiers in CF care is the extension of CFTR modulator eligibility to pwCF with non-F508del rare *CFTR* variants. It is generally accepted that conducting clinical trials in pwCF with relatively rare variants is not a viable option (12), even though combining relatively rare (presumably responsive) variants in one clinical trial could be useful for rare variants with relatively high frequency (27). Another possibility, which was approved by the FDA, but not by the EMA, is to rely on the results of *in vitro* studies (e.g., in FRT cells). However, this option

has also limitations as the unpublished data in FRT cells submitted to the FDA suggested that N1303K was not responsive to ETI (17); a recent report shows that ETI restores CFTR function to 9.4% of wild type CFTR, a level just below the accepted 10% threshold that predict effectiveness (28), in FRT cells. The finding that ETI induced significant clinical benefits in pwCF with N1303K/no F508del variant challenges this 10% threshold, at least for the N1303K variant. Other in vitro models (e.g., other cell lines (29, 30), nasal cells (21, 23, 26, 31) and rectal organoids (20, 32)) have also suggested that ETI may improve N1303K CFTR function. As our study shows, individual data of pwCF treated with off-label ETI in multiple clinical units can be collated and analyzed to evaluate treatment effectiveness in the largest possible number of pwCF with rare variants. We suggest that regulatory agencies should consider using real-world off label data for expanding the indication of approved CFTR modulators (e.g., ETI) to rare *CFTR* variants. We further argue that the current paradigm for expanding drug eligibility criteria should be revised since currently, only the drug manufacturers can file a request for approval from regulatory agencies. We suggest that physicians and/or patient associations should be able to file for approval, if they provide sufficient evidence of effectiveness, especially for drugs with an established safety profile. Expansion of CFTR modulator eligibility to rare variants would be a good example of this proposal.

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Figure legends

Figure 1 . Comparison of sweat chloride concentration and ppFEV$_1$ before ETI and with ETI for all patients with at least one N1303K, those with N1303K/N1303K, N1303K/stop codon (including E193X, E819X, E585X, G452X, Q493X, R553X, W1162X, and W1282X) **or N1303K other** (including H199R, M1V, V754M/delexon 3-10 14b-16, 711+1G>T, 1898+5G>A, 2789+5>A, 3120+1G>A, 3221-1G>A, 3659delC, 4326delTC). A. Sweat chloride concentrations B. ppFEV$_1$. Box plots: median [IQR] (error bars, 10-90 percentile) with outliers. Data were analyzed using the nonparametric Wilcoxon's test.

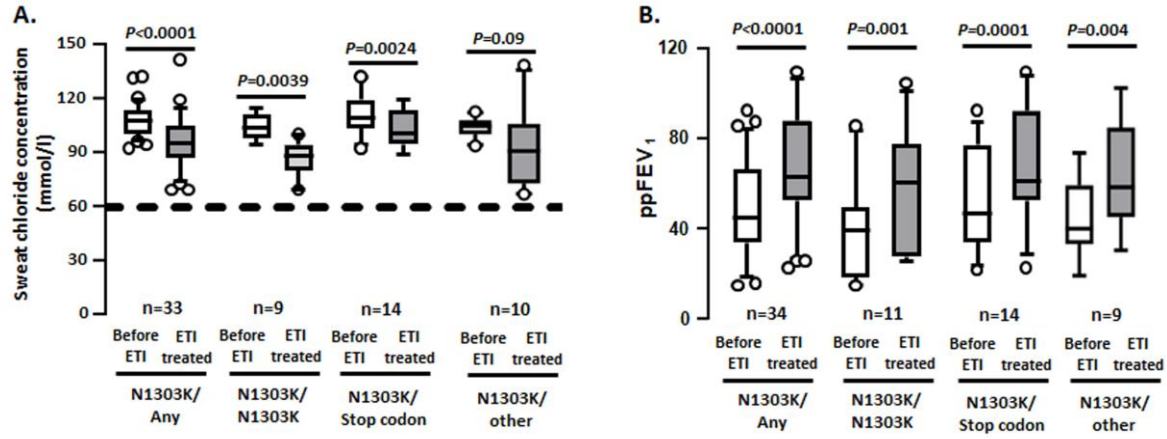

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Table 1. Individual data showing the effects of 4-8 weeks of ETI in 34 pwCF with a least one N1303K variant.

Patient	Data origin	CFTR variant #1	CFTR variant #2	Modulator at ETI initiation	Sweat chloride concentration (mmol/l)		Percent predicted FEV_1		Cough and sputum	Decision to continue ETI
					Before ETI	ETI treated	Before ETI	ETI treated	ETI treated	
1	France (19)	N1303K	N1303K	None	109	87	19	30	Decreased	Yes
2	France (19)	N1303K	N1303K	None	105	96	33	92	Disappeared	Yes
3	France (19)	N1303K	N1303K	None	93	92	44	69	Decreased	Yes
4	France (19)	N1303K	N1303K	None	114	76	23	32	Decreased	Yes
5	France (19)	N1303K	N1303K	None	96	91	20	30	Decreased	Yes
6	France (19)	N1303K	N1303K	None	N/A	N/A	23	34	Decreased	Yes
7	France (19)	N1303K	R1162X	None	99	90	32	61	Decreased	Yes
8	France (19)	N1303K	R1162X	None	131	95	46	54	Decreased	Yes
9	France (21)	N1303K	G542X	None	104	96	26	27	Unchanged	Yes
10	France (21)	N1303K	V754M//delexon3-10,14b-16	None	102	94	48	73	Disappeared	Yes
11	Israel (20)	N1303K	W1282X	None	130	118	81	111	Decreased	Yes
12	Israel (20)	N1303K	E819X	None	115	110	97	114	Decreased	Yes
13	Israel (20)	N1303K	W1282X	None	119	112	30	39	Decreased	Yes
14	Israel (20)	N1303K	W1282X	None	107	114	68	86	Decreased	Yes
15	Israel (20)	N1303K	3221-1G>A	None	114	114	85	111	Decreased	Yes
16	Israel (20)	N1303K	G542X	None	96	95	56	66	Decreased	Yes
17	Israel (20)	N1303K	N1303K	None	111	80	90	109	Decreased	Yes
18	Israel (20)	N1303K	N1303K	None	98	88	47	65	Decreased	Yes
19	USA (18)	N1303K	E193X	None	108	95	87	108*	Disappeared *	Yes
20	USA (22)	N1303K	Q493X	TEZ-IVA	115	113	84	93	Disappeared	Yes
21	Germany (23)	N1303K	N1303K	None	99	68	54	64	Unreported	Yes
22	France unpublished	N1303K	N1303K	None	103	99	79	82	Disappeared	Yes
23	France unpublished	N1303K	H199R	None	95	75	40	60	Disappeared	Yes
24	France unpublished	N1303K	2789+5G>A	None	100	71	N/A**	N/A**	Decreased	Yes
25	France unpublished	N1303K	1898+5G>A	None	106	68	50	53	Disappeared	Yes
26	France unpublished	N1303K	4326delTC	None	108	90	92	128	Disappeared	Yes
27	France unpublished	N1303K	M1V	None	106	105	43	64	Disappeared	Yes
28	France unpublished	N1303K	711+1G>T	None	109	140	63	73	Decreased	Yes
29	France unpublished	N1303K	E585X	None	118	89	53	82	Disappeared	Yes
30	France unpublished	N1303K	R553X	None	91	88	41	58	Disappeared	Yes
31	France unpublished	N1303K	R553X	None	107	103	50	60	Decreased	Yes
32	France unpublished	N1303K	W1282X	None	109	103	49	65	Disappeared	Yes
33	France unpublished	N1303K	3120+1G>A	None	110	101	61	101	Decreased	Yes

34	France unpublished	N1303K	3659delC	None	101	84	67	80	Disappeared	Yes
35	France unpublished	N1303K	N1303K	None	N/A	84	48	71	Unreported	Yes

***** after 10 months of treatment; ** no reproducible measure of ppFEV$_1$ due to young age; N/A: not available.