Heliyon 10 (2024) e29188

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Longitudinal improvements in clinical and functional outcomes following initiation of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis

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ARTICLE INFO

Keywords:
Cystic fibrosis
Highly effective modulator therapies
Micro-optical coherence tomography
Mucociliary abnormalities

ABSTRACT

Background: Use of elexacaftor/tezacaftor/ivacaftor (ETI) for treatment of cystic fibrosis (CF) has resulted in unprecedented clinical improvements necessitating development of outcome measures for monitoring disease course. Intranasal micro-optical coherence tomography (μOCT) has previously helped detect and characterize mucociliary abnormalities in patients with CF. This study was done to determine if μOCT can define the effects of ETI on nasal mucociliary clearance and monitor changes conferred to understand mechanistic effects of CFTR modulators beyond CFTR activation.

Methods: 26 subjects, with at least 1 F508del mutation were recruited and followed at baseline (visit 1), +1 month (visit 2) and +6 months (visit 4) following initiation of ETI therapy. Clinical outcomes were computed at visits 1, 2 and 4. Intranasal μOCT imaging and functional metrics analysis including mucociliary transport rate (MCT) estimation were done at visits 1 and 2.

Results: Percent predicted forced expiratory volume in 1 s ($ppFEV_1$) showed a significant increase of +10.9 % at visit 2, which sustained at visit 4 (+10.6 %). Sweat chloride levels significantly decreased by −36.6 mmol/L and −41.3 mmol/L at visits 2 and 4, respectively. μOCT analysis revealed significant improvement in MCT rate (2.8 ± 1.5, visit 1 vs 4.0 ± 1.5 mm/min, visit 2; P = 0.048).

Conclusions: Treatment with ETI resulted in significant and sustained clinical improvements over 6 months. Functional improvements in MCT rate were evident within a month after initiation of ETI therapy indicating that μOCT imaging is sensitive to the treatment effect of HEMT and suggests improved mucociliary transport as a probable mechanism of action underlying the clinical benefits.

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https://doi.org/10.1016/j.heliyon.2024.e29188
Received 8 September 2023; Received in revised form 28 March 2024; Accepted 2 April 2024
Available online 16 April 2024

1. Introduction

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in epithelial dysfunction that leads to excessive mucus stasis, persistent inflammation and airway damage [1,2]. The advent of highly effective CFTR modulator therapies (HEMT), including elexacaftor/tezacaftor/ivacaftor (ETI) aimed at correcting the basic CFTR defect have recently led to substantial clinical improvements in CF patients [3–6]. Landmark approval of ETI in 2019 expanded the therapeutic applicability of HEMT to ~85 % of people with CF (PwCF) with the F508del mutation in the United States [4,7]. These remarkable improvements in clinical outcomes have highlighted challenges in the long term disease monitoring due to the lack of outcome measures outside of traditional clinical endpoints [8]. Early evidence suggests limited clinical correlation between changes in lung function and CFTR activity by means of nasal potential difference testing, further underscoring the inadequacies in clinical outcome measures to detect functional responses following initiation of modulator therapy [9,10]. Hence, there is an imperative need to improve our understanding of the functional response of the respiratory epithelium-a key biological target of ETI therapy which is critical to addressing the prolonged pulmonary effects of ETI therapy and to appreciate aspects of altered epithelial function that are not directly treated by HEMT.

To better define the function of the respiratory epithelium, our research group has developed micro-optical coherence tomography (μOCT) imaging that measures epithelial properties such as mucociliary transport rate (MCT), airway surface liquid (ASL) and periciliary layer (PCL) depths, percent of ciliary coverage (pCC), and ciliary beat frequency (CBF). μOCT imaging has been successfully used to define multiple functional and anatomic aspects of the CF defect *in vitro,* [11],[13] and *in vivo* model systems [12–14]. We have previously used the μOCT imaging in patients with CF to characterize mucociliary abnormalities. In comparison to healthy normal controls, participants with CF demonstrated striking defects in nasal epithelium including reduced or slowed MCT (mean, 11.2 mm/min controls vs. 5.1 mm/min CF, $P < 0.0001$), depletion of PCL depths (mean, 6.9 mm controls vs. 5.6 mm CF, $P < 0.01$), loss of ciliation (72.1 % controls vs. 38.2 % CF, $P < 0.05$), and increase mucus reflectance indicating that the μOCT nasal imaging technology has the potential to monitor disease state in a minimally invasive manner and inform factors crucial to CF airway disease pathogenesis [15].

Treatment with ETI has resulted in improvements in lung function as well as improved CFTR function reflected by means of decreased sweat chloride levels as early as 14 days following initiation of therapy and have sustained for up to 6 months on treatment [3,4]. To discern effects of ETI on the respiratory epithelium, we followed subjects for over six months following initiation of ETI therapy and conducted μOCT imaging before and after one month of initiation of ETI therapy to quantify functional outcomes in relation to clinical parameters. We found significant improvement in clinical outcomes consistent with recently published reports in addition to improvements in mucociliary transport indicating that μOCT imaging in patients with CF is sensitive to changes in functional metrics and suggests improved mucociliary clearance as a likely mechanism of action contributing to the clinical benefits of lung health.

2. Methods

2.1. Subjects

Participants at the University of Alabama at Birmingham were recruited to a sub-study for μOCT imaging conducted under the multicenter prospective observational study to evaluate biological and clinical effects of significantly corrected CFTR Function (the PROMISE study, NCT 04038047) between November 2019 and May 2020 [3,16]. PwCF, 12 years and older, with at least one copy of F508del mutation were recruited into the single center observations sub-study. Key inclusion and exclusion criteria are included in the supplementary material. As previously described [3,16], study visits were designed to be conducted at baseline (visit 1), 1 month (visit 2), 3 months (visit 3) and 6 months (visit 4) following initiation of ETI therapy. ETI therapy was dosed at Elexacaftor 100 mg, ivacaftor 75 mg, and tezacaftor 50 mg, plus ivacaftor 150 mg 12 h apart. Due to several missing clinical visits owing to the COVID-19 pandemic, limitations in in-person follow up and remote data collection [17], protocol amendments were required to be made [3] and results for visits 1, 2 and 4 are reported here. μOCT visits were conducted at visits 1 and 2.

2.2. Clinical visits and data collection

Standard clinical status assessments including obtaining detailed clinical history, physical examination, and medication reconciliation was done at each of the three visits. Laboratory testing for complete blood counts, basic metabolic and liver function panels, hemoglobin A1c levels were done at visits 1 and 4. Lung function testing with spirometry was conducted in accordance with American Thoracic Society guidelines to report percent predicted FEV1 and FVC [18] Sweat Chloride testing using macroduct and pilocarpine iontophoresis [19] was performed at each of the three visits. Individuals part of the PROMISE study, who were 14 years and older were enrolled for μOCT imaging visits conducted at baseline (visit 1) and at one month following initiation of ETI therapy (visit 2). Key exclusion criteria included inability to provide informed consent, current pregnancy, concurrent diagnosis of asthma/COPD, history of sinus surgery that will alter nasal anatomy and preclude imaging of the nares, and any condition likely to affect safety of the procedure. The imaging procedure was well tolerated overall with no adverse events including occurrence of mucosal injury during or immediately after the procedure. Quantitative metrics were extracted and analyzed by a team blinded to clinical visit. Details of μOCT technology, image acquisition, stabilization, and analysis are described in detail in the supplementary material.

Statistical analysis. Means were computed for each subject when at least two measures for each of the metrics were valid; mean

values were used for subsequent cohort analysis. Data statistics are presented as means (SD), unless indicated otherwise. Clinical outcomes are reported at each time point using paired *t*-test analysis with 95 % confidence interval ranges. Differences in each μOCT metric between baseline and one month into ETI therapy was also compared using paired *t*-test analysis. Two-tailed *P* values are reported. P values of <0.05 were considered statistically significant. Linear regression and the Pearson correlation coefficient (r) were used for correlation analysis between clinical outcomes and μOCT parameters. Statistical analyses were performed using GraphPad Prism (version 9.1.0, GraphPad Software, San Diego, California USA).

2.3. μOCT technology, image acquisition, stabilization, and analysis

The μOCT device is based on the principles of spectral-domain optical coherence tomography. Participants underwent μOCT imaging unsedated following nasal examination with an illuminated rhinoscope, and per previously described methods [15]. A total of 20 distinct anatomical locations from both nares were imaged. On each side of the naris, μOCT data were acquired from both the turbinate and floor of the nasal meatus. This imaging procedure resulted in an average of 29.6 30-s μOCT videos recorded from each subject. The videos were analyzed by an investigative team blinded to patient visit. Each of the videos were first corrected for lateral scan non-uniformity before being scaled to achieve isotropic pixel-to-length representation. Since data were acquired by manual placement of the probe in unsedated subjects, stabilization of the μOCT videos had to be performed before they could be further analyzed. This was accomplished by first computing the local correlation maxima between two adjacent frames within a running 256 μm square window. The lateral shifts corresponding to the global correlation maxima were then used to register the frames. The level above which the correlation maxima exceeded the standard deviation was used to benchmark how well the in-plane registration worked which was then used to automatically select sections of the μOCT videos that were stable over a minimum of 20 frames or longer for further analysis of CBF. CBF were computed by Fourier analysis of the μOCT signals modulated by the beating action of the cilia. MCT measurements were determined by tracking native mucus particles within 70 μm of the epithelial surface. To ensure that readings were taken from particles that were transported by native ciliary motion, those that mirrored the trajectory of the probe were deemed to be artificially influenced by the motion of the probe and were excluded in the analysis. The thicknesses of PCL were determined by direct geometrical measurements on scaled images. pCC was determined by calculating the percentage of the epithelial surface that was covered in motile cilia in a randomly selected frame within each acquired video.

3. Results

3.1. Subjects

26 participants, 12 years and older, with at least 1 F508del mutation were enrolled. 2 subjects failed screening and 24 subjects were recruited for longitudinal follow-up and followed over 3 visits: baseline (visit 1), +1 month (visit 2) and +6 months (visit 4) following initiation of ETI therapy. μOCT imaging was conducted at visits 1 (n = 23) and 2 (n = 22). Planned visit 3 per the original PROMISE study protocol [16] at 3 months was not completed for majority of the subjects since visit windows were affected by the COVID-19 pandemic [17]. 23 subjects completed visit 2 (at 49 ± 19 days) and 18 subjects completed visit 4 (at 279 ± 63 days). Of the 24 subjects at baseline, 50 % were receiving prior modulator therapy and 50 % were modulator naïve (n = 12 each). Average age of the participants at baseline was 27 ± 8.8 years, 67 % were female (n = 16), 92 % identified as White (n = 22), 54 % were genotypically homozygous for F508del mutation (n = 13), and the average body mass index (BMI) was 23.1 ± 3.4 kg/m^2. Baseline lung function measured by percent predicted forced expiratory volume in 1 s (ppFEV1) was 76.7 ± 24.2 %, and baseline sweat chloride, marker for CFTR activity was 81.8 ± 15.7mMol/L (Table 1).

Table 1
Baseline characteristics at Visit 1.

	Total	Modulator naïve	On prior 2-drug modulator therapy
Number enrolled	24	12	12
Age (years ± SD)	27 ± 8.8	27.7 ± 7.0	26.2 ± 10.6
Sex (males/females, N)	8/16	3/9	5/7
Race/Ethnicity (N)	22	10	12
- White	1	1	–
- Black	1	1	–
- Other: Hispanic			
Genotype	13	1	12
- F508del homozygous	11	11	–
- F508del heterozygous, minimal function	–	–	–
- F508del heterozygous, G551D			
BMI (kg/m^2± SD)	23.1 ± 3.4	24.4 ± 3.6	24.4 ± 3.6
FEV1 (% predicted ± SD)	76.7 ± 24.2	70.7 ± 27.2	82.8 ± 21.4
Sweat Chloride (mMol/L ± SD)	81.8 ± 15.7	87.6 ± 14.8	76.04 ± 15.7

BMI, body-mass index is weight in kilograms divided by the square of the height in meters.
CFQ-R, cystic fibrosis questionnaire-revised respiratory domain score.

3.2. Treatment with ETI significantly improves clinical outcomes

Consistent with recent reports [3], longitudinal follow-up in our subjects showed that ETI therapy significantly improved lung function and CFTR activity within one month of initiation of therapy (Fig. 1). ppFEV$_1$ revealed a significant change with an absolute increase of +10.9 % (95%CI 6.38, 15.35) at visit 2. This absolute change in lung function remained stable at visit 4 + 10.6 %; (95%CI 5.17, 16.07; p = 0.034 by ANOVA). Subgroup analysis showed a much higher improvement in the ppFEV1 in the modulator naïve group at 1 month compared to those already receiving modulator therapy (+15.4 %; 95 % CI 8.9, 21.9 modulator naïve vs +5.8 %; 95 % CI 0.3, 11.4 on prior modulator at visit 2). The absolute increase in lung function at 6 months was also higher in the modulator naïve group (+11.7 %; 95 % CI 3.6, 27.1 modulator naïve vs +10.04 %; 95 % CI 3.6, 16.5 on prior modulator at visit 4). Concomitantly, sweat chloride levels significantly decreased by an absolute value of −36.6 mmol/L (95%CI -43.82, −29.36) and −41.28 mmol/L (95% CI -48.06, −34.49) at visits 2 and 4, respectively (p < 0.0001 by ANOVA). Subgroup analysis based on prior modulator status revealed comparable decrease in sweat chloride levels between the two groups (−36 ± 16.7 mmol/L, modulator naïve vs −37.3 ± 9.3 mmol/L, on prior modulator therapy at visit 2; and −42.4 ± 15.6 mmol/L, modulator naïve vs. −40.3 ± 12.6 mmol/L on prior modulator therapy at visit 4). No significant increase in BMI was noted across the 3 visits (mean BMI 23.1 ± 3.4 kg/m^2 at visit 1 vs 23.64 ± 3.5 kg/m^2 at visit 2 vs 24.9 ± 3.9 kg/m^2 at visit 4). However, a trend towards increase was most notable in the modulator naïve group at 6 months (+1.74 kg/m^2; 95 % CI 0.71, 2.76). Patients had 0.71 ± 0.84 (mean ± SD) exacerbations requiring inpatient hospital stay and 3.08 ± 2.64 outpatient exacerbations treated with oral antibiotics 1 year prior to initiation of ETI therapy compared to a significantly reduced 0 inpatient stays (p < 0.0001) and 0.8 ± 1.09 outpatient antibiotic treatments (P = 0.0018) in the year following initiation of ETI therapy.

3.3. Treatment with ETI significantly improves mucociliary transport and epithelial integrity

Participants from the clinical cohort were enrolled for μOCT imaging as part of the PROMISE sub study. 22 subjects completed both imaging visits 1 and 2. μOCT imaging characterizes and permits for quantitation of functional respiratory epithelial parameters of the mucociliary clearance apparatus [15,20]. Parameters that can be readily estimated are periciliary liquid depth (PCL), as a marker of hydration, airway surface liquid depth (ASL), cilia beat frequency (CBF), percent ciliary coverage (pCC) - that corresponds to area of active ciliary beating, and the mucociliary transport (MCT) rate. A blinded investigator team interpreted data for subjects with CF between visit 1 (baseline, n = 23) and visit 2 (one month following initiation of ETI, n = 22). The success rate of having at least 1 technical replicate value cumulatively for both visits 1 and 2 for each of the quantitative metrics were 96 % for pCC, 51 % CBF, 89 % for PCL, and 51 % for MCT.

Paired μOCT analysis revealed significant improvement in MCT rates at one month of being on ETI therapy (2.8 ± 1.5 mm/min at baseline vs 4.0 ± 1.5 mm/min at one month following initiation of ETI, $P = 0.048$ by paired t-test). The mean difference in MCT between CF and non-CF cohorts was ~50 % of normal based on prior studies [15]. Despite significant differences in ppFEV1 improvement between the modulator groups, no appreciable differences were found on MCT subgroup analysis between those that were modulator naïve and those that were on prior 2 drug modulator therapy. Unlike the overall improvement in MCT rates, no meaningful changes were found in the other functional μOCT metrics of CBF (14.64 ± 1.34Hz pre ETI vs 14.44 ± 1.73Hz post ETI), PCL (4.65 ± 0.48 mm pre ETI vs 4.73 ± 0.48 mm post ETI), or pCC (21 ± 21.13 % pre ETI vs 20.35 ± 19.08 % post ETI) at this early time point (Fig. 2). Analysis of ASL depths was excluded in this study due to limited number of cases in which the prerequisite for ASL measurement, i.e., preservation of a clear air layer between the mucus layer and the imaging probe, was satisfied. No significant correlation was found between clinical outcomes of change in FEV1 or sweat chloride in comparison to change in MCT at 1 month following ETI initiation (ΔMCT vs Δsweat chloride; r = 0.314, P = 0.32; and ΔMCT vs ΔFEV1; r = 0.174, P = 0.53 using simple linear regression).

Qualitative paired analysis of the μOCT images revealed an improvement in epithelial integrity and albeit persistent in some subjects, an overall decrease in immune cell infiltration following one month of ETI therapy (Fig. 3). This demonstrates that μOCT can visualize and measure dynamic outcomes of mucus clearance with pharmacological therapy.

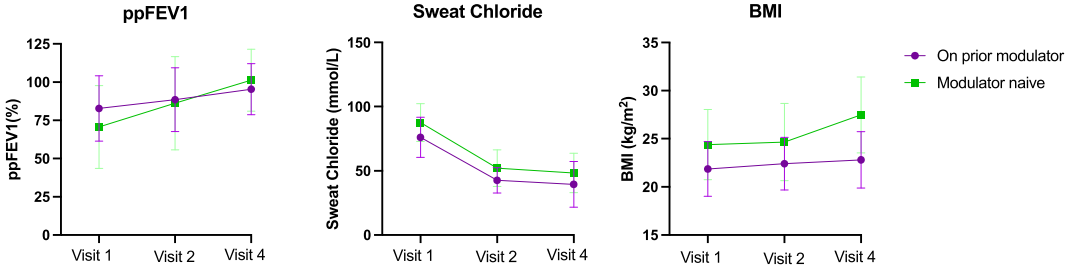

Fig. 1. Clinical parameter changes across visits 1, 2 and 4. Graphs indicating means with standard deviation bars. ppFEV$_1$ showed a significant change with an absolute increase of +10.9 % (95%CI 6.38, 15.35) at visit 2, which persisted at visit 4 + 10.6 %; (95%CI 5.17, 16.07; $P = 0.034$ by ANOVA). Sweat chloride levels significantly decreased by −36.6 mmol/L (95%CI -43.82, −29.36) and −41.28 mmol/L (95%CI -48.06, −34.49) at visits 2 and 4, respectively ($P < 0.0001$ by ANOVA). No significant change in BMI was found between the visits.

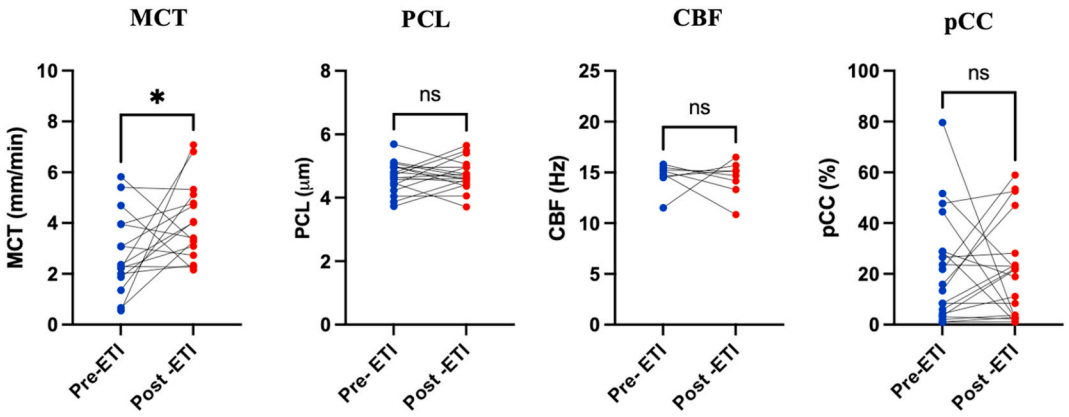

Fig. 2. Functional microanatomical μOCT parameters. Dot plots indicating MCT, PCL, CBF and pCC measurements of subjects at visit 1, pre-initiation of ETI (blue) and at visit 2 one month following initiation of ETI (red). Data points represent the mean measurement of the parameter for each individual. Comparison of data by paired *t*-test, $^*P < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

CFTR mediated epithelial dysfunction leads to persistent mucus stasis and airway damage that often contributes to progression of lung disease and morbidity in PwCF [21,22]. Treatment with ETI in CF patients with F508del mutations have shown improvements in clinical outcomes including lung function, quality of life, and decreased exacerbations [3,23]. However, mechanistic effects of CFTR modulators beyond CFTR activation are still largely unexplained, especially as it pertains to epithelial function. Restoration of CFTR function in the respiratory epithelium thus merits characterization of cellular level physiology to determine the role of CFTR function in clinical improvements and to identify changes not fully realized by HEMT. The *in vivo* clinical μOCT system has been shown to successfully interrogate the functional microanatomy of respiratory epithelia in human nasal airways [15,24] and was used here to define the effects of ETI therapy on nasal mucociliary clearance as a means to understand the mechanistic effects of ETI on the respiratory epithelium. Here, we provide the first evidence of meaningful improvements in mucociliary transport function as demonstrated by μOCT nasal imaging after initiation of ETI therapy, supporting the concept that improved epithelial function and mucus clearance contributes to the significant clinical lung health benefits conferred by HEMT [25].

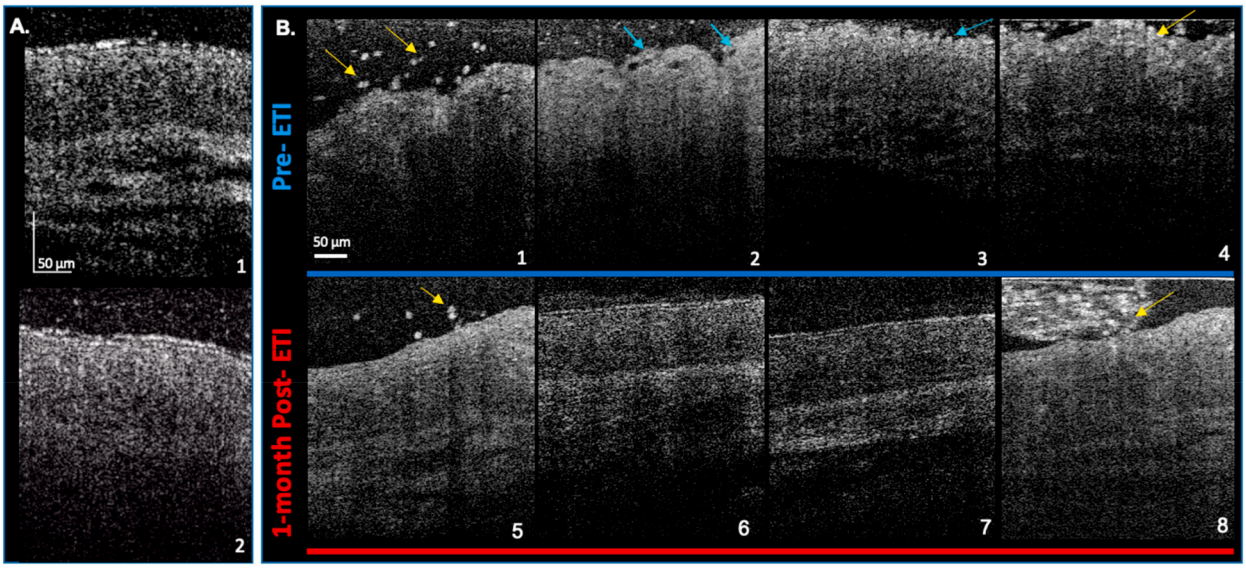

Fig. 3. Qualitative μOCT imaging features. Figs. 3A,1–2 representative μOCT imaging in normal controls with uniform PCL layer, preserved epithelium, and minimal mucus accumulation. Fig. 3B Qualitative μOCT analysis in 4 patients before initiation of ETI (Figs. 3B,1–4) shows increased inflammatory infiltration (yellow arrows), epithelial disruption (blue arrows) and mucus accumulation (Figs. 3B, 5–8); with decreased immune cell infiltration, and improvement in epithelial integrity seen 1 month post initiation of ETI therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Optimal functioning of the mucociliary apparatus requires a balanced interplay of epithelial ion transport, airway hydration, and mucus viscoelasticity. CFTR dysfunction consequently alters airway surface liquid hydration and mucus viscosity, leading to mucus stasis and accumulation that are cardinal to the origin and progression of CF pulmonary disease [26]. In this study, μOCT imaging demonstrated significant improvement in MCT within one month of ETI initiation. In concert, we noted a qualitative decrease in overall mucus accumulation, cellular infiltration, and improved structural integrity of the epithelium, each of which could contribute to improved MCT seen within one month after ETI initiation. Despite these favorable observations, we were not able to detect statistically significant improvements in μOCT metrics indicative of airway hydration or ciliary function as evidenced by the lack of discernible changes in PCL depth, CBF, or number of motile cilia (measured by pCC). This finding remains unexplained but suggests that multiple factors contribute to MCT rate, reducing the relative impact (and thus detection sensitivity) for any one of the specific μOCT parameters but which together may contribute to measurable mucus clearance.

The difference in MCT improvement did not meaningfully vary among a sub-group analysis based on being modulator naïve or on prior 2-drug modulator therapy. This suggested detectable improvements in MCT may be more related to achieving a specific threshold of MCT rather than the absolute degree of improvement in mucus clearance and that significant activation of CFTR function is required to achieve MCT improvements. Through 4 weeks of treatment, ETI resulted in only partial, incomplete restoration of epithelial function, as suggested by residual MCT decrement, mucus accumulation, and inflammatory cell infiltration as compared to non-CF individuals, and in comparison to prior studies, the post-ETI treatment remained only ~50 % of MCT rates of normal individuals [15]. Since CFTR activation as reflected by sweat chloride levels significantly improved by one month at the time of μOCT imaging, we speculate that factors such as persistence of inflammation and infection [27] may be contributing to the residual defects in nasal mucociliary transport. The nasal epithelium, as a compartment that has first contact with the environment within the respiratory tree, may also be particularly at risk for continued influence of airway dehydration and persistent infection [28]. Future longitudinal studies may be able to assess whether the functional parameters measured here can continue to improve in the context of augmented CFTR function by ETI or other CFTR modulators.

Consistent with recent reports, our study highlights that treatment with ETI has resulted in an average 10 % improvement above baseline in $ppFEV_1$ and remained stable at 6 months in both those who are modulator naïve and those that were previously receiving modulator therapy. Similarly, sweat chloride levels, a marker of CFTR function, decreased significantly and achieved a mean level of <60 mmol/L, below the diagnostic threshold for adults CF. The magnitude of lung function improvement and decrease in sweat chloride levels were more pronounced in those that were naïve to modulator therapies highlighting that partial CFTR rescue with ongoing 2-drug modulator therapies may have already been contributing to the extent of clinical improvements within that group. Lung function improvements with CFTR directed modulator therapies have previously been attributed to effective mucociliary clearance as demonstrated by gamma scintigraphy with ivacaftor [29], and lumacaftor-ivacaftor therapies [30], and more recently following ETI therapy using the lung clearance index as a proxy for mucus transport rates [31]. Our study supports these findings, and parallels unpublished results demonstrating improved mucociliary clearance by Tc99 gamma scintigraphy in other individuals enrolled in the PROMISE study [32]. Given the short duration of the study, we did not document improved BMI as observed consistently with more prolonged treatment. Overall, this shows that the cohort studied here was a reasonable proxy for the CFTR modulator treated population and exhibited the expected benefit of ETI over the study time frame.

This study is limited due to the short duration of follow-up for μOCT imaging following initiation of ETI therapy and the small sample size that was not powered to capture the gamut of functional therapeutic responses. This resulted in the inability to confirm changes in airway hydration. We note that the early improvements in MCT may have been statistically influenced by outliers with higher-than-average increase in the post-ETI group, and this subset of subjects did not have accompanying improvements in any other μOCT parameters. Aside from statistical power and that multiple contributing factors may combine to alter mucus clearance, sampling bias from exclusively interrogating the nasal mucosa may also be a factor, as only portions of the nasal epithelium are in appropriate position to obtain reliable OCT measurements [15]. We know that mucus strands [33] and adherent flakes [34] occur in CF – presently quantitation of completely adherent mucus, inflammatory infiltration, and extent of epithelial disruption is challenging and have not have been estimated within the present study.

As the CF care paradigm shifts with the advent of genetic therapies, challenges remain, and the long-term effects of modulator therapies especially on airway biology are still largely unknown. Variability in patient response to modulator therapy remains a major concern where patients continue to experience frequent pulmonary exacerbations, and only a small group (<30 %) clear bacterial pathogens from the airways as recently reported by the PROMISE investigators [27]. As such, the majority continue to experience chronic and exaggerated inflammatory responses that drive disease progression [35,36]. Our data supports the unparalleled improvements previously reported in clinical outcomes up to 6 months following ETI therapy. The corresponding significant increase in MCT within one month of ETI therapy suggests that MCT improvement may directly contribute to this improvement in lung function. Given that μOCT is sensitive to functional outcomes, a longer follow-up with use of μOCT imaging to interrogate airway functional microanatomy will shed light on the important aspects of CFTR mediated physiology of therapeutic responses.

5. Approvals

This study was approved by the University of Alabama institutional review board (UAB IRB-300002244, UAB IRB-300002245) and Advarra (Pro 00029275, Pro 00031843); and the Partners institutional review board, Massachusetts General Hospital (2016-P000272, 2018-P002554).

Funding information

This study was funded by the NIH (P30 DK072482-14 to SMR and GMS), (1K08HL138153-01A1 to GMS), and CFF (PROMISE-OB-18 to SMR and GMS).

Data availability statement

Data used to support findings in this study are all included within the study text.

CRediT authorship contribution statement

Kadambari Vijaykumar: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Hui Min Leung:** Writing – original draft, Investigation, Formal analysis, Data curation. **Amilcar Barrios:** Formal analysis. **Justin Wade:** Investigation. **Heather Y. Hathorne:** Investigation. **David P. Nichols:** Writing – review & editing, Conceptualization. **Guillermo J. Tearney:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Steven M. Rowe:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **George M. Solomon:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Steven M. Rowe and Guillermo J. Tearney has patent pending to Unlicensed patent on the use of optical coherence tomography.

Acknowledgements

We thank the patients and their families for their participation in the trials.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29188.

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