Impact of Cystic Fibrosis Transmembrane Conductance Regulator Therapy on Chronic Rhinosinusitis and Health Status

Deep Learning CT Analysis and Patient-reported Outcomes

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Abstract

Rationale: Elexacaftor, tezacaftor, and ivacaftor (ETI) in triple combination improves pulmonary health for people with cystic fibrosis (PwCF). However, its impact on objective measures of sinus disease and health utility is unestablished.

Objectives: To evaluate the impact of ETI on chronic rhinosinusitis (CRS) and general health status incorporating computed tomography (CT), quality-of-life (QOL) and productivity loss.

Methods: Adult PwCF+CRS with CF transmembrane conductance regulator genotype F508del/F508del or F508del/minimal function who clinically initiated ETI participated in a prospective, observational study. The primary endpoint was change in percent sinus CT opacification (%SO) after 6 months of ETI assessed via deep learning-based methods. Secondary endpoints included changes in sinonasal QOL, health utility value and productivity loss, which were evaluated monthly via validated metrics.

Results: 30 PwCF provided baseline data; 25 completed the study. At baseline, the cohort had substantial CRS, with mean 22-question SinoNasal Outcome Test (SNOT-22) score 33.1 and mean sinus CT %SO 63.7%. At 6-month follow-up, %SO improved by mean 22.9% ($P < 0.001$). %SO improvement trended toward greater magnitude for those naïve to prior modulator therapy ($P = 0.09$). Mean SNOT-22 scores and health utility improved by 15.3 and 0.068 [6.8%] (all $P \leq 0.007$). Presenteeism, activity impairment and overall productivity loss improved (all $P \leq 0.049$). Improvements in SNOT-22 scores and health utility occurred by one month and remained improved over the study.

Conclusions: ETI is associated with substantial improvements in sinus CT opacification and productivity loss, and clinically meaningful improvements in sinonasal QOL and health utility. Most improvements were rapid, robust, and durable over the study.

Keywords: cystic fibrosis; chronic rhinosinusitis; machine learning; CFTR modulator; computed tomography

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Treatment paradigms for cystic fibrosis (CF) care have been rapidly evolving since the approval of the benchmark, targeted CF transmembrane conductance regulator (CFTR) modulator therapy, ivacaftor, in 2012. In 2019, robust results from trials of elexecaftor, tezacaftor, and ivacaftor (ETI) in triple combination led to approval of this regimen in the United States for people with CF (PwCF) who were homozygous or heterozygous for F508del (1–3). With this advance and subsequent approval in other countries, ETI is now available for nearly 90% of adults with CF in many regions.

Beyond lower airway disease, significant morbidity from CF stems from the disease's impact on other organ systems. Many adult PwCF develop comorbid chronic rhinosinusitis (CRS) due to an inability to clear thick secretions from the upper airway and paranasal sinuses. Over half of adults with CF report symptomatic sinus disease, two-thirds have nasal polyposis, and nearly all have radiologic or endoscopic sinus inflammation (4–10). CF-related CRS is detrimental to quality of life (QOL) and associated with substantial productivity loss (11–16).

Evaluating outcomes in addition to pulmonary status is crucial as PwCF are maintaining improved lung function and experiencing longer lives (17, 18). Although only limited investigations into the potential extrapulmonary effects of ETI have been performed, evolving literature has shown that single and dual combination CFTR modulator therapy is associated with improvements in certain extrapulmonary domains, including sinus disease (19). Studies on ivacaftor suggested it improved CF-related sinus disease and certain aspects of QOL in individuals with specific rare CFTR mutations (20–22). Case reports and a retrospective series demonstrated that ivacaftor is associated with improvement in evidence of sinus computed tomography (CT) opacification after 5–12 months of treatment (22–24).

CRS disease severity can be evaluated via multiple methods, including radiologic studies to assess paranasal sinus opacification, clinical evaluations, and QOL assessments. A recent study demonstrated that ETI is associated with improvements in sinonasal QOL after 3 months of treatment (25). No studies have evaluated how ETI impacts sinus CT opacification or investigated the time course over which ETI leads to improvements in markers of CRS. Further, no work has evaluated changes in productivity loss, which represent indirect costs of disease, or general health statuses that are associated with ETI.

Therefore, the aim of this study was to prospectively assess the impact of ETI on a broad array of sinonasal and health outcomes, including sinus CT opacification, sinonasal QOL, productivity loss, and health utility value. For objective analysis of sinus CT images, a deep learning technique that leverages a convolutional neural network to automatically segment paranasal sinus cavities and thus enable volumetric quantification of opacification was employed (26, 27).

Methods

Population and Study Design

Participants were recruited for this prospective, observational study between August 2019 and October 2020 at National Jewish Health (Denver). Study participants included adults with CF and CRS who received ETI for clinical purposes. All subjects provided written informed consent for this Institutional Review Board-approved study.

Outcome data were collected at baseline and 6-month follow-up, including sinus CT images, spirometry, and validated patient-reported outcome measures (PROMs). Monthly phone conferences occurred to collect additional PROM data and verify compliance with ETI. Additional details on the study design and population can be found in the online supplement.

Inclusion Criteria

Inclusion criteria: age ⩾18 years, diagnosis of CF via genetic assessment and/or sweat chloride testing (28), guideline-based diagnosis of CRS (29–32), eligible for ETI based on genotype of F508del/F508del (F/F) or F508del/minimal function (F/MF) mutation, and elected to initiate ETI.

Exclusion Criteria

Participants were excluded if they were not eligible for or elected not to initiate ETI, were heterozygous for F508del and a residual function (one that confers some CFTR function) mutation, underwent sinus surgery in the 6 months preceding study start or were anticipated to undergo sinus surgery during the study, or were acutely ill within two weeks of the screening visit.

Outcome Measures

Sinus CT Opacification

Change in sinus CT opacification assessed via a deep learning algorithm was the primary outcome. This algorithm precisely segments the paranasal sinuses, facilitating calculation of volumetric sinus opacification

Table 1. Characteristics of 25 individuals with cystic fibrosis and chronic rhinosinusitis who completed the study

Characteristics	Mean (SD)	*N* (%)
Age, years	33.9 (9.2)	
Sex, male		8 (32)
Sex, female		17 (68)
Race, Caucasian		25 (100)
Genotype: F508/F508		15 (60)
Genotype: F508/minimal function		10 (40)
History of prior sinus surgery		20 (80)
Number prior sinus surgeries	2.3 (2.3)	
Body mass index (kg/m^2)	22.4 (4.0)	
Prior CFTR modulator therapy		16 (64)
ppFEV$_1$	67.4 (26.4)	
Cystic fibrosis-related diabetes		10 (40)
Pancreatic insufficiency		25 (100)
Chronic *Pseudomonas aeruginosa* (*n* = 23)		14 (61)

Definition of abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator; ppFEV$_1$ = percent predicted forced expiratory volume in 1 second; SD = standard deviation. Pseudomonas infection status based on > 50% culture positivity rate in the 12 months preceding study start. Two individuals did not have multiple cultures over this time period and were excluded.

Table 2. Medication usage rates reported by participants for 25 individuals with cystic fibrosis and chronic rhinosinusitis at baseline and after 6 months of elexacaftor/tezacaftor/ivacaftor therapy

Medication, *N* (%)	Baseline	Follow-Up
Dornase alpha	21 (84%)	21 (84%)
Azithromycin	12 (48%)	11(44%)
Inhaled antibiotic	18 (72%)	18 (72%)
Inhaled bronchodilator	24 (96%)	24 (96%)
Inhaled hypertonic saline	9 (36%)	9 (36%)
Inhaled corticosteroids	6 (24%)	4 (16%)
Intranasal corticosteroids	13 (52%)	13 (52%)
Intranasal saline irrigations	3 (12%)	3 (12%)
Intranasal antibiotics	1 (4%)	0 (0%)
Oral antibiotics (excluding azithromycin)	5 (20%)	4 (16%)
Oral corticosteroids	2 (8%)	2 (8%)
Antihistamines	7 (28%)	6 (24%)

(27). Total sinus opacification percent (%SO) was calculated as the percentage of segmentation volume occupied by CT pixels with intensity values between −500 and +200 Hounsfield Units, representing fluid/soft tissue (27). Sinus CT images were evaluated via the Lund-Mackay (LM) system (range: 0–24) (27). LM scoring was performed by a fellowship-trained rhinologist (DMB) blinded to clinical data and imaging timing.

Sinonasal Quality-of-Life

The 22-item SinoNasal Outcome Test (SNOT-22) instrument evaluated sinonasal QOL impairment (range: 0–110) (33). Beyond the total SNOT-22 score, this survey represents five symptom domains: rhinologic, extranasal rhinologic, ear and facial pain, psychological dysfunction, and sleep dysfunction (34).

Health Utility and Productivity Loss

Health utility represents overall health status that is independent of a specific disease (range: 0.0–1.0) (35–38). The 5-dimensional EuroQol (EQ-5D) questionnaire was used to calculate health utility (38–41). The Work Productivity and Activity Impairment-Specific Health Problem (WPAI) survey was tailored to evaluate CF-specific productivity loss (42). Components of productivity loss include absenteeism (time missed from school/work), presenteeism (reduced productivity at work/school), and overall work impairment/productivity loss (43).

Further descriptions of the outcome measures used in this study can be found in the online supplement.

Statistical Analysis

Power calculations were based on the minimal clinically important difference (MCID) for changes in the SNOT-22 questionnaire and preliminary data demonstrating improvement in %SO with CFTR modulator therapy (33, 44). Changes for outcomes were modeled using multiple linear regression. For PROMs with monthly responses, linear mixed models were used. Tests comparing baseline to other time points were adjusted using the Dunnett-Hsu procedure. A two-sided alpha value of 0.05 was used. Further information on the analysis and power calculations is in the online supplement.

Results

Final Study Population and Baseline Characteristics

During the study period, adult subjects at National Jewish Health with CF and CRS with genotype of either F/F or F/MF who were clinically initiated on ETI were screened. Overall, 31 subjects with CF and CRS initially elected to participate in this study. One individual was excluded for a concurrent pulmonary exacerbation at enrollment and 30 participants completed baseline data collection. Of these 30

Table 3. Overall changes in outcomes measures for 25 individuals with cystic fibrosis before and after 6 months of elexacaftor/tezacaftor/ivacaftor

Outcome Measure	Baseline (SD)	6-Month Follow-Up (SD)	Mean Change	SD Change	*P* Value	MCID (33, 45, 53)
Sinus CT opacification (%)	63.7 (21.1)	40.8 (15.1)	−22.9	15.2	<0.001	—
Lund-Mackay total CT score	11.6 (3.6)	8.1 (2.2)	−3.6	2.9	<0.001	—
SNOT-22 total score	33.1 (14.5)	17.8 (11.5)	−15.3	11.3	<0.001	−8.9
SNOT-22 domains						
Rhinologic	9.8 (3.9)	4.5 (3.2)	−5.1	3.7	<0.001	−3.8
Extranasal rhinologic	6.2 (2.9)	2.4 (1.9)	−3.6	2.8	<0.001	−2.4
Ear and facial pain	4.2 (3.3)	2.9 (2.7)	−1.4	3.1	0.04	−3.2
Psychological dysfunction	9.9 (6.5)	5.9 (5.2)	−4.2	5	<0.001	−3.9
Sleep dysfunction	9.5 (5.8)	5.5 (4.6)	−3.9	4.9	<0.001	−2.9
Health utility value	0.80 (0.12)	0.87 (0.08)	0.07	0.11	0.006	0.04
Absenteeism*	0.18 (0.34)	0.06 (0.14)	−0.13	0.27	0.09	—
Presenteeism*	0.34 (0.32)	0.18 (0.25)	−0.16	0.24	0.02	—
Activity impairment*	0.39 (0.31)	0.17 (0.19)	−0.23	0.23	0.003	—
Overall productivity loss*	0.35 (0.37)	0.20 (0.26)	−0.16	0.27	0.049	—

Definition of abbreviations: CT = computed tomography; MCID = minimal clinically important difference; SD = standard deviation; SNOT-22 = 22-question SinoNasal Outcome Test.
Decreasing (negative) values signify improvement in all outcome measures except health utility value
*For productivity loss outcomes, 14 patients were included in analysis based on being employed or in school.

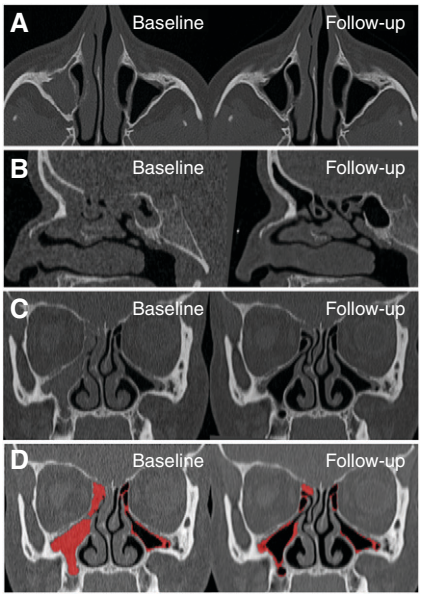

Figure 1. (*A*) Axial, (*B*) sagittal, and (*C* and *D*) coronal sinus computed tomography images from an individual with cystic fibrosis and chronic rhinosinusitis before (left column) and after (right column) 6 months of elexacaftor/tezacaftor/ivacaftor. At baseline, total sinus opacification was 72% based on machine learning, convolutional neural network analysis and Lund Mackay score was 15. After treatment, total sinus opacification and Lund Mackay score decreased to 30% and 6, respectively. (*D*) demonstrates red overlay representing sinus opacification that improved with elexacaftor/tezacaftor/ivacaftor.

individuals, 25 completed baseline and 6-month data collection for the duration of the study, and this subset was utilized for final analyses (Figure E1). Nine of 25 individuals had slight delays in their in-person follow-up visit due to a COVID-19 research closure. The impact of this on the study was only modest; follow-up assessments for the entire cohort occurred at mean 6.6 (standard deviation 0.8) months.

Demographic data and baseline disease characteristics are listed in Table 1. There were no differences in baseline characteristics between the 25 individuals who completed the study and the 5 people who did not (Table E1). Compliance with ETI was high for the enrolling cohort based on patient-reported adherence and medication refill data (data not shown). Mean compliance at 6 months was 93.7% (standard deviation [SD] 12.4%), with 10 individuals at 100%, 15 additional subjects above the 90th percentile, 3 additional participants above the 80th percentile, one individual at 65%, and one participant at 40%. In addition, participants demonstrated stability in non-modulator medication use for CF and CRS over the study course (Table 2). At baseline, this cohort had CRS of substantial severity as evidenced by elevated SNOT-22 scores (mean 33.1, SD 14.5, Table 3).

Changes for each outcome measure are presented in the following sections. In addition, for all outcome measure, worse baseline severity was associated with greater improvement after ETI. For example, %SO improvement was greater by 0.49% for each 1% unit increase in baseline opacification ($P < 0.001$). A similar trend existed for LM, SNOT-22, health utility, and productivity loss scores (all $P < 0.02$).

Sinus CT Opacification

%SO improved from baseline to follow-up (mean improvement 22.9%, SD 15.2, $P < 0.001$) for the entire cohort (Figure 1, Table 3, Figure E2). Individuals who were naive to prior CFTR modulator therapy trended toward greater improvement in %SO ($P = 0.09$). There was no effect on magnitude of improvement from either genotype or history of prior sinus surgery (Table 4). LM score improved over the study period (mean improvement 3.6, SD 2.9, $P < 0.001$) (Table 3). There was good correlation between the change in %SO and LM score (rho = 0.54, $P = 0.005$, Figure E3).

Sinonasal Quality of Life

Study participants reported improvements in total SNOT-22 score from baseline to 6-month follow up (mean improvement 15.3, SD 11.3, $P < 0.001$) (Table 3). Improvements in SNOT-22 total score occurred after one month of ETI and persisted for the 6-month study course after adjusting for multiple comparisons (Figure 2). Subjects also reported improvements in all five subdomains of the SNOT-22 measure: rhinologic, extranasal rhinologic, ear and facial pain, psychological dysfunction, and sleep dysfunction (Table 3, Figure E4). Change in total SNOT-22 score was not impacted by prior CFTR modulator therapy, genotype, or history of sinus surgery (Table 4).

Health Utility Value

Subjects reported improvements in health utility score from baseline to 6-month follow up (mean improvement 0.068 [6.8%], SD 0.11, $P = 0.006$) (Table 3). Health utility improvement was not impacted by prior CFTR modulator therapy, genotype, or history of sinus surgery (Table 4). Like changes in SNOT-22 scores, subjects experienced improvement in health utility after one month of ETI that was sustained over the study course, after adjusting for multiple comparisons (Figure 2).

Productivity Loss

14 of 25 participants were either employed or in school during the study, enabling their data to be incorporated into productivity loss assessments from the WPAI. Subjects reported improvement in presenteeism, activity impairment, and overall productivity loss over the study period (Table 3). In addition to the general trend of improvement, pairwise comparisons identified improvements in presenteeism and activity impairment after 5 months, after adjusting for multiple comparisons (Figure 2). Study participants reported nonsignificant improvements in absenteeism after 6 months of ETI (mean improvement 0.13 [13%], SD 0.27, $P = 0.09$) (Table 3). No changes in any productivity loss components were affected by history of sinus surgery (Table 4).

Discussion

Findings from this prospective study show that use of ETI improves objective and subjective assessments of CF-related CRS. These improvements include volumetric sinus CT opacification, evaluated via novel deep learning-based techniques and the established LM visual scoring system, and sinonasal QOL. Additionally, markers of general health status and productivity loss that extend beyond CRS also improved with ETI, including health utility, presenteeism, activity impairment and overall productivity loss. Improvements in QOL and health utility occurred after one month of ETI and remained durable for the course of the study.

This study employed deep learning imaging analysis to precisely quantify the degree of sinus inflammation on CT images (Figure 1). This methodology has been validated by our group and enables automatic, rapid, and reproducible assessment of sinus CT images (26, 27). In this study, sinus CT opacification improved substantially after 6 months of ETI, with a mean improvement of 22.9%. This finding is

Table 4. Changes in main outcomes measures for 25 individuals with cystic fibrosis after 6 months of elexacaftor/tezacaftor/ivacaftor accounting for covariates

Category	Mean Change	95% CI	*P* Value
Sinus CT opacification (%)			
No previous modulator use, *n* = 9	−40.0	(−59.9 to −20.1)	0.09
Previous modulator use, *n* = 16	−12.2	(−29.2 to 4.8)	
F508/F508, *n* = 15	−36.0	(−54.5 to −17.6)	0.22
F508/minimal function, *n* = 10	−16.1	(−34.6 to 2.3)	
History of prior sinus surgery, *n* = 20	−24.0	(−31.1 to −16.9)	0.61
No prior sinus surgery, *n* = 5	−28.2	(−43.8 to −12.6)	
SinoNasal Outcome Test-22 total score			
No previous modulator use, *n* = 9	−15.8	(−30.0 to −1.6)	0.98
Previous modulator use, *n* = 16	−16.0	(−28.1 to −3.9)	
F508/F508, *n* = 15	−10.6	(−23.8 to 2.5)	0.36
F508/minimal function, *n* = 10	−21.1	(−34.3 to −8.0)	
History of prior sinus surgery, *n* = 20	−16.6	(−21.7 to −11.6)	0.80
No prior sinus surgery, *n* = 5	−15.1	(−26.3 to −4.0)	
Health utility value			
No previous modulator use, *n* = 9	0.11	(−0.04 to 0.26)	0.51
Previous modulator use, *n* = 16	0.03	(−0.09 to 0.16)	
F508/F508, *n* = 15	0.07	(−0.07 to 0.21)	0.99
F508/minimal function, *n* = 10	0.07	(−0.07 to 0.21)	
History of prior sinus surgery, *n* = 20	0.08	(0.03 to 0.14)	0.78
No prior sinus surgery, *n* = 5	0.06	(−0.05 to 0.18)	
Absenteeism, *n* = 14			
History of prior sinus surgery, *n* = 11	−0.17	(−0.36 to 0.02)	0.38
No prior sinus surgery, *n* = 3	0.02	(−0.39 to 0.43)	
Presenteeism, *n* = 14			
History of prior sinus surgery, *n* = 11	−0.18	(−0.35 to −0.02)	0.77
No prior sinus surgery, *n* = 3	−0.13	(−0.48 to 0.22)	
Activity impairment, *n* = 14			
History of prior sinus surgery, *n* = 11	−0.27	(−0.43 to 0.12)	0.28
No prior sinus surgery, *n* = 3	−0.08	(−0.41 to 0.25)	
Overall productivity loss, *n* = 14			
History of prior sinus surgery, *n* = 11	−0.18	(−0.37 to 0.01)	0.86
No prior sinus surgery, *n* = 3	−0.14	(−0.55 to 0.27)	

Definition of abbreviations: CI = confidence interval; CT = computed tomography.
Decreasing (negative) values signify improvement in all outcome measures except health utility value. Results are based on multiple linear regression that included history of sinus surgery, previous modulator use, and F508 gene predictors. For absenteeism, presenteeism, activity impairment, and overall productivity loss, F508 was removed due to overparameterization.

broadly aligned with a prior retrospective series of 12 individuals with CF and a G551D mutation who were treated with ivacaftor and demonstrated improvement in sinus CT opacification (23). As anticipated, individuals who were naïve to prior CFTR modulator therapy in this study trended toward greater improvement, given absence of prior partial CFTR correction by single or dual modulator therapy. Radiologic improvement assessed via the innovative deep learning analysis was corroborated by changes in the established LM scoring system. Changes in these two measures were well correlated, consistent with prior work (27). The consistency in improvement across both radiologic measures lends validity to the overall finding that ETI improves CRS.

Study participants experienced improvements in SNOT-22 scores that exceeded clinically relevant thresholds after one month of treatment with ETI, and these improvements persisted for the duration of the study (33). Subjects reported improvements in all five symptom areas of the SNOT-22 instrument, the rhinologic, extranasal rhinologic, ear and facial pain, psychological dysfunction, and sleep dysfunction domains, with improvements exceeding clinically relevant thresholds in four of these domains (Table 3) (45). The MCID for SNOT-22 total score is 8.9 and the MCIDs for SNOT-22 rhinologic, extranasal rhinologic, ear and facial pain, psychological dysfunction, and sleep dysfunction domain scores are 3.8, 2.4, 3.2, 3.9, and 2.9, respectively (31, 33, 45). The salient finding of clinically relevant improvement in SNOT-22 scores is consistent with prior reports on this topic (25, 46). Additionally, Rowe and colleagues reported statistical improvements in SNOT-20, the precursor version of the SNOT-22, after 1, 3, and 6 months of ivacaftor treatment in people with a G551D mutation (47). These SNOT-20 improvements with ivacaftor occurred in the rhinologic, psychological and sleep dysfunction domains (48).

CRS in PwCF leads to substantial QOL impairment and is thought to adversely impact lower airway status (11, 12, 14, 49). With the widespread uptake of ETI, disease severity of CRS is predicted to decline. It seems likely that ETI will lead to lower rates of sinus surgery for PwCF, a boon for the CF community. Longer term impact of ETI on CRS will be assessed in the 2-year endpoint assessments for the study.

While ETI was associated with clinically meaningful improvements in sinus disease in this study, ETI did not fully resolve sinus disease after 6 months of treatment. The mean SNOT-22 score in

adults without sinonasal disease is 11 (50). Individuals without sinusitis had a mean LM score of 4.3 (51). %SO values in control population are anticipated to be similarly low to LM scores, given high correlation between %SO and LM scores (27). In this study, follow-up SNOT-22, LM, and %SO values after 6 months of ETI were 17.8, 8.1, and 40.8%, respectively, demonstrating a residual degree of CRS. This persistent component of sinus disease merits further study to improve the lives of PwCF.

Health utility value is a generalized marker of health status that can be used to interpret health between different diseases. The mean EQ-5D-derived health utility for healthy individuals in the United States ranges from 0.78 to 0.93, with younger individuals having higher values (35). For the decile closest to the mean age of participants in this study, 30–39 years, mean health utility for healthy individuals is 0.92 (35). A study by Bradley and colleagues of PwCF with moderate lung disease (mean ppFEV$_1$ 58%) reported a mean EQ-5D-derived health utility of 0.85 (52). In the current study, a cohort of PwCF with moderate pulmonary disease (mean baseline ppFEV$_1$ 67.4%) and significant sinonasal symptoms (mean baseline SNOT-22 score 33.1) reported mean health utility of 0.80. It is likely that comorbid CRS in our study lowered baseline health utility compared with Bradley and colleagues. Participants in this study experienced improvements in health utility beyond the clinically meaningful threshold of 0.04 (4%) after one month of ETI (Figure 2) (53). It is possible that PwCF reported relatively modest health utility impairments at baseline, which would lead to an underestimate of the improvement seen with ETI.

PwCF have substantial productivity loss (13, 54). In this study, components of productivity loss were quantified using a version of the validated WPAI tailored to include CF-specific questions (42). This enabled us to assess productivity loss as it related to not only employment but also scholastic participation. In this study, the cohort had substantial productivity loss at baseline, pre-ETI, in multiple areas. Following 6 months of ETI, PwCF and CRS reported improvements in presenteeism, activity impairment and overall productivity loss. Improvements in productivity loss manifested after several months. Absenteeism trended toward improvement (mean improvement 13%) but did not reach statistical significance after 6 months of ETI. This issue may be due to the fact that only a subset of patients in this study ($n = 14$) were employed or in school, providing a smaller sample from which to evaluate changes in productivity loss and absenteeism. As productivity loss data was assessable for relatively few individuals, improvements in these areas may be underestimated or subject to type 2 error. The improvement that was seen with ETI in presenteeism, activity impairment, and overall productivity loss speaks to the systemic effect of this regimen, and thus reflects impact beyond sinus disease alone. Improvements in productivity loss in this study are aligned with findings from non-CF CRS research that demonstrate that management of CRS is associated with improvements in productivity loss (55, 56).

Therapy with the benchmark CFTR modulator, ivacaftor, has been associated

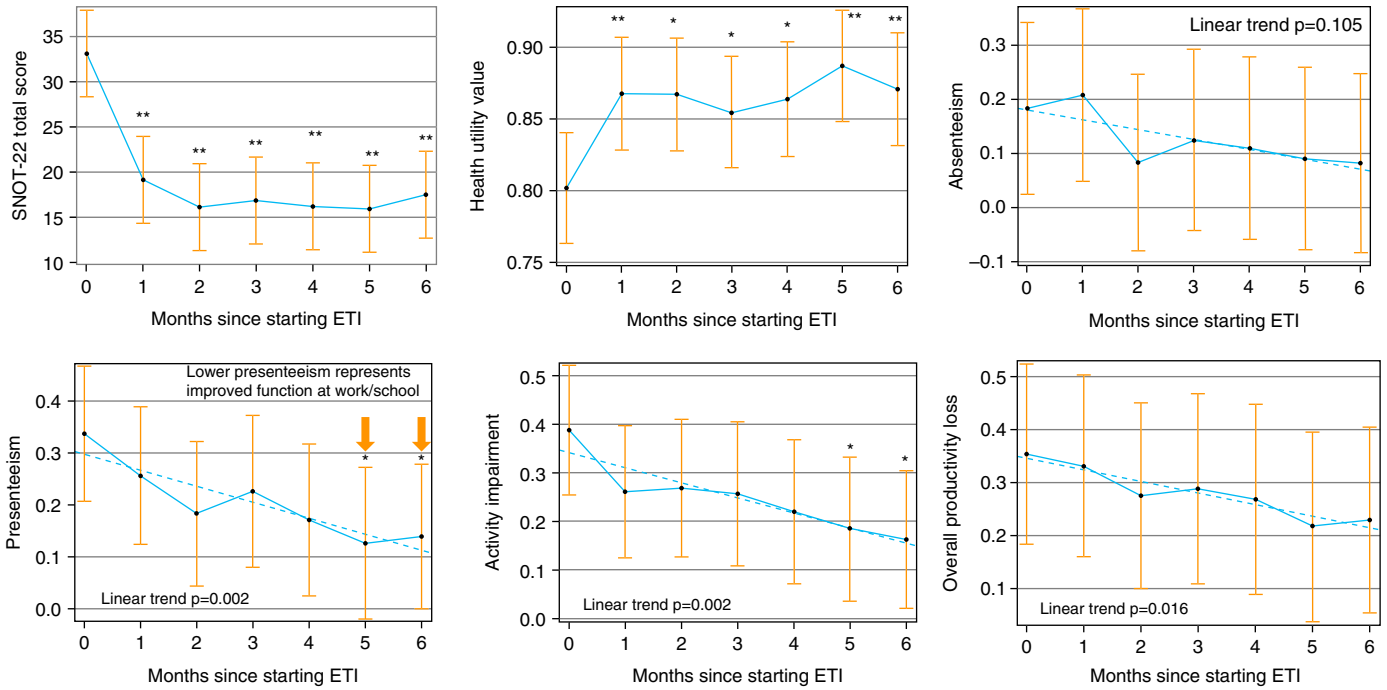

Figure 2. Changes in mean patient reported outcome measures by month in individuals with cystic fibrosis and chronic rhinosinusitis after initiating elexacaftor/tezacaftor/ivacaftor based on linear mixed model fits. Values at each month were compared with baseline, and significance values are represented by asterisks after adjustment for multiple comparisons. For outcomes with more gradual changes, a linear trendline over 6 months of change is superimposed (blue dashed line). $^{**}P \leq 0.001$ relative to baseline value. $^{*}P < 0.05$ relative to baseline value.
ETI = elexacaftor, tezacaftor, and ivacaftor; SNOT-22 = 22-question SinoNasal Outcome Test.

with improvements in sinonasal, gastrointestinal, musculoskeletal, pancreatic, and central nervous systems in individuals with at least one qualifying CFTR mutation, although most of these findings were classified as low quality evidence in a review article (19). While the extrapulmonary effects of ETI are still burgeoning, recent findings demonstrated that this regimen improved sinonasal QOL (25). Findings from the current study are consistent with these trends, establish the impact of this regimen on radiologic sinus inflammation, and provide prospective evidence regarding the benefits of ETI on sinonasal QOL, health utility, and productivity loss. Interpretation of changes when incorporating covariates reveal interesting trends. In general, effect sizes for improvement in %SO and health utility for participants who were naïve to prior CFTR modulator therapy were potentially greater, although this did not reach statistical significance, which may be due to limited sample size of groups. It is also likely that assessments of genotype are closely linked with prior modulator use. Improvements in SNOT-22 scores and health utility after one month of ETI in this study are consistent with data from the Phase 3 studies on ETI, which demonstrated improvements in $ppFEV_1$, sweat chloride levels, and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain by 4 weeks (1, 2). We theorize that radiologic improvement in sinus CT scans occurs prior to 6 months of treatment given the rapid improvement in SNOT-22 scores, however this measurement was not assessed prior to the 6 month time point in this study.

Strengths of this study include a prospective design, use of validated subjective and objective metrics across outcomes, use of an innovative, deep learning technique to assess sinus CT opacification, confirmation of adherence to ETI, and incorporation of methods to control for multiple comparisons. Non-modulator treatments for both CF and CRS were stable over the course of the study (Table 2), suggesting that changes were related to ETI. However, findings from this study should be interpreted in the context of potential limitations. This study was not a randomized controlled trial. There was no blinding. No external control group was included given the rapid uptake of ETI and difficulty enrolling control subjects, which is a study limitation. Based on the progressive nature of CF, and the outcomes for the placebo-controlled phase III study of ETI in participants heterozygous for F508del, if a control group of individuals who did not initiate ETI had been included, CRS severity would likely have remained stable or worsened over the 6 months of the study in this control group (1, 57, 58). Therefore, it is highly unlikely that we would have observed average improvements for study subjects if they had not received treatment with ETI. It is possible that type 2 error existed when assessing for changes in outcomes by category. Because CFQ-R assessments were included in initial Phase 3 studies of ETI, they were omitted in this study to decrease survey burden on the participants, however this limited our ability to compare general CF QOL in this cohort to that in the phase 3 studies.

Conclusions

ETI is associated with substantial improvements in sinus CT opacification and multiple areas of productivity loss, and clinically meaningful improvements in sinonasal QOL and health utility. Improvements in QOL and health utility occurred after 1 month of ETI and were sustained over the 6-month study course. While ETI was associated with substantial improvements in CRS, a degree of sinus CT inflammation and sinonasal QOL deficit remained after 6 months of this regimen. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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