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The effect of elexacaftor/tezacaftor/ivacaftor on non-pulmonary symptoms in adults with cystic fibrosis

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ABSTRACT

Background: Elexacaftor/Tezacaftor/Ivacaftor (ETI) is a CFTR modulator that has led to large benefits in lung function, pulmonary exacerbation rates, and respiratory symptoms. Less is known about the effect of ETI on non-pulmonary symptoms. The objective of this study was to examine the changes in patient reported outcomes after starting ETI in multiple non-pulmonary symptoms.

Methods: This was a prospective cohort study of adults with CF. Participants completed questionnaires prior to starting ETI and then at weeks 2, 4, 6, 8, 10, 12, and 14 after starting ETI. They completed the following validated instruments: PROMIS Pain Intensity, PROMIS Pain Interference, FACIT Fatigue, SNOT22, PAC-SYM, PHQ8, GAD7 and Pittsburgh Sleep Quality Index. Longitudinal changes for outcomes were modelled using linear regression based on general estimating equations.

Results: 22 participants enrolled who answered questionnaires before and after starting ETI. The median age was 35.3 years (IQR 11.1) and 13 (59.1%) were male. In models adjusted for age, sex, and baseline value there were significant improvements in pain interference ($\beta = -2.57$; 95% CI -4.92, −0.23), sinus symptoms ($\beta = -4.50$; 95% CI -7.59, −1.41), and sleep disturbance ($\beta = -1.90$; 95% CI -2.71, −1.09) over 14 weeks after starting ETI. No symptom areas worsened over the study period.

Conclusions: In this prospective study we found statistically significant improvements in three different non-pulmonary symptom areas in people with CF started on ETI. While this was a small, uncontrolled study it suggests that use of highly effective CFTR modulators can result in benefits for patients beyond pulmonary symptoms.

1. Introduction

While pulmonary complications are responsible for much of the morbidity and mortality in cystic fibrosis (CF) [1], it is a multi-system disease with many non-pulmonary complications [2]. Therapy for CF has resulted in dramatic improvements in life expectancy [3], and as people with CF are living longer, non-pulmonary symptoms have been found to be common and can greatly impact quality of life. These non-pulmonary complications include pain [4,5], fatigue [6], sinus disease [7], gastrointestinal problems [8], depression [9], anxiety [10], and sleep disturbance [11].

The triple combination CFTR modulator drug Elexacaftor/Tezacaftor/Ivacaftor (ETI) was approved by the US FDA in October 2019 [12] after phase 3 trials showed convincing improvements in lung function, respiratory symptoms and risk of acute pulmonary exacerbations [13,14]. ETI was shown to be effective for anyone with CF with at least one copy of the F508del variant, which makes it indicated for close to 90% of people with CF. Studies are ongoing to determine the impact and mechanisms of ETI on physiologic functioning both in the respiratory system and beyond [15], but little is known about the effect of ETI on non-pulmonary patient

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reported outcomes (PROs).

While the introduction of ETI was met with great enthusiasm in the CF community, there have been concerns that it may have negative impacts on mental health symptoms [16] and gastrointestinal symptoms such as constipation [17]. It is unknown whether it has effects, either beneficial or harmful, on other symptoms such as pain, fatigue and sleep disturbance.

The objective of this study was to assess short-term changes in a number of non-pulmonary, patient reported outcomes before and following initiation of ETI in adults with CF.

2. Methods

2.1. Study design and population

This was a prospective observational study conducted at a single adult CF center. Subjects were recruited between January 2020 and July 2020. Solicitation emails were sent to eligible patients followed in the Johns Hopkins Adult CF program. Inclusion criteria included CF diagnosis per medical records, age $\geq$18 years old, eligible to begin ETI, a patient of the Johns Hopkins CF outpatient clinic, able to read/understand English, and have access to technology required to take online surveys (i.e., smartphone, computer, etc.). Exclusion criteria consisted of prior or concurrent use of ETI, self-reported pregnancy, and history of lung transplant.

All subjects provided oral consent for this institutional review board approved study (Johns Hopkins eIRB IRB00231799).

Demographic and clinical data were collected using the electronic patient record. Participants completed online surveys administered at baseline (within 7 days before starting ETI), and then at week 2, 4, 6, 8, 10, 12, and 14 following initiation of ETI.

2.2. Outcome measures

At each time point participants completed a survey with validated PRO questionnaires covering the following general areas: pain intensity and interference (PROMIS Pain Interference/Pain Intensity, 9 items); fatigue (FACIT-Fatigue, 13 items); sinus symptoms (SNOT-22: Sino-Naso Outcome Test, 22 items); constipation (PAC-SYM Patient Assessment of Constipation, 12 items); depression (PHQ-8, 8 items); anxiety (GAD-7, 7 items) and sleep (Pittsburgh Sleep Quality Index, 13 items).

We also collected information on patient reported adherence to ETI at each time point.

The PROMIS pain interference short form questionnaire is a 6-item validated measure of the degree to which pain interferes with one's activities, whereas the PROMIS pain intensity contains three items quantifying pain severity. They are reported as T-scores with a mean score of 50. The FACIT-Fatigue scale is a 13-item validated PRO with scores ranging from 0 to 52, with higher scores indicating less fatigue. The minimally important difference has been reported as 3 points [18]. The SNOT-22 is a validated PRO for symptoms of rhinosinusitis. Scores range from 0 to 110, with higher scores indicating worse symptoms. The MCID is estimated to be 8.9 points and scores over 50 are considered consistent with severe symptoms [19]. The PAC-SYM questionnaire is a 12 item instrument that is reliable and accurate for assessing the severity of constipation. Scores range from 0 to 48 with lower scores indicating fewer symptoms of constipation [20,21]. The PHQ-8 is a shortened version of the PHQ-9 scale for depression and is scored from 0 to 27 with higher scores indicating more symptoms of depression. The GAD-7 is a measure of symptoms of anxiety and is scored from 0 to 21, with higher scores indicating more symptoms of anxiety. For both the PHQ-8 and GAD-7, values above 10 are often used as a cut point to prompt clinical evaluation of depressive or anxiety symptoms [22]. The Pittsburgh Sleep Quality Index global score ranges from 0 to 21 with higher scores indicating worse sleep quality. A global score above 5 is consistent with poor sleep quality [23].

2.3. Statistical analyses

The study was designed to enroll 60 participants in order to achieve 80% power to detect clinically significant differences (>3 point difference) in change in pain intensity and interference. Two main events negatively impacted the ability to meet enrollment goals. First, ETI was expected to receive FDA approval in January 2021. However, the drug was successfully fast-tracked for approval, which was granted in October 2019, which was before this study was ready to begin enrolling patients. Patient uptake of drug was rapid, leaving many interested participants ineligible for the study inclusion criteria of not having started ETI. Second, study interest dropped significantly in March 2020 due to the COVID-19 pandemic.

Demographic and clinical characteristics of the study population were summarized using medians and interquartile ranges or counts and percentages for continuous and categorical variables, respectively. Means and standard deviations were used to summarize PRO measures at each time point. The change in each outcome measure over the 98 day follow-up period was evaluated using unadjusted and multivariable linear regression models based on generalized estimating equations with an exchangeable correlation structure to account for subject's repeated measures. Adjusted models included the following *a priori* identified variables: age, sex, and baseline value of the measure. Results of regression models are presented as the β coefficient representing the 14-week change from baseline and corresponding 95% confidence intervals (CI). A two-sided P value of 0.05 was considered statistically significant. All analyses were conducted using STATA Version 16.0 (*StataCorp*, College Station, TX, USA).

3. Results

A total of 31 people were enrolled; however, eight did not start ETI. The final study population included 22 participants that completed the pre-ETI survey and at least one follow-up survey. Of the 22 participants, 19 had complete follow-up to 14 weeks, one

completed up to week 12, one completed to week 6, and one stopped after week 2. The median age was 35.3 (IQR 11.1), 13 (59.1%) were male, and all were white, non-Hispanic. Additionally, 59.1% of the sample had taken previous modulator therapy prior to starting ETI (Table 1). Participants reported taking ETI as prescribed 96% of the time throughout the duration of the study and no participants discontinued ETI.

Patient reported symptom questionnaire scores at baseline and during follow-up are presented in Table 2. In general, the study population had scores indicating relative mild symptoms of pain, fatigue, sinus disease, constipation, depression, anxiety, and sleep disturbance at baseline and at each time point. Across all time points, the within-person variability in measures ranged from a low of 0.361 for pain interference to a high of 0.867 for the FACIT. Fig. 1A–H displays the average PRO scores from baseline through follow-up. Tables S1–S8 in the online supplement show the distribution of change broken down by the pre-ETI baseline score. Most participants had small or no change over time in their symptom scores. For depression the largest increase was a five point increase in PHQ8 score, but it was in someone with a low baseline score of 2. The biggest decrease in PHQ8 scores was a seven point decrease and that was in someone with a high initial score of 17. Similar trends were seen in GAD7 anxiety scores. For both anxiety and depression, there were no participants who moved from a score below 10 to a score above 10, which would trigger a flag that they should be evaluated further regarding symptoms of anxiety and depression.

Age, sex, and baseline levels of subjective symptoms are often associated with subsequent levels and changes in those measures, and we therefore sought to control for those baseline factors. After adjustment for age, sex and baseline PRO value there were three outcomes that improved after starting ETI (Table 3); pain interference ($\beta = -2.57$; 95% CI -4.92, −0.23), sinus symptoms ($\beta = -4.50$; 95% CI -7.59, −1.41), and sleep disturbance ($\beta = -1.90$; 95% CI -2.71, −1.09) all improved significantly. There were no interactions between prior modulator use and any of the outcomes over time. No PROs worsened significantly over the course of the study.

4. Discussion

This study assessed the effect of the highly effective CFTR modulator combination therapy ETI, on patient reported extrapulmonary symptoms including pain, fatigue, sinus disease, gastrointestinal concerns, depression, anxiety, and sleep disturbance. Over a period of three months there were statistically significant improvements in pain, sinus symptoms, and sleep. Additionally, no symptom areas worsened after starting ETI.

CFTR modulator drugs have repeatedly been shown to have dramatic effects on chloride transport as measured by sweat chloride levels and this has translated to improved lung mucociliary clearance and improved lung health. The latter has been quantified with measures such as FEV_1, pulmonary exacerbation rates, and respiratory quality of life. However, Individuals with CF have many non-pulmonary symptoms, some of which can be directly linked to CFTR dysfunction, e.g. sinus congestion and intestinal malabsorption, but others are likely multifactorial and more complicated, such as pain, fatigue, depression, and anxiety. The impact of CFTR modulators on these symptoms has received relatively little attention, though there have been concerns about off target side effects from ETI such as worsened anxiety, depression [16] and sleep disturbance [24].

Of the symptoms assessed in this study, sinus symptoms can be most closely linked to CFTR dysfunction, and it is therefore reassuring to see that the SNOT-22 scores improved over the three months following ETI initiation. This is consistent with improvements seen in the GOAL study for patients with the G551D CFTR variant who started ivacaftor [25], and other studies looking specifically at ETI initiation [26,27].

Sleep disturbance is a more complicated outcome to understand. Improved lung health and associated decreases in cough, dyspnea, and improved gas exchange can contribute to better sleep, but many other factors are likely involved such as anxiety, depression, pain, and fatigue. While symptoms of sleep disturbance improved on ETI, more research is warranted to understand the underlying mechanisms which may have contributed to the observed change.

Pain has been shown to be common in CF and is associated with worse pulmonary outcomes in CF [4,5,28]. While pain intensity did not decrease significantly after starting ETI in this study, pain interference did. The reason for this discrepancy is not clear, though it is

Table 1
Patient characteristics.

	Overall (n = 22)
Age (years), median (IQR)	35.3 (11.1)
Male, n (%)	13 (59.1)
White, n (%)	22 (100)
delF508 mutation category, n (%)	
Homozygous	12 (54.6)
Heterozygous	10 (45.5)
Previous modulator therapy, n (%)	13 (59.1)
FEV1pp, median (IQR)	78 (32)
CFRD, n (%)	7 (31.8)
CFLD, n (%)	1 (4.6)
Pancreatic insufficient, n (%)	15 (68.2)
Anxiety, n (%)[a]	4 (18.2)
Depression, n (%)[a]	2 (9.1)

[a] Diagnosis of anxiety and depression is based on a clinical diagnosis from the medical record.

Table 2
Summary of PRO measures at baseline and during follow-up.

	Pre-ETI mean (SD), n = 22	Day 14 mean (SD), n = 21	Day 28 mean (SD), n = 21	Day 42 mean (SD), n = 22	Day 56 mean (SD), n = 20	Day 70 mean (SD), n = 21	Day 84 mean (SD), n = 21	Day 98 mean (SD), n = 20
Pain intensity T-score	35.9 (6.76)	35.6 (6.63)	37.3 (6.60)	35.1 (5.27)	34.0 (3.77)	34.8 (4.81)	35.1 (5.19)	35.1 (5.80)
Pain interference T-score	44.7 (7.29)	46.5 (9.83)	45.9 (6.32)	43.6 (4.93)	42.1 (3.15)	43.3 (4.97)	42.2 (3.93)	44.2 (5.54)
FACIT Fatigue	37.4 (7.48)	39.8 (5.29)	40.7 (5.38)	40.6 (6.89)	41.4 (5.08)	40.2 (6.11)	40.6 (5.41)	40.3 (5.69)
SNOT22 Sinus symptoms	21.7 (16.91)	14.4 (10.66)	13.4 (11.78)	15.5 (13.24)	14.2 (14.23)	14.2 (11.10)	13.8 (12.79)	12.7 (11.32)
PAC-SYM Constipation	5.6 (5.26)	5.1 (4.79)	4.9 (5.59)	5.1 (5.88)	5.4 (6.10)	4.2 (4.88)	4.5 (5.80)	4.5 (5.55)
PHQ8 Depression	4.9 (5.27)	3.3 (3.09)	3.8 (3.91)	3.6 (4.56)	2.9 (3.30)	4.3 (4.57)	3.7 (3.87)	3.4 (3.70)
GAD7 Anxiety	4.1 (5.44)	3.0 (3.68)	3.2 (3.69)	2.5 (3.16)	3.3 (4.60)	3.0 (3.58)	3.0 (3.43)	3.1 (3.46)
PSQI Sleep Quality	7.1 (3.31)	6.2 (3.02)	5.6 (3.08)	5.6 (3.23)	4.8 (2.23)	4.6 (2.50)	4.9 (2.61)	4.9 (2.39)

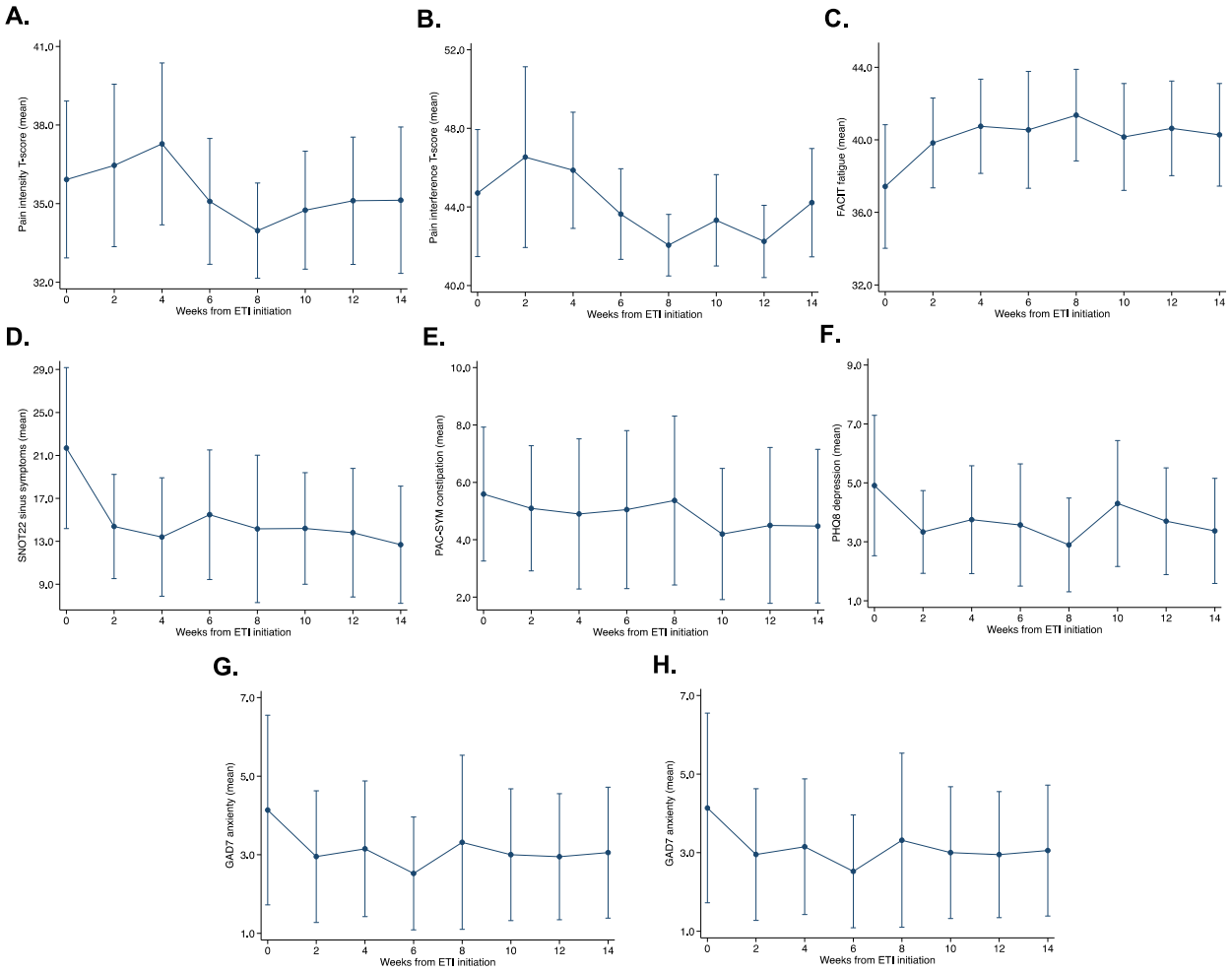

Fig. 1A–H. Mean patient reported outcomes at baseline and through 14 week follow-up.

possible that minor decreases in pain intensity translate to larger improvements in functioning and less interference with daily activities. Additionally, while the PROMIS Pain Interference questions ask specifically about pain interfering with activities, perhaps the overall improvement in health after starting ETI resulted in an overall sense of well-being and ability to do activities, which respondents perceived as less interference due to pain.

Table 3
Unadjusted and adjusted linear regression based on generalized estimating equations evaluating the change in patient reported outcome measures.

	Unadjusted β (95% CI)	Adjusted[a] β (95% CI)
Pain intensity T-score	−1.47 (−3.32, 0.37)	−1.47 (−3.29, 0.36)
Pain interference T-score	**−2.59 (-4.97, -0.21)**	**−2.57 (-4.92, -0.23)**
FACIT Fatigue	1.12 (−0.28, 2.52)	1.20 (−0.15, 2.55)
SNOT22 Sinus symptoms	**−4.66 (-7.67, -1.65)**	**−4.50 (-7.59, -1.41)**
PAC-SYM Constipation	−1.10 (−2.25, 0.05)	−1.03 (−2.25, 0.19)
PHQ8 Depression	−0.29 (−1.28, 0.71)	−0.13 (−1.12, 0.86)
GAD7 Anxiety	−0.344 (−1.41, 0.74)	−0.19 (−1.25, 0.87)
PSQI Sleep Quality	**−1.68 (-2.60, -0.77)**	**−1.90 (-2.71, -1.09)**

[a] Adjusted for age, sex, and baseline value of measure.

Elevated symptoms of depression and anxiety are reported by approximately 20–30% of adults with CF [9]. In this study the baseline levels of anxiety and depression symptoms were relatively low, with only two participants scoring 10 or higher, and the mean score on the GAD7 and PHQ8 declined by about 1 point, this was not statistically significant given the high variance around the mean. Importantly, no participants had increases in symptoms of anxiety or depression sufficient to move them into a category that would have prompted clinical attention. Given the complicated nature of these symptoms, it may not be surprising that they did not uniformly decrease after starting ETI. It is possible that some people with CF have higher levels of psychological stress in the period after starting ETI since a promising new medication introduces new uncertainties and possibilities into one's life. Additionally, this study was conducted during a global pandemic, which inevitably introduced a great deal of stress and impacted participants' mental health.

CFTR modulators have multiple gastrointestinal effects including increasing luminal secretions and increasing intestinal pH [29], however, the clinical changes are highly variable and likely change over time. Anecdotally, some patients report constipation in the short term after starting ETI, but gastrointestinal symptoms may improve over time. While we did not see improvement or worsening of constipation symptoms, the study may have been too short to see longer term changes.

This study prospectively collected multiple, validated PROs before and at multiple time points after starting ETI. However, there are several limitations of this study. Most notably, this study was small and only recorded PROs up to 14 weeks after starting ETI. Female sex and non-white minorities were underrepresented in this study. The sample size was smaller than originally planned due in part to challenges posed by rapid FDA approval and rapid patient uptake of ETI prior to enrollment in this study, and challenges posed by the COVID-19 pandemic. Participants were required to have access to technology to take online surveys, which may have introduced selection bias. In addition, we did not collect medication usage data for any non-ETI medications that may have impacted extrapulmonary symptoms during the observational period. Nevertheless, we were still able to show significant changes in three PROs. Also, our study population had generally mild extrapulmonary symptoms prior to starting ETI, which may have made it difficult to see significant improvement.

ETI has dramatically changed the care and outlook for the majority of people with CF. While the pulmonary effects have received the most attention, it is important to understand the extrapulmonary effects of ETI. In this study we found statistically significant improvements in three disparate symptom areas over the first three months after ETI was started. Encouragingly, there were no PROs that worsened over this period. Larger and longer-term studies will be needed to gain a more complete understanding of how extrapulmonary symptoms change with ETI. While this information may be of interest to all in the CF community, it is particularly relevant when considering starting CFTR modulators in people who have undergone lung transplantation, where the goal is to improve extrapulmonary symptoms.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Dr. Lechtzin has served as a site principal investigator for Vertex Pharmaceuticals clinical trials. Dr. Allgood received research support from the Blaustein Pain Fund.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20110.

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