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Original Article

A longitudinal study assessing the impact of elexacaftor/tezacaftor/ivacaftor on gut transit and function in people with cystic fibrosis using magnetic resonance imaging (MRI)

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ABSTRACT

Background: Gastrointestinal (GI) symptoms in cystic fibrosis (CF) are common and disruptive. The effect of cystic fibrosis transmembrane conductance regulator (CFTR) modulators on the GI tract is not fully understood. The aim was to use magnetic resonance imaging (MRI) to determine if elexacaftor/tezacaftor/ivacaftor (ETI) changed GI function and transit.

Methods: This was an 18 month prospective, longitudinal, observational study. We enrolled 24 people with CF aged 12 years or older to undergo MRI scans before starting ETI and 3, 6, and 18 months after starting ETI. The primary outcome measure was change in oro-caecal transit time (OCTT) at 6 and 18 months. Secondary outcome measures included change in small bowel water content (SBWC), change in the reduction in small bowel water content following a meal (DeltaSBWC) and change in total colonic volume (TCV).

Results: A total of 21 participants completed MRI scans at 6 months and 11 completed at 18 months. After 18 months of ETI, median OCTT significantly reduced, from >360 min [IQR 240->360] to 240 min [IQR 180–300] ($p = 0.02$, Wilcoxon signed-rank). Both SBWC and DeltaSBWC increased after starting ETI. TCV reduced significantly after 18 months ($p = 0.005$, Friedman).

Conclusions: Our findings suggest an improvement in small bowel transit, small bowel response to food and a reduction in colonic volume after starting ETI. These effects may relate to CFTR activation in the small bowel. To our knowledge this is the first study to show a physiological change in GI transit and function in response to CFTR modulator use through imaging studies.

Abbreviations: AUC, Area under the curve; BMI, Body mass index; BSA, Body surface area; CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; ETI, Elexacaftor/tezacaftor/ivacaftor; GI, Gastrointestinal; IBS-C, Irritable bowel syndrome with constipation; MRI, Magnetic resonance imaging; OCTT, Orocaecal transit time; PAC-SYM, Patient Assessment of Constipation Symptoms; PROM, Patient reported outcome measure; pwCF, People with cystic fibrosis; SBWC, Small bowel water content; TCV, Total colonic volume.

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1. Introduction

Gastrointestinal (GI) symptoms in cystic fibrosis (CF) are common [1,2] and negatively impact upon quality of life [2,3]. These symptoms persist even following the use of CFTR modulators [2]. The most common GI symptoms experienced by people with CF (pwCF) include flatulence, bloating, straining, abdominal pain, and fatty stools [1,2,4]. These symptoms may be severe and result in up to two-thirds of pwCF missing school or work [3].

The James Lind Alliance Priority Setting Partnership achieved a consensus on the priorities for clinical research in CF, through engagement with the CF community [5,6]. This process identified reducing GI symptoms [5,6] and evaluating the extra-pulmonary effects of CFTR modulators [5] as research priorities in CF. CFTR modulator use has significantly improved pulmonary function and body mass index (BMI) [7,8]. Improvements in GI symptoms have been reported in those taking elxacaftor/tezacaftor/ivacaftor (ETI), using the CFAbd-Score, a CF-specific patient reported outcome measure (PROM) [9,10]. However, GI symptoms remain prevalent despite modulator use [2] and the mechanisms underlying these symptoms are not fully understood. The purpose of the Gut Imaging for Function and Transit in Cystic Fibrosis 3 (GIFT-CF3) study was to study the mechanisms of GI dysfunction in CF and the effects of ETI on gut physiology and symptoms.

A previous magnetic resonance imaging (MRI) study by our group, compared GI function and transit in pwCF to controls [11] and found: delayed passage of food through the small bowel; increased volume of fluid in the small bowel lumen; a smaller reduction in the volume of small bowel water in response to a meal; and increased colonic volume [11]. These findings may indicate a partial physical or functional obstruction in the region of the ileocaecal valve, delaying the transit of ileal contents into the colon, and increasing the volume of water in the small bowel. This may contribute to symptoms of bloating, abdominal distension, and discomfort. Our previous work also showed no improvement in these abnormalities of GI function and transit after a short course of tezacaftor/ivacaftor [12], raising the question of whether these would resolve with longer-term use of ETI.

In the GIFT-CF3 study (NCT04618185), our objective was to determine whether 18 months of ETI use altered MRI measures of GI function and transit and whether these changes were linked to changes in GI symptoms. We planned to measure oro-caecal transit time (OCTT), small bowel water content (SBWC) and total colonic volume (TCV) before and during ETI use. We also considered the effects of ETI on a new metric: the change in volume of water in the small bowel in response to a meal, termed the delta small bowel water content (DeltaSBWC) [11–13]. This measurement aims to quantify the gastro-ileal reflex whereby eating stimulates emptying of ileal contents into the colon [14,15]. This emptying is due to increased ileal motility from the fasted quiescent to the more active fed state after a meal [15,16]. From our previous studies, the DeltaSBWC is reduced in pwCF [11,13]. We hypothesise that in CF, the reduced volume of contents being emptied from the terminal ileum into the caecum is due to increased viscosity of contents in the distal small bowel and/ or ileal inflammation. We also planned to use the CFAbd-Score and the Patient Assessment of Constipation Symptoms (PAC-SYM) PROMs to determine whether changes in MRI measures correlated to changes in GI symptom burden.

2. Methods

This study was approved by London – Chelsea Research Ethics Committee (20/PR/0508, 21/10/2020).

2.1. Aims

We conducted a prospective, longitudinal observational study comparing MRI measurements of GI function and transit at baseline and 3, 6 and 18 months after starting ETI. A detailed study protocol is

available in the **Supplementary Materials** (and at <https://clinicaltrials.gov/study/NCT04618185?tab=table>)

Our primary outcome measure was the difference in median OCTT, in minutes, at baseline before ETI, compared to 6 and 18 months post starting ETI. OCTT is a measure of the time taken for a study meal to pass from the mouth to the first part of the colon (caecum).

Secondary outcome measures were taken at baseline and at 3, 6 and 18 months after initiation of ETI and include:

- Change in SBWC volume over 360 min (by measuring area under the curve), corrected for body surface area (BSA) between baseline and 3 months (12 weeks in protocol), 6 months (24 weeks in protocol), and 18 months (76 weeks in protocol).
- Postprandial change in SBWC between scanning timepoints 240 min (T240) and 300 min (T300) (the DeltaSBWC measurement) at baseline and 3, 6 and 18 months [13] (see “Procedures”).
- Change in TCV (area under the curve over 360 min), corrected for BSA, between baseline and 3 months, 6 months, and 18 months.
- Change in CFAbd-Score and PAC-SYM scores between baseline and 3 months, 6 months, and 18 months.
- Stool calprotectin at baseline and 3, 6, and 18 months.
- Stool elastase at baseline and 3, 6, and 18 months.
- Height, weight and spirometry FEV1 % (Global Lung Function Equation) [17] at baseline and 3, 6, and 18 months.

The results of stool microbiome analysis, from GIFT-CF 3 participants, have recently been published by our group [18].

2.2. Study population

Participants were aged 12 years and older, had at least one copy of the p.Phe508del gene and were eligible to receive ETI. Participants were recruited from the tertiary service at Nottingham University Hospitals NHS Trust from outpatients clinics or ward attendance. Our aim was to study changes in MRI metrics, in pwCF, following ETI. We did not include a non-CF control group because our previous work has shown how MRI metrics in pwCF differ from controls [11].

2.3. Procedures/ study day

The study day was the same as previously described (NCT03566550) [11]. Participants arrived fasted and prior to their first scan, completed the PAC-SYM [19] and CFAbd-Scores [20]. Participants received a high carbohydrate rice pudding meal after baseline scan and a high fat meal after the T240 scan (see **Supplementary Materials**). Additional food and drink were not permitted. Participants took their usual dose of pancreatic enzyme replacement therapy with each test meal.

2.4. Scanning protocol and image analysis

Scans were performed at the Sir Peter Mansfield Imaging Centre, using a 3-Tesla Philips Ingenia MRI scanner (Philips Healthcare, Best, The Netherlands) using the scanning protocol we have previously published [11] (see **Supplementary Materials**).

MRI image analysis was conducted using two software packages. OCTT and TCV were analysed using Medical Image Processing, Analysis and Visualisation (MIPAV, NIH, Bethesda) [Anon., 21]. SBWC and DeltaSBWC were analysed using in-house software written in MATLAB® (The MathWorks Inc., Natick, MA, USA) [22].

All images were blinded and randomised before image analysis. SBWC, DeltaSBWC and TCV data were reviewed by one reviewer with a second reviewer repeating 10 % of images to ensure accuracy. Discrepancies were resolved by a third independent reviewer. OCTT images were reviewed independently by two reviewers and a consensus reached. A third reviewer adjudicated if a consensus wasn't reached.

2.5. Statistical plan

Statistical analysis was undertaken using the Stata 18 software package (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC). Sample size was not based on a formal power calculation but based on sample sizes from previous MRI studies of GI function and transit in CF [11,12].

2.5.1. MRI outcome measures

The primary outcome measure was the difference in median OCTT between baseline and 6 months after ETI initiation, and baseline and 18 months after ETI initiation. OCTT is determined when the head of the first meal is observed to reach the caecum and is assessed at each scan timepoint. Once observed, the OCTT is considered completed at that timepoint even if it occurred between scans. Therefore, the OCTT data are not continuous data. Statistical significance for change in median OCTT, was determined using paired Wilcoxon-signed rank analysis.

Data for the secondary outcome measures SBWC, DeltaSBWC and TCW were adjusted for a participant’s BSA, calculated using the Mosteller formula, to allow for comparisons between participants [11,12]. Changes in secondary outcome measures over the whole study period were analysed using a non-parametric repeated measures test (Friedman test). For repeat measure tests at 18 months, those participants who did not complete scans at 18 months were excluded. All data will be presented as median (interquartile range).

2.5.2. Patient reported outcome measures

PAC-SYM and CFAbd-Scores were analysed as total and domain scores. Data were paired and the Wilcoxon-signed rank test used for paired analysis of baseline versus 3 months, baseline versus 6 months and baseline versus 18 months.

2.6. Stool analysis

Stool microbiome analysis was prioritised over calprotectin and elastase. Microbiome results have been published [18] and faecal calprotectin and elastase will be published when available.

3. Results

In total, 24 participants were recruited with 21 completing baseline, 3 months, and 6 months scans and 11 of the 21 completing scans at 18 months (see Fig. 1).

Demographics of the participants who completed a baseline scan are summarised in Table 1.

Faecal calprotectin and faecal elastase results will be presented in a future publication. No adverse events were reported by participants during the study period. One participant withdrew from the study as ETI was stopped by their clinical team.

Table 1

Clinical characteristic of pwCF who completed scans at baseline / 6 months and baseline / 18 months. Of those on laxative medications one was on a combination of macrogol 3350, sodium docusate and senna, one on a combination of macrogol 3350 and sodium docusate and one was using macrogol 3350 alone. One participant used hyoscine butylbromide. Participants stopped these medications on the day of the MRI study.

| Characteristic | Those who completed 6 months | Those who completed 18 months |
|--|------------------------------|-------------------------------|
| Participants | 21 | 11 |
| Male (%) | 17 (81 %) | 10 (90.9 %) |
| Age (Mean ± SD) | 21.1 (± 8.3) | 20.5 (± 9.5) |
| Baseline BMI (Mean ± SD) | 20.6 (± 3.8) | 20.8 (± 3.2) |
| F508 Homozygous (%) | 13 (62 %) | 7 (63.6 %) |
| Pancreatic Insufficient (%) | 21 (100 %) | 11 (100 %) |
| Cystic Fibrosis-related diabetes (%) | 4 (19 %) | 2 (18 %) |
| Baseline Total CFAbd-Score (Median, [IQR]) | 5.96 [3.63–17.88] | 6.5 [5.6–25.3] |
| Number on CFTR modulator prior to ETI (%) | 13 (62 %) | 7 (63.6 %) |
| Number on laxative medications* | 3 (14 %) | 1 (9 %) |
| Number on smooth muscle relaxant* | 1 (5 %) | 1 (9 %) |
| Number on long-term oral antibiotics | 13 (62 %) | 7 (64 %) |

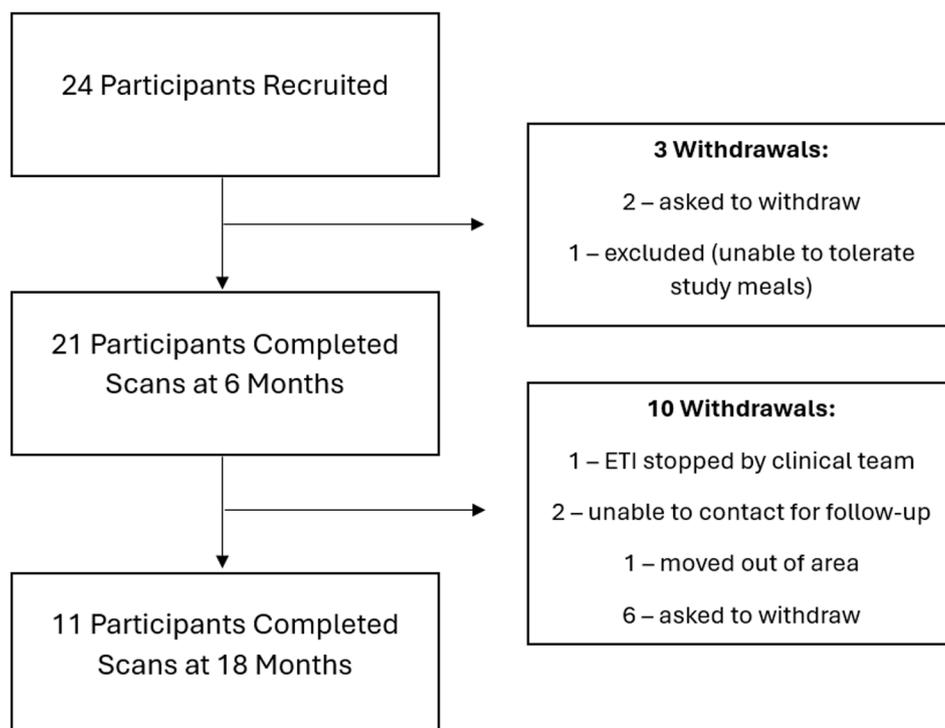


Fig. 1. Flow chart showing number of participants at each stage.

3.1. MRI results

3.1.1. Primary outcome (Orocaecal transit time, OCTT)

There was no significant change in median OCTT between baseline and 6 months after initiation of ETI (baseline >360 min [360->360] vs 6 months >360 min [300->360], $p = 0.67$, Wilcoxon signed-rank). However, after 18 months (excluding those who did not complete 18 month scans), a significant reduction in median OCTT of ≥ 120 min was observed (baseline >360 min [240->360] vs 18 months 240 min [180–300], $p = 0.02$, Wilcoxon signed-rank). Fig. 2 shows OCTT results at baseline versus 6 months and baseline versus 18 months.

Changes in individual OCTT can be found in the **Supplementary Materials**.

3.1.2. Small bowel water content (SBWC)

Median SBWC AUC increased after initiation of ETI at all follow-up visits (baseline 54.1 L.min/m² [38.3–83.8], 3 months 62.3 L.min/m² [49.2–118.9], 6 months 72.2 L.min/m² [54.3–95.8], 18 months 58.4 L.min/m² [43.1–86.9]). The increased SBWC AUC after ETI initiation was significant at 6 months ($p = 0.001$, Friedman). The 11 participants who completed scans at 18 months were also found to have a significant increase in SBWC AUC after 18 months ($p = 0.001$, Friedman). Fig. 3 summarises SBWC AUC results.

3.1.3. Delta small bowel water content – (DeltaSBWC)

DeltaSBWC increased from baseline following initiation of ETI (baseline -7 mL/m² [-47.4–68.2], 3 months 74.9 mL/m² [28.2–121.2], 6 months 69.8 mL/m² [-6.4–128.7], 18 months 63.3 mL/m² [-2.6–116.7]).

The increased DeltaSBWC after starting ETI was significant at both 6 months ($p = 0.002$, Friedman) and 18 months ($p = 0.004$, Friedman). Fig. 4 summarises DeltaSBWC results.

3.1.4. Total colonic volume – (TCV)

TCV was observed to decrease at 3, 6 and 18 months (baseline 208.9

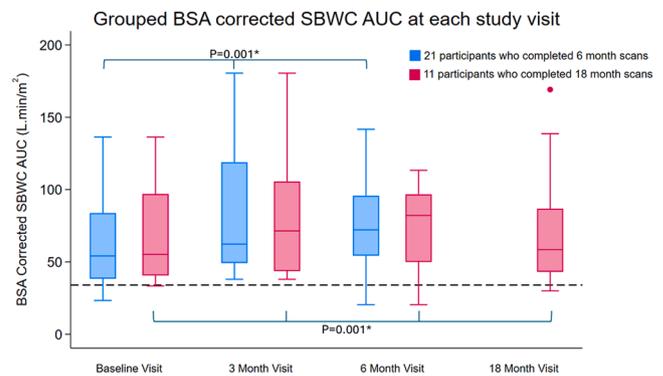


Fig. 3. Box and whisker chart showing the changes in BSA corrected SBWC AUC between visits. Reference line is for expected SBWC AUC in controls (34 L.min/m² [11]) and * denotes statistical significance.

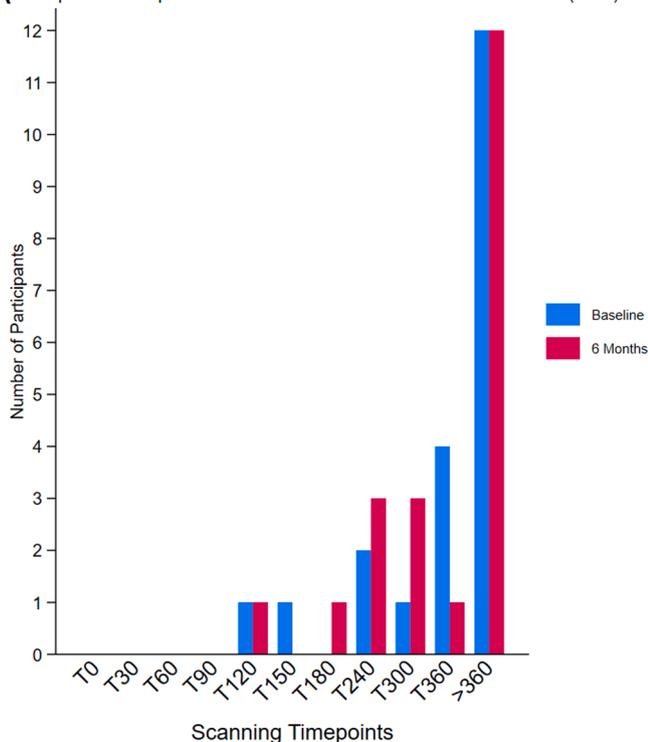
L.min/m² [169.6–230], 3 months 192.9 L.min/m² [174.6–229.8], 6 months 187.7 L.min/m² [151.6–205.1] and 18 months 151.8Lmin/m² [117.3–179.0]). The decreasing TCV AUC was not significant at 6 months ($p = 0.67$, Friedman). However, after 18 months the decrease in TCV from baseline was significant ($p = 0.005$, Friedman). Fig. 5 shows the TCV results at each visit.

3.2. Patient reported outcome measures

3.2.1. CFAbd-Score

No significant change in median total CFAbd-Score was seen in this cohort after starting ETI (baseline 6 [3.6–17.9], 3 months 9.5 [4.1–13.9], 6 months 9.5 [5.6–17.4], 18 months 8.1 [5.4–25.3]). The highest scoring domain at baseline was disorders of bowel movement (20 [7.5–27.5]) which did not change significantly after starting ETI (3 months 15 [10–27.5], 6 months 17.5 [10–25], 18 months 20 [12.5–32.5]). There was no significant change in gastro-oesophageal

A Timepoint for completion of oro-caecal transit at baseline and 6 months (n=21)



B Timepoint for completion of oro-caecal transit at baseline and 18 months (n=11)

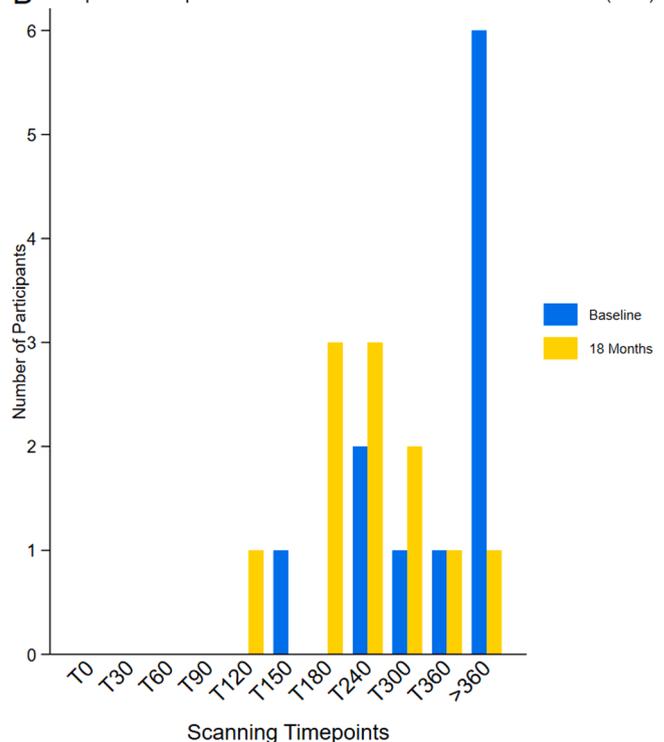


Fig. 2. Bar charts showing the OCTT of participants at baseline versus 6 months (Panel A) and baseline versus 18 months (Panel B).

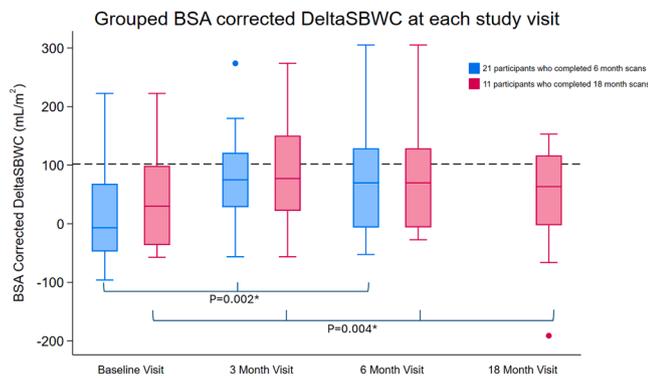


Fig. 4. Box and whisker chart showing the changes in BSA corrected DeltaSBWC between visits. Reference line is for expected DeltaSBWC in controls (102 mL/m^2 [11]) and * denotes statistical significance.

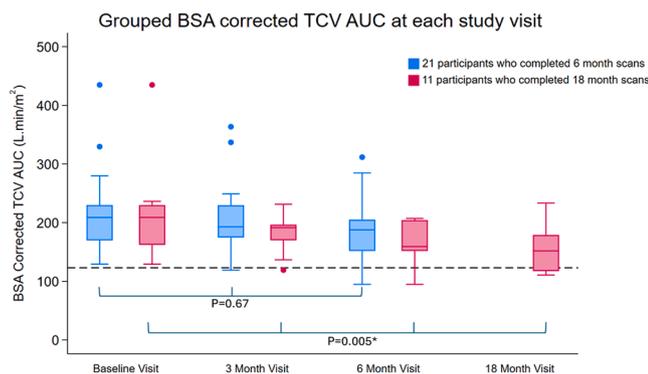


Fig. 5. Box and whisker chart showing the changes in BSA corrected TCV AUC between visits. Reference line is for expected TCV AUC in controls (123 L.min/m^2 [11]) and * denotes statistical significance.

reflux disease symptoms (baseline 6.7 [0–20], 3 months 13.3 [0–20], 6 months 13.3 [0–20], 18 months 13.3 [0–26.7]) or impairment of quality of life (baseline 0 [0–15], 3 months 2.5 [0–12.5], 6 months 5 [0–10], 18 months 2.5 [0–17.5]) subdomains.

The domains pain symptoms and disorders of appetite had median scores of 0 across all visits. Further analysis can be found in **Supplementary Materials**.

3.2.2. PAC-SYM

There was no significant change in PAC-SYM score from baseline after starting ETI (baseline 0.2 [0–0.8], 3 months 0.2 [0–0.5], 6 months 0.2 [0–0.7], 18 months 0.4 [0.1–0.6]). There was no significant change in PAC-SYM subscale scores (abdominal, rectal and stool subscale). More detail can be found in **Supplementary Materials**.

4. Discussion

We have demonstrated changes in GI function and transit, using MRI, following the commencement of ETI. The improvement in GI function and transit, in pwCF after starting ETI, is seen in multiple MRI measures (including OCTT, DeltaSBWC, TCV) which move towards values seen in healthy controls [11]. To our knowledge, this is the first study to identify changes in GI function and transit in pwCF using MRI following the start of a CFTR modulator.

PwCF have a delay in small bowel transit [11,23–25], with a significantly longer OCTT [11] and reduced small bowel motility [26]. Our results suggest that, after 18 months of ETI use, small bowel transit improves, with OCTT decreasing from ≥ 360 min to 240 min. OCTT in controls is expected to be around 210 min [11]. Prolonged transit times

and dysmotility in the small bowel interplays with bacterial overgrowth and intestinal inflammation, contributing to the underlying pathophysiology of the GI tract in CF [1,27].

We have previously shown that the drop in volume of small bowel water following a meal, is less in pwCF [11]. Our hypothesis is that this results from a partial physical or functional obstruction at the ileo-caecal valve. We found that our participants had a significant increase in DeltaSBWC after 3, 6 and 18 months of ETI treatment. This increased DeltaSBWC after starting ETI suggests an improvement in the flow and transit of chyme through the ileocaecal region. If the reduced DeltaSBWC and increased OCTT in pwCF is due to a partial physical or functional obstruction in the region of the ileocaecal valve, the increased DeltaSBWC and decreased OCTT seen after starting ETI, could suggest a partial resolution of this obstruction.

Improvements in transit whilst taking ETI may not be confined to the small bowel. Increased TCV has been associated with irritable bowel syndrome with constipation and a prolonged whole gut transit time [28]. Within CF, an increased colonic volume has also been associated with increased flatulence [23]. Increased TCV may reflect slower transit of faeces through the colon, and therefore increased colonic volume. After 18 months of ETI, TCV was found to significantly reduce by 27%. Although the measurement of whole gut transit time was not assessed, the reduction in colonic volume seen may suggest an improvement in the transit of faeces through the colon in pwCF after starting ETI.

The results of this study may also show a change in small bowel function. SBWC AUC was found to increase after starting ETI. CFTR function in the proximal intestine results in secretion of chloride and bicarbonate to help neutralise acidic contents entering from the stomach (in addition to pancreatic secretions) [29]. CFTR function in the intestine is also responsible for secretion of fluid intraluminally [29]. The increased SBWC seen after starting ETI suggests increased small intestinal secretions due to CFTR activation in the small intestine. Interpretation of SBWC results also needs to take account of the effect of not only secretion but also transit. SBWC is the product of both flow and transit time which may explain why greater SBWC is found in pwCF not on modulators in whom small bowel transit is slowed [11,13]. The increase in SBWC and simultaneous fall in transit time seen after ETI may be due to increased secretion which is not fully compensated for by increased flow (and a fall in viscosity).

The changes in GI function and transit after starting ETI found using MRI did not result in changes in symptom burden or quality of life. Neither the CFAbd-Score or PAC-SYM data show a significant change, despite ETI having been shown to improve symptoms and quality of life using the CFAbd-Score previously in two separate studies including pwCF from England, Ireland and Germany [9,10]. The cohort recruited for this study also reported a lower baseline total CFAbd-Score and PAC-SYM score compared to previous studies [11,20] with the median total CFAbd-Score being lower than the scores reported in healthy controls in previous studies [20]. Therefore, it is possible our findings may be subject to a recruitment bias. CF patients with troublesome GI symptoms may have been more likely to participate (hoping the study would lead to a better understanding of their symptoms) or less likely to take part (because of the burden of having eleven MRI scans at each visit). The CFAbd-Score at baseline was relatively low (5.96 [IQR 3.63–17.88]), suggesting that GI symptoms were mild at baseline and so little change in the CFAbd-Score with modulator treatment might be expected.

Three participants were noted to be using laxative medications at the start of the study. Laxative agents used included movicol®, sodium docusate and senna. Potential participants were only excluded if, on the day of the study, they were unable to stop medications which alter bowel habit.

The main strength of this study was the length of follow up. Our previous MRI study collected data between 21 and 28 days after starting tezacaftor/ivacaftor [12]. In this previous study, we speculated that the follow up time used was relatively short and not long enough to allow

for changes in the gut to occur after modulator introduction.

The main limitation is the high participant attrition between the 6 and 18 month MRI study days which we attribute to the onerous protocol (eleven scans over seven hours) and (in one case) cessation of ETI. This attrition may have resulted in underpowering of 18 month follow up data or have introduced unknown bias. Another limitation, and area for further work, is understanding how the changes seen post-ETI correlate to symptom burden and what they may mean clinically.

The next step in our research is to link the physiological changes seen with ETI treatment with the changes in symptoms reported by pwCF. To this end, we are currently undertaking the GRAMPUS-CF study (Gut Research Advancing a Mechanistic and Personalised Understanding of Symptoms in CF) [Anon., 30]. This study will collect symptom data on 300 adults with CF and determine if there are distinct phenotypes of gut symptoms. We will then investigate the mechanisms underpinning each phenotype with MRI and studies of microbiome, inflammation, and diet.

5. Conclusion

We have been able to demonstrate changes in GI transit and function in pwCF following initiation of ETI using MRI. These changes include a reduction in small bowel transit time, improved postprandial response in the small bowel, reduced colonic volume and a possible reactivation of CFTR within the small intestine resulting in increased small intestinal secretions. These results suggest that ETI may improve measures of GI function and transit (either directly or indirectly). Whether these changes are maintained and their impact upon symptoms are yet to be determined.

These results also enhance the understanding of the pathophysiology of GI disease in CF by demonstrating a prolonged gut transit and a reduction or absence of CFTR secretory function in the small bowel. The improvement in small bowel transit with ETI may also indicate some resolution of a partial physical or functional obstruction at the ileocaecal valve. An improved understanding of these mechanisms could be used to design and test therapeutic interventions for reducing GI symptoms in CF and to rationalise existing drug therapies.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AR, CH, FL, and ND have nothing to disclose. This work was supported by an investigator-initiated grant from Vertex Pharmaceuticals including salary support for AY and CN. CZ reports an investigator-initiated grant from Vertex Pharmaceuticals. JGM reports investigator-initiated grants from Vertex Pharmaceuticals and has received honoraria previously for lectures from Vertex, Pari and Chiesi. JGM also reports participation in monitoring or advisory board previously for Vertex, Viatrix and Chiesi. GM reports investigator-initiated grants from Vertex Pharmaceuticals. GM also reports previous employment to Société Produits Nestlé during this study period. GM reports receiving support to attend conferences from Société Produits Nestlé previously. PG reports investigator-initiated grants from Vertex Pharmaceuticals paid to their institution. IS reports grants from the Rayne Foundation Fellowship.

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Fibrosis Trust, Cystic Fibrosis Foundation, LifeArc and is a board member and chief medical officer for MiDx[®] company.

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Credit author statement

The study was designed by CN, ND, CH, GM, HB, PG, IS, LM, RS, & AS. MRI scanning protocol design, data acquisition and analysis were conducted by AY, AR, FL, ND, CH, PG, & LM. JGM developed the CFAbd-Score and JGM & CZ analysed the data generated by the score in this study. Statistical analysis was by AY & IS. All authors contributed to the interpretation of study data. The first draft of the manuscript was written by AY, IS, HB, LM, RS & AS. All authors have reviewed and approved the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jcf.2024.08.001](https://doi.org/10.1016/j.jcf.2024.08.001).

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