

The Return of the Pancreas: Evaluating impact of CFTR modulators on pancreatic function

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Background

Cystic fibrosis (CF) is an inherited disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene affecting approximately 100,500 individuals worldwide. While respiratory disease is the primary cause of morbidity and mortality in cystic fibrosis (CF), the condition also impacts the liver, pancreas, and gastrointestinal system. CFTR modulating therapies have been utilized to enhance and even restore functional expression of the CFTR protein. Following the initiation of CFTR modulators, the transition from pancreatic insufficiency (PI) to pancreatic sufficiency (PS) has been observed in five case reports, four case series, and twelve studies involving a total of 80 patients, identified by fecal pancreatic elastase levels of ≥ 200 . Most individuals with cystic fibrosis who experienced a shift to PS were treated with Ivacaftor (64%, n=51). Research suggests that starting CFTR modulators at a younger age is linked to a higher likelihood of recovering pancreatic function. However, such cases have been documented in individuals up to age 60. There is currently no known correlation between gender, genotype, or the choice of CFTR modulator and the conversion to PS.

A total of 12 documented cases report discontinuation of pancreatic enzyme replacement therapy (PERT) after the conversion from pancreatic insufficiency (PI) to pancreatic sufficiency (PS) following CFTR modulator (CFTRm) initiation (Cho, Megalaa, Munce). Among these cases, three individuals developed pancreatitis, and one individual reported weight loss (Cho, Megalaa, Munce). The recent report from the INSPIRE cohort evaluated children with pancreatic insufficiency secondary to either chronic pancreatitis or acute recurrent pancreatitis. This retrospective cohort study demonstrated a reduction in acute pancreatitis episodes, with more than 40% remaining free from additional episodes over a two-year period following PERT discontinuation (Freeman 2024).

In summary, analysis of prior studies on pancreatic insufficiency in the context of CF reveals major knowledge gaps in the field. The current study is among the first to prospectively investigate the transition from PI to PS in people with CF following CFTR modulator (CFTRm) therapy. The mechanisms and variables associated with the restoration of pancreatic function remain largely unexplored. Additionally, this research uniquely focuses on the efficacy and safety of discontinuing PERT in patients who achieve PS due to CFTRm therapy. Previous studies have not yet thoroughly evaluated the clinical outcomes and risks associated with stopping PERT. Furthermore, this study pioneers the incorporation of therapeutic drug monitoring of elexacaftor, tezacaftor, and ivacaftor levels in people with CF. The pharmacokinetics and optimal therapeutic ranges of CFTR modulators, particularly in relation to pancreatic function, remain underexplored.

The impact of this study will be twofold: (i) generate feasibility data to justify and rationally design a larger prospective trial and (ii) define characteristics linked to the transition from PI to PS, thereby developing tailored therapeutic strategies for people with CF, ensuring both efficacy and safety in the management of this complex disease.

Significance and Specific Aims

Pancreatic insufficiency (PI), defined as fecal elastase (FE) $<200 \mu\text{g/g}$, is the most common nutritional cause of morbidity for persons with CF (PwCF). CFTR modulating therapies have been utilized to enhance functional expression of the CFTR protein. As outlined above, our preliminary data indicate that the use of CFTR modulators correlates with improvement in FE and, in some cases, normalization of pancreatic function. The significance of this finding is that it may allow the clinician to withdraw pancreatic enzyme replacement therapy (PERT). The ability to stop PERT is important for several reasons: it would decrease pill burden which could

improve psychosocial outcomes, reduces health system costs, and minimize medication complications such as the rare but severe complication of fibrosing colonopathy.

The knowledge gap that now exists is the extent to which PERT can be withdrawn in PwCF who have normalized pancreatic function while on a CFTR modulator. This objective is to define the safety and feasibility of discontinuing PERT in individuals with normalization of FE.

To that end, we propose two aims (figure 1):

1. Define quantitative and qualitative outcomes in persons with normalized FE at baseline and after 6 months off PERT while on CFTR modulator therapy.
2. Identify variables associated with successful PERT withdrawal.

The proposed studies will impact patient care regardless of whether our hypothesis is supported or refuted by the data. This innovative study will address a largely unexplored need in evaluating the safety and feasibility of PERT withdrawal and, if successful, determining factors that predict successful PERT withdrawal. The data will serve as the foundation for an external grant proposal aimed at validating the findings in a second, large, randomized cohort. This will enable more robust analyses to identify broader factors with enhanced sensitivity and specificity for effectively risk-stratifying the successful discontinuation of PERT.

Variables

Patient Identifiers:

- Name
- Date of birth
- Medical record number (MRN)

Demographics:

- Age
- Gender
- Race/Ethnicity
- Cystic Fibrosis Genotype

Past Medical History:

- GI symptoms (malabsorption)
- History of advanced CF liver disease
- History of pancreatitis
- Age at initiation of enzymes
- Medication compliance to pancreatic enzyme replacement
- Sweat chloride result history
- Fecal pancreatic elastase result history
- Fat-soluble vitamins (Vitamin A, D, E, and INR)
- Lipase
- Hepatic function panel
- Gamma-glutamyl transferase (GGT)

Medication history:

- Age at initiation
- Time since initiation
- Medication compliance to CFTRm
- Current modulator
- Previous modulator
- Dosing of modulator
- Pancreatic enzyme dosing and administration route

Nutrition:

- Enteral supplementation
- Feeding route
- Weight: percentile and Z score

- Height: percentile and Z score for individuals ≥ 2 years
- Length: percentile and Z score for individuals <2 years
- BMI: percentile and Z score for individuals ≥ 2 years
- Weight for length: percentile and Z score for individuals <2 years

Inclusion/Exclusion Criteria

Inclusion criteria for this study include individuals with cystic fibrosis and pancreatic insufficiency, aged 18 years or younger, who have been on a CFTR modulator for a minimum of 2 months. Exclusion criteria encompass individuals with CF-related diabetes requiring insulin use, advanced CF liver disease, short gut syndrome, history of surgical bowel resection, and moderate to severe malnutrition.

Inclusion:

- People with cystic fibrosis and pancreatic insufficiency as defined by fecal pancreatic elastase <200 at baseline
- Age ≤ 18
- Current use of a CFTR modulator such as ivacaftor, Elexacaftor/tezacaftor/ivacaftor, or vanzacaftor/tezacaftor/deutivacaftor

Exclusion:

- CF-related diabetes requiring current insulin use
- Advanced CF Liver disease as defined by nodular liver, advanced fibrosis (F4), multi-lobular cirrhosis with or without portal hypertension, non-cirrhotic portal hypertension
- Short Gut syndrome as defined by need for surgical bowel resection and subsequent need for parenteral nutrition for > 60 days or bowel length less than 25%.
- Moderate to severe malnutrition as defined by either weight for length or BMI z score -2 or greater.

Study Procedures

The participants will submit the following lab samples after enrollment. When the stool sample for fecal elastase is obtained, this will be known as day 0 of the study. Fecal elastase results will determine which arm of the study the participant will be.

1. Group A: fecal elastase result is < 200
2. Group B: fecal elastase result is ≥ 200

Participants in Group A and Group B must submit the following blood tests on day 0 (± 28 days):

- Hepatic function panel
- CFTR modulator trough levels (participants must hold AM dose)

Participants in Group A and Group B will complete the following survey questions on day 0 (± 28 days). The parent or guardian of participants age <7 years will complete the survey for the participant. For participants ≥ 7 years, the participant will complete the survey with assistance from their parent or guardian. Included within this survey is the validated PAGI-SYM © Acute scoring system with consent for use obtained from the Mapi Research Trust valid through June 2026. The second validated scoring system is The Hunger Vital Sign™. The rest of the survey questions are original to this study. The survey questions can be found within the Protocol Attachments.

If a participant has a fecal elastase of < 200 , they will be part of Group A and therefore complete the study. If a participant has a fecal elastase result of ≥ 200 , they will be a part of Group B and will discontinue PERT.

At 3 months (± 28 days), participants in Group B must complete the survey.

At 6 months (± 28 days), participants must submit a fecal elastase, blood work, and the survey. The blood work required at this visit includes:

- Vitamin A (Retinol)
- Vitamin D (25-hydroxyvitamin D)
- Vitamin E (alpha tocopherol)
- INR

- Hepatic function panel
- CFTR modulator trough levels (participants must hold AM dose)

After the submission of the 6-month fecal elastase, blood work, and survey, Group B completed the study.

If a participant in group B restarts pancreatic enzymes during the study for any reason, the participant would complete the study at this time.

After the completion of the study, the participants in Group B who discontinued enzymes may continue off of enzymes with the plan to continue routine every 3-month follow-up with the cystic fibrosis team which includes pediatric pulmonology and dietician. Pediatric gastroenterology will be available as needed follow-up for participants who have discontinued enzymes.

The following information will be collected by the researchers via chart review or the electronic medical record and CF Database:

Past Medical history:

- Cystic fibrosis genotype
- History of CF-related diabetes requiring current insulin use
- History of advanced CF Liver disease as defined by nodular liver, advanced fibrosis (F4), multi-lobular cirrhosis with or without portal hypertension, non-cirrhotic portal hypertension
- History of Intestinal Failure or Short Gut Syndrome as defined by need for parenteral nutrition for >60 days or bowel length less than 25%.
- History of surgical bowel resection
- Moderate to severe malnutrition as defined by either weight for length or BMI z score -2 or greater.
- Dietary history including route of feeding and use of supplemental formula
- History of acute pancreatitis as defined by 2 or more of the following acute epigastric abdominal pain, lipase level 3 times the upper limit of normal, and imaging findings consistent with acute pancreatitis
- Date of initiation of CFTR modulator, current CFTR modulator prescribed, previous CFTR modulators prescribed, and dosing of current CFTR modulators
- Date of initiation of pancreatic enzyme replacement therapy (PERT), current PERT dosing, and route of administration of PERT

Laboratory results:

- Sweat chloride results
- Fecal pancreatic elastase results
- Annual fat-soluble vitamin levels (Vitamin A, Vitamin D, Vitamin E, INR)
- Lipase levels if available
- Annual hepatic function panel

Growth:

- Weight: percentile and Z score
- Length: percentile and Z score
- Height: percentile and Z score
- BMI: percentile and Z score
- Weight for length: percentile and Z score

Serum and stool samples will be stored and frozen for future analysis. Secondary analysis could include the effect of blood metabolome and stool microbiome on pancreatic function or absorption of CFTR modulators. A second informed consent will be obtained for participants willing to have the samples

added to the biorepository. Stored biospecimen will be deidentified to protect the confidentiality of the donor. The biospecimens will be saved indefinitely for future analysis.

Commitment to Health Equity

Our research project endeavors to uphold principles of equity, racial justice, diversity, and inclusion. By focusing on the impact of CFTR modulators on pancreatic function in individuals with cystic fibrosis (CF), we aim to address disparities in healthcare outcomes and access within the CF community. Our commitment to health equity is reflected in our inclusive study design, which aims to enroll participants of diverse racial and ethnic backgrounds and to consider the unique needs and experiences of individuals with CF. Through our research, we seek to advance understanding and improve outcomes for all individuals affected by CF.

Reporting of Adverse Events

Principal investigators and study personnel are responsible for identifying and assessing adverse events occurring during the study. Adverse events may be identified through participant reports, investigator observations, study assessments, or other means. Upon identification of an adverse event, study personnel will assess the severity, duration, causality, and any necessary medical interventions or follow-up required. Adverse events will be documented in the study records, including the date of occurrence, description of the event, severity grading (if applicable), and any actions taken. Serious adverse events related to the study will be reported to the IRB including hospitalizations from unrelated etiologies.

Protection of Human Subjects

In accordance with ethical principles and the protection of human subjects, the research team will review study data every 6 months to employ strategies to ensure the safety and well-being of participants. If a participant screens positive for the Hunger Vital Signs, the participant will be provided with a social work consultation or contact information for community resources. For the participants who discontinue Pancreatic Enzyme Replacement Therapy (PERT), close monitoring through questionnaire screening will be conducted every 3 months (+/- 28 days) and laboratory evaluation every 6 months (+/- 28 days) to detect any signs of malabsorption or nutritional deficiencies. Should participants manifest malabsorptive symptoms such as diarrhea, bloating, steatorrhea, or flatulence, discussion between the provider and participant will ensure regarding the potential resumption of PERT. Further, if participants exhibit poor weight gain, defined as falling below the fifth percentile for weight on standardized growth charts or experiencing a decrease in weight percentile of more than 2 major percentile lines, it is recommended to restart PERT. Similarly, PERT will be reinstated if participants present with repeat fecal pancreatic elastase levels below 200, indicating pancreatic insufficiency. Additionally, careful consideration for restarting PERT is advised if CFTR modulator drug become suboptimal after the discontinuation of PERT. In the event of recurrent acute pancreatitis, which is defined as more than one episode of acute pancreatitis separated by a period of symptom improvement, a discussion will occur between the provider and participant about restarting PERT. These safeguards are designed to prioritize participant welfare and uphold ethical standards throughout the study.

Study Withdrawal/Discontinuation

Participants who wish to withdraw from the study should inform the principal investigator or designated study personnel as soon as possible. Participants can withdraw from the study at any time without providing a reason. Upon notification of withdrawal, the participant will be provided with information regarding the implications of withdrawal and any potential consequences. Participants will be asked if they are willing to provide a reason for withdrawal to aid in study analysis and reporting. However, providing a reason is optional. If the participant agrees to provide a reason, study personnel will document the reason for withdrawal in the study records. Data collected from the participant up until the point of withdrawal will be retained and included in the study analysis unless the participant explicitly requests otherwise. If the participant requests the removal of their data, study personnel will comply with this request to the extent possible while adhering to ethical and regulatory guidelines. Participants who withdraw from the study may be contacted for follow-up to assess their well-being and to offer any necessary support or resources. If applicable, participants will be informed of any remaining obligations or procedures related to their withdrawal, such as returning study materials or discontinuing study-related interventions.

If a participant does not fulfill all the suggested study requirements, they may continue to remain enrolled in the study. However, it is important to acknowledge that incomplete participation may result in missing data. The research team will make every effort to encourage full participation and minimize missing data, but the continuation of the participant in the study despite incomplete adherence to the requirements is permitted. The potential implications of missing data on the study's outcomes will be carefully considered and documented in the final analysis.

Statistical Considerations

We aim to enroll 100 patients during the study based on current prevalence and projected enrollment into the study. If 10% of participants have pancreatic sufficiency and the sample size is 90 (81 with insufficiency, 9 with sufficiency), the power will be 80% to detect an effect size of 1.0.

We will first perform bivariate comparisons to determine which variables are associated with regaining pancreatic sufficiency. We will use Fisher's exact test to determine if categorical variables differ by pancreatic sufficiency status and either two-sample t-tests (normally distributed data) or Mann Whitney U-test (non-normal data) for continuous data. If there is an adequate number of cases of pancreatic sufficiency (10 or more cases), we will attempt to conduct a stepwise logistic regression with regained pancreatic sufficiency (yes/no) as the outcome and all significant variables from the bivariate regression as independent variables to identify a parsimonious model. We will perform regression analysis on the association between fecal elastase levels, hepatic function panel results, fat soluble vitamin levels, TDM levels, GI symptoms, demographic features, nutritional status, medication history, and past medical history.

Privacy/Confidentiality Issues

Data will be stored in a password-protected computer to ensure privacy. Patient identifiers, name, date of birth, and the medical record number, will be stored within RedCap which is to be password-protected. Upon downloading and distributing the data, the patient identifiers will be removed from the data set. Confidentiality is protected because no patient identifiers will be stored with the primary data set, and only one patient identifier will be documented during the study.

Follow-up and Record Retention

We anticipate the duration of this study to be 3 years and record retention for 6 years. Information may be archived on a password-protected hard drive at the conclusion of the study to facilitate future information retrieval if necessary.

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