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Change In The Expanded Digestive Symptoms Score Following An Increase In Pancreatic Enzymes

A. Study Purpose and Rationale

Exocrine Pancreatic Insufficiency (PI), defined as <100 µg/g in the stool, occurs in approximately 85% of cystic fibrosis (CF) patients.Signs and symptoms of PI include malabsorption, steatorrhea, bloating, pain, and flatus, which develop soon after birth. Poor nutritional status associated with untreated or insufficiently treated PI impairs growth, compromises pulmonary outcomes, weakens immune response, and shortens the life expectancy of CF patients. The use of oral pancreatic enzymes significantly improves the nutritional status of CF patients, which is closely linked to improvements in lung function. The use of oral pancreatic enzymes significantly improves the nutritional status of CF patients, which is closely linked to improvements in lung function. Pancreatic enzymes are typically a mixture of porcine-derived pancrelipase, which is a combination of three enzymes: lipase, amylase and protease. Current gastric acid-protected products are designed to release enzymes in the upper small intestine to aid digestion and improve nutrient absorption.

Most pancreatic enzymes were developed prior to current FDA regulations. However, there was noted to be great variability in enzyme content of various capsules. It was discovered that manufacturers were overfilling capsules to account for enzyme degradation. A side effect of pancreatic enzymes is fibrosing colonopathy and colonic strictures which tends to occur when patients are exposed to high-doses for long periods of time. FDA sought proper approval to attenuate these risks and required manufacturers to demonstrate efficacy and safety in randomized placebo-controlled trials. Many of these were completed in 2009 and 2010 and this lead to tighter controls and less variability in capsules.

Nonetheless, patients with PI continue to have gastrointestinal symptoms, including diarrhea, steatorrhea, bloating, and flatulence. A study that examined patients with cystic fibrosis and included those that were pancreatic sufficient found there to be no correlation between dose of pancreatic enzyme and symptoms. In their conclusion, however, they asked readers to find a more sensitive measure of effectiveness of pancreatic enzymes in order to guide therapy for pancreatic insufficiency.

I am interested in finding an alternative method, one that is clinically applicable and feasible, that may be able to help guide therapy. The gold standard for testing fecal fat is a 72 hour collection but this is incredibly cumbersome and difficult for the patient and/or guardians. In this study we will be using a routine fecal fat as a method of finding patients that might benefit from an increase in pancreatic enzymes. We will also be utilizing a recently developed, and currently being validated, scale to assess symptoms called the Extended Digestive Symptoms Scale to determine if symptomatically patients improve following the treatment change.

B. Study Design and Statistical Analysis

This study will be a two period randomized crossover trial measuring gastrointestinal symptomatology on the patient's current home regimen and following an increase in pancreatic enzyme dose.

Subjects will be patients aged 6-21 with Cystic Fibrosis (CF) who are also Pancreatic Insufficient (PI) confirmed by laboratory fecal elastase exam. They will be enrolled and consented during their annual visits. Participants will enter a “run-in” phase of the study to help account for compliance issues prior to enrollment in the study. During this phase, participants will be given the study medication, which is their current home dose of pancreatic enzymes distributed by the study pharmacy, for 7 days. Following the run-in phase, the participants will submit a baseline stool sample, which will be evaluated qualitatively for stool fat by ARUP laboratories, and will fill out a baseline survey of Gastrointestinal (GI) symptoms, The Expanded Digestive Symptoms Scale (EDSS), that is currently being validated. Patients will need to report compliance with the study medication during the previous week, have an elevated or abnormal stool fat, and a score representing at least mild GI symptoms on the EDSS to be included in the treatment phase and randomized. The treatment phase will consist of two periods of 1 week each. The participant will be randomized to the experimental group or the control group for the first week and then will cross over to the other arm for the second period. The experimental group will receive an increased dose of their pancreatic enzymes (rounded to the nearest appropriately dosed capsule). The control group will receive pharmacy medication but it will continue to be at their home dose (which will look by appearance to be more medication but will be partly placebo). Every day during the treatment phase, the patients will be sent an email reminding them to fill out an online GI symptom tracker. At the midpoint of the treatment phase, and again at the end of the treatment phase, patients will complete the EDSS and submit a random stool sample. At the conclusion of the study, patients will return to their home dose of pancreatic enzymes and will be free to have a discussion with their doctors regarding any changes to the current regimen.

The primary outcome in this study will be categorical: whether the patient’s symptoms improved or did not improve on the Expanded Digestive Symptoms Scale. A one sided chi-square test will be used to compare the distributions. It is unknown from previous studies how much of an effect, or decrease in symptoms, should be expected. In the control situation, the participants are still receiving their home dose of medication and patients may have relatively few complaints or GI symptoms. Given this assumption I am hoping to see at least a 30% effect. Additionally, given the fact that submitting a stool sample is not always easy, I will be powering this study to show at least a 10% change. The study uses a crossover design and patients will be their own controls so I have calculated that at least 36 patients will needed to be enrolled in the study.

Secondary outcomes are improvements in symptoms as noted on the GI Symptom Tracker and the results of the stool fats following the two periods in the treatment phase.

C. Study Procedure.

Three times during the study the participant will be asked to collect a random stool sample. They will be given the materials necessary to collect the sample in the comfort of their home and will return it to clinic.

The participants will fill out the Expanded Digestive Symptoms Scale three times during the study. If the patient is between the ages of 6-11 an interviewer will assist them with the survey. The questions on the survey are not unlike those that would be asked at a typical patient encounter in which abdominal symptoms are being discussed.

The participant will also be reminded by daily email to complete an online Daily symptom tracker which will record daily GI symptoms.

D. Study Drugs
Pancreatic Enzymes have been approved for use in patients with malabsorption due to pancreatic insufficiency. This is standard care for patients with malabsorption. Patients will be continued on their home dose during the run-in phase of the study and during the treatment phase will be randomized to continue to receive their home dose or dose increased by one appropriately sized capsule per meal and with snacks.

A known side effect of the medication is fibrosing colonopathy and colonic strictures which are infrequent and have been observed in patients receiving large doses of the medication over long periods of time.

E. Medical Device.
No medical devices will be used.

F. Study Questionnaires
The Expanded Digestive Symptoms Scale is currently being completed and validated. The questionnaire will discuss gastrointestinal symptoms such as abdominal pain, cramping, nausea, vomiting, diarrhea, constipation, steatorrhea, stool frequency, and incontinence and will be validated for the use of subjects from age 6-21.

G. Study Subjects
Inclusion criteria are as follows:
- Parents must submit written consent and patients must submit written assent.
- Participants must have Cystic Fibrosis and Pancreatic Insufficiency as demonstrated by fecal elastase measurement.
- Must be using pancreatic enzymes to help treat the malabsorption from the Pancreatic Insufficiency.
- After the run-in phase, only patients with an elevated fecal fat will be included.
- After the run-in phase, patients must have at least mild symptomatology as denoted on the EDSS.

Exclusion criteria are as follows:
- Patients <6 or ≥22 years old.
- Patients with current pulmonary exacerbation.
- Patients with fevers, vomiting, severe abdominal pain.
- Patients with allergy to pork derivatives or to the pancreatic enzymes.
- Patients already receiving the maximum dose of pancreatic enzymes.

H. Recruitment of Subjects
The pulmonary department will be made aware of the study and potential subjects will be identified by their physicians and enrolled in a rolling fashion at their regularly scheduled visits.

I. Confidentiality of Study Data
Participants in the study will be given a unique identifier and all of their identifying information will be coded and safeguarded to protect their confidentiality. All study data will be kept in a locked and secured cabinet accessible only to the investigators.

J. Potential Conflict of Interest
There is no conflict of interest to report.

K. Location of the Study

The study will take place at Morgan Stanley Children's Hospital of New York.

L. Potential Risks
Potential risks to the participant include side effects of the medication which include fibrosing colonopathy and colonic strictures. This risk is mitigated as patients will be screened and excluded if they are already receiving maximal dosages of the medication.

M. Potential Benefits
Participants may benefit from the increased dose of pancreatic enzyme and following the study will be able to discuss with their physician the possibility of increasing the dose appropriately.

A potential benefit to the community is a better understanding of how to appropriately titrate the dose of pancreatic enzymes in patients with GI symptoms.

N. Alternative Therapies
It is standard therapy to be prescribed pancreatic enzymes in patients with pancreatic insufficiency.

0. Compensation to Subjects
Participants will not be compensated for participation in this study.

P. Costs to Subjects
Participants will not incur any costs during this study.

Q. Minors as Research Subjects
The study will be primarily enrolling minors as research subjects. Parental consent will be obtained and participant assent will be obtained prior to enrollment.

R. Radiation or Radioactive Substances
There will be no radiation or radioactive substances used in this study.

References: