

Pancreatic Enzyme Replacement
Therapy for treatment of Exocrine
Pancreatic Insufficiency in Patients with
Unresectable Pancreatic Cancer

NCT02985801

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IRB Minimal Risk Protocol Template

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General Study Information

Principal Investigator: Massimo Raimondo, M.D.

Study Title: Pancreatic Enzyme Replacement Therapy for treatment of Exocrine Pancreatic Insufficiency in Patients with Unresectable Pancreatic Cancer

Protocol version number and date: version 5, 5/15/2018

Purpose

Hypothesis:

Pancreas enzyme replacement therapy (PERT) decreases weight loss and improves quality of life in patients with unresectable pancreatic cancer.

Aims, purpose, or objectives:

1. Assess prevalence of pancreatic exocrine insufficiency (PEI) with fecal elastase-1 test (FE1) in patients with unresectable pancreatic cancer, without evidence of pancreatic duct (PD) or common bile duct (CBD) obstruction based on MRI or / and EUS.
2. Patients with PEI (FE1 <200) receive Pertzye or placebo in a cross-over fashion, each for 4 weeks. 3 capsules are taken with or after meals and 2 capsules with or after snacks (approximating 500 lipase units/kg/meal).

3. Body weight, body mass index (BMI), body composition (Bodystat Bioimpedance), are measured at the time of diagnosis of PEI and at 4 and 8 weeks of cross-over treatment. Baseline measurement of Vitamin D-25, Vitamin A, iron (ferritin, TIBC, iron), Vitamin B12, Tissue transglutaminase IgA (tTG) with total Immunoglobulin A (IgA)
4. Quality of Life (pain, diarrhea, weight, bloating, etc.) assessed at 0,4,8 weeks with
 - a.
 - b. Functional Assessment (FACT-Hep) for physical, social, emotional, and functional QOL²

Background

Pancreatic exocrine insufficiency (PEI) is a known complication of pancreatic cancer. Several mechanisms of PEI have been described in context of pancreatic cancer, including pancreatic atrophy secondary to tumor induced pancreatic duct obstruction and pancreatic fibrosis, both leading to PEI in patients with unresectable pancreatic cancer.³

Although the majority of patients with pancreatic cancer are inoperable at the time of diagnosis, only few authors addressed PEI in this patient cohort. Small studies with 8 to 12 patients detected PEI in 75% to 100%. The prevalence of PEI tended to be higher in setting of significant pancreatic duct obstruction.^{4,5} The largest cohort study included 194 patients with advanced pancreatic cancer which was defined as metastatic or unresectable due to local invasion. 50% of study participants had PEI.⁶ As a next step, Sikkens et al prospectively assessed the progression of PEI in 32 patients with unresectable cancer of the pancreatic head region. Based on FEI testing, 67% of patients had PEI at the time of pancreatic cancer diagnosis and 89% at 2 months follow up (median).⁷

Despite a high prevalence of PEI in patients with unresectable pancreatic cancer, clinical symptoms like steatorrhea are not uniformly present. In fact, 2 hallmark studies, including one with 12 and one with 194 patients, found no statistically significant correlation between the dyspepsia, number of bowel movements on the one hand and the presence of fat malabsorption on the other hand in patients with unresectable pancreatic cancer. Only 16.7% of patients with very severe PEI had clinically evident steatorrhea, whereas 5.2% of patients had subjective steatorrhea without PEI.^{5,6} Weight loss is another well-known complication of pancreatic cancer. Perez et al. who found a significant correlation between fat-protein malabsorption and weight loss in non-surgical patients with pancreatic cancer however not between diminished caloric consumption and weight loss.⁵

As of now, multiple studies showed improved fat absorption with pH-sensitive microsphere formulation in comparison to conventional pancreatic enzyme preparations or placebo in chronic pancreatitis patients with PEI.⁸⁻¹⁴ However, only few studies addressed the utility of PERT for patients with inoperable pancreatic cancer, including a randomized study by Bruno et al. with 21 patients with unresectable pancreatic cancer and pancreatic duct obstruction. Patients randomized into PERT for 4 weeks had reduced weight loss compared with patients who were treated with placebo.¹⁵ A retrospective study by Domínguez-Muñoz et al. included 76 patients with inoperable pancreatic cancer. Patients who received PERT (Creon[®]) had a longer median survival than patients with palliative therapy alone.¹⁶ Of note, PEI was not formally assessed in either of those studies. Based on these limited results current pancreatic cancer guidelines recommend PERT for patients with unresectable pancreatic cancer, in the realm of palliative therapy.¹⁷ However the efficacy of PERT in patients with unresectable pancreatic cancer was never proven in a randomized controlled trial.

A further concern is the adverse drug reaction profile of PERT. In adult population no severe side effects of PERT are documented. Hyperuricosuria and especially colonic fibrosis are the most feared severe adverse drug reaction (ADR) of long term PERT, however they were reported only in children with cystic fibrosis.^{18,19, 20,21}

However dyspepsia, heartburn and bloating are well described mild ADR of PERT. In this context, several randomized controlled trials revealed a higher incidence of bloating and abdominal pain in patients who received PERT for PEI for mostly benign pancreatic conditions.^{21,22,23,24} The impact of ADR on the quality of life was never assessed in a randomized controlled fashion in patients with unresectable pancreatic cancer. Finally, the high costs of PERT, which range up to \$2000 a month, emphasize the importance to clarify the pros and cons of PERT for patients with unresectable pancreatic cancer, to avoid unnecessary and costly treatments.

Subject Information – charts, records, images, or specimens are considered ‘subjects’

*Target accrual is the proposed number of subjects to be included in your study at your site. “Subjects” may include Mayo Clinic charts, records, or specimens, **and/or** charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application:*

Target accrual:
30 completed patients

Subject population:

Inclusion Criteria:

- Patients 18- 100years
- Underlying pancreatic adenocarcinoma, unresectable (local invasion or distant metastasis)
- On established chemotherapy regimen for pancreas cancer, which will be continued over the time of study
- Fecal elastase-1 test (FE1) less than 200 mcg pancreatic elastase/g stool

Exclusion Criteria:

- Common bile duct obstruction resulting in obstructive jaundice
- Celiac disease
- Crohn’s disease
- Benign pancreatic conditions
- Bowel obstruction
- Surgically altered bowel anatomy

Yes No Will a Certificate of Confidentiality (COC) be obtained from NIH? If yes, Who is obtaining the COC: Mayo Clinic investigator, study sponsor, other:
Explain why a COC is needed:

Study Design

Methods:

Patients with unresectable pancreatic adenocarcinoma (local invasion or distant metastasis) receive pancreatic enzyme replacement therapy (PERT) by the oncology team as presumed standard of care. Patients will be offered to participate in study, which lasts 10 weeks.

Pancreatic enzyme insufficiency (PEI) will be detected by (fecal elastase-1) FE1 testing. Patients with FE1 less than 200 mcg pancreatic elastase/g stool are eligible for study. Patients will be randomized into first placebo or first treatment group (cross over study) by enclosed envelope.

Patients will received either Pertzye (Pancrelipase) 500 lipase units/kg/meal or placebo, each for 4 weeks. Dosing will be 3 capsules 3 times a day with or after meals and 2 capsules with or after snacks. No treatment will be administered at weeks 5 and 6 to assure adequate washout. Pertzye or placebo will be given for another 4 weeks (week 7 - 10) in a cross-over fashion.

Body weight, body mass index (BMI), body composition (Tanita, TBF-310GS, Bodystat Bioimpedance), FACT-Hep quality of life assessment will be measured at randomization and at last day of treatment or placebo (week 4 and 10).

Resources:

Patients will be recruited in oncology or gastroenterology clinic by oncology fellow or gastroenterology fellow in the setting of their regular clinical work.

Pertzye and placebo will be sponsored by pharmaceutical company.

Check all that apply. If none apply, leave blank:

- This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:
- Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement.*
- This study is to establish and/or maintain an ongoing database or registry for research purposes only.
- The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.
- The study involves photographing, audiotaping or videotaping subjects (and guests).

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset.

Check all that apply:

- This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

This study involves only data and/or specimens that will be collected after submission to the IRB.

The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained. When appropriate, check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol.*

IRB Number/s - Data Only: _____

IRB Number/s - Specimens Only: _____

IRB Number/s - Data and Specimens: _____

Note: When subjects provided consent for use of their data and/or specimens, as described in this protocol.

Other data sources will be utilized in this study, e.g. receiving data/specimens from an external party. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. **NOTE:** Identifiers apply to subjects enrolled in your study and to the subject’s relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.

External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS Check all that apply	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	x	
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	x	

Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	x	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. Note: Recording a year only is not a unique identifier.	x	
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	<input type="checkbox"/> None	<input type="checkbox"/> None

Statistical Information

Statistical Considerations

Data Analysis Plan and Power Statement:

Statistical significance will be calculated with pair t-test.

According to Bruno et al and Dominguez-Munoz et al a 5% weight difference between the treatment groups is expected within 4 weeks. Standard deviation is expected to be less than 5% based on the cross over fashion. Assuming a patient drop out of 30%, a minimum of 13 patients need to be included in the trial to detect a statistically significant difference, with a power of 80% and alpha error of 5%. Eventually, we target to include 30 patients to assure adequate power, given the statistical limitations of previously reviewed studies.

Endpoints

Primary:

1. Weight change

Secondary:

1. Quality of life (QOL)
2. Change in body composition

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