Pancreatic enzyme supplementation

Pancreatic enzyme replacement therapy in cystic fibrosis

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Background

Exocrine pancreatic insufficiency (EPI) is diagnosed by low levels of measured fecal pancreatic elastase-1 (<100 µg/g stool) and occurs in 85-90% of patients through their life. Pancreatic damage begins in utero and continues into infancy or early childhood when complete loss of pancreatic acinar tissue occurs. EPI leads to malabsorption of nutrients as fat, protein and carbohydrates and liposoluble vitamins A, D, E and K. Untreated EPI during infancy and childhood quickly results in malnutrition, delayed growth and loss in body weight in adults. In both children and adults with CF, persistent malnutritional status is associated with poorer general health, more severe pulmonary disease and shorter life expectancy. While salivary amylase and gastric pepsin may contribute to the digestion of carbohydrates and proteins, respectively, lingual and gastric lipases are minor contributors to fat digestion.

EPI occurs when postprandial enzyme output is ≤10% of normal. Enzyme preparations need to be taken whenever food is taken, and the dose needs to be adjusted according to the lipid content of each meal.

Pancreatic enzyme replacement therapy (PERT) has been the mainstay for patients with CF and EPI, but the current therapy with exogenous pancreatic enzymes must be further refined. Several factors, including reduced pancreatic bicarbonate secretion, reduced bile acid secretion, increased gastric acid secretion and abnormal gastrointestinal motility may impact on the efficacy of PERT in CF patients. Recently, it has been reported that in CF pigs models proinflammatory, complement cascade, proapoptotic, and profibrotic pathways may contribute to progression of pancreatic disease, regardless of pancreatic replacement therapy.

Available porcine-derived pancreatic enzyme products contain all the 3 main groups of active enzymes, namely lipase, amylase and protease, that normally act only when the pH exceeds 5.5 within the duodenum. They are denatured by pepsin and gastric acids, so PERT is usually administered as enteric-coated preparations to prevent inactivation in the stomach and the upper small intestine.

Management of EPI by PERT can be rarely complicated by several factors as unavailability of preparations for infants and young children, side effects such as abdominal pain, perianal irritation, constipation, hyperuricemia and hyperuricosuria and, occasionally, complications such as fibrosing colonopathy when larger doses of PERT have been proposed.

Several objectives have been addressed:

- the use of oral pancreatic enzyme products (PEPs) significantly improves the nutritional status of CF patients;
- PERT is closely linked to improvement in lung function, as well as to increased life expectancy;
- supplementation with PEPs at meals and snacks is the mainstay of therapy for EPI;
- current gastric acid-protected porcine-derived products are designed to release enzymes in the upper small intestine to aid digestion and improve nutrient absorption;
- among currently marketed PEPs for PI, great variability in the amount of enzymes included in each capsule is available, due in part to the manufacturer practice of overfilling capsules to account for enzyme degradation that occurs over the course of the product’s shelf life;
- variability in the product enzyme content can lead to inconsistent therapeutic effects by either providing too much or too little of the required enzymes, which may lead to the suboptimal treatment of patients with CF and EPI.

Data from a randomised double blinded cross over trial in adolescents with CF and EPI showed that PERT markedly attenuates postprandial hyperglycaemia by slowing gastric emptying and augmenting incretin hormone secretion.

There is insufficient evidence to make a recommendation regarding the association of specific PERT dosing and CFA% on growth. Consensus-based guidelines can be used for care. These include dosage as either 500 to 2,500 lipase units/Kg/meal and 10,000 lipase units/Kg/day or 4,000 lipase units/gram dietary fat/day.

More recently, consensus guidelines developed by an international multidisciplinary working group, in accordance with officially accepted standards reviewed by ESPGHAN and ECFS, suggest supplementation with pancreatic enzyme lipase according to age and dietary fat.

Issues

1. To evaluate the efficacy and safety of PERT in children and adults with CF by registering primary outcomes as changes in nutritional status, and secondary outcomes as bowel symptoms, days in hospital, quality of life, any adverse events attributed to PERT as fibrosing colonopathy, fecal fat excretion or coefficient of fat absorption (CFA%), lung disease (number of exacerbations requiring oral or intravenous antibiotics, FEV1 and FVC rate of decline);
2. To compare the efficacy and safety of different formulations of PERT and their appropriateness in different age groups;
3. To compare the effects of PERT in CF according to different age groups and different stages of pancreatic function;
4. To evaluate adherence to pancreatic enzyme supplementation.

What is known
A systematic review on the efficacy and safety of PERT is needed to define dose and choice of supplements, according to assessment of pancreatic function and treatment starting time.

1 CDSR (Somaraju Usha Rani, 2016) included one parallel trial and 12 cross-over trials of 512 children and adults with CF. The number of participants in each trial varied between 14 and 129. All the included trials had a duration of four weeks. No combined data could be detected from all the trials as they compared different formulations. Findings from individual studies provided insufficient evidence to determine the size and precision of the effects of different formulations. A few studies reported information on the review’s primary outcome (nutritional status). No conclusive data could estimate gain in body weight when considered as an outcome. Combined data from the same studies gave statistically significant results favouring enteric-coated microspheres over enteric-coated tablets on secondary outcomes as stool frequency, abdominal pain and fecal fat excretion.

There is limited evidence of the benefit from enteric-coated microspheres when compared to non-enteric coated pancreatic enzyme preparations up to one month. There is no evidence on the long-term effectiveness and risks associated with PERT. There is also no evidence on the relative dosages of enzymes needed for people with different levels of severity of EPI, as well as to define the optimum time to start treatment and variations based on differences in meals and meal sizes.

A DARE (Taylor Jr, 2010) included a total of 12 manuscripts. Most studies (10/12) compared pancreatic enzyme supplements that used different delivery systems, while using similar quantities of enzymes. These studies found no consistent difference in fat malabsorption or gastrointestinal symptoms between different active treatments. Two small placebo-controlled trials (65 enrolled patients) demonstrated that pancreatic enzyme supplements are superior to placebo on fat absorption. Data are inadequate to determine whether pancreatic enzyme supplements lead to weight gain or improvement in diarrhoea.

Many trials have been performed and nearly all completed. Several clinical trials have focused on new formulas with mainly different doses and to verify their efficacy and safety:

- A RCT study (NCT00432861) conducted to compare the efficacy of enteric coated pancrelipase with bicarbonate (Pancrecarb) capsules versus placebo followed by a 72-h stool collection employing an ingested stool dye marker. Mean coefficient of fat absorption with EC-bicarbonate-buffered PERT was 82.5% compared with 46.3% with the placebo. Similar improvements in nitrogen absorption were observed. Overall stool frequency and stool weight decreased (p<0.001) (Konstan MW et al, 2013);
- 1 trial (NCT01427725) aimed at collecting the information related to the safety and effectiveness in CF patients with EPI, receiving the treatment with LipaCreon in order to evaluate the effective and safe use on the long term;
- 3 clinical trials (Trapnell BC et al, 2011, Konstan MW 2010 et al, Graff GR et al, 2010) have been published related to the evaluation of efficacy and safety of new formulations of pancrelipase (MT20, Pancreacea, Pancrelipase MT);
- 1 trial (NCT00880100), ended in 2011, aimed to assess the efficacy of Panzytrat™ 25.000 compared to Creon 25.000 in the control of steatorrhea in CF with EPI;
- a multicenter, randomized, open-label, crossover study to evaluate the mode of administration and safety of EUR-1008 in infants 1 to 12 months of age with CF and PA was completed in 2011;
- a multicenter, explorative phase IIb study (NCT00880100) designed to assess the efficacy of Ultrace MT12 in the control of steatorrhea and clinical signs and symptoms of malabsorption in CF children (2-6 years) with EPI was completed in 2010;
- a completed randomised, double-blind, active-controlled, two-treatment, crossover, multinational, multicentre study (NCT1641939) compared two pancreatic enzyme products (EUR-1008 25.000 Units and Creon 25.000 Units) in the treatment of EPI in subjects with CF;
- a randomized, double-blind, multicenter, two-period crossover study (NCT01710644) to assess the efficacy and tolerability of NM-BL (Burluplase) in patients with CF and EPI compared to placebo, where the primary variable is the coefficient of nitrogen absorption (CNA%), has been completed in USA;
- a parallel-study group (NCT02579498) has been completed and provided additional efficacy and safety data of Liprotamase, a non-porcine, soluble and stable mixture of three digestive enzymes, including lipase, protease, and amylase compared to approved, porcine-derived, enterically-coated and encapsulated PERT, as the change in the GFA in CF patients with EPI;
- a double-blind, randomized, multicenter, cross-over study to compare the effect of Creon N and Creon® on fat absorption; 83/96 patients randomized into 2 treatment sequences (APT/KREON or KREON/APT) that completed the study demonstrated both non-inferiority and equivalence to KREON in fat absorption. APT demonstrated safety and tolerability similar to KREON.

Based on data from randomized cross-over trials, pancreatic enzyme supplements appear to improve fat malabsorption. No specific branded product or specific delivery system is superior for treatment of fat malabsorption in patients with EPI. The MyCyFAPP project (Calvo-Lerma J et al, 2017), an European study that aims at developing specific tools for improvement of self-management, assesses nutritional status, daily energy and macronutrient intake, and PERT dosing with reference to new guidelines. Findings of this study document the lack of a general criterion to adjust PERT and suggest the potential benefit of educational and self-managerial tools to ensure adherence to therapies.

**Unresolved questions**

Longer-term studies are probably needed to more adequately assess the effects of PEPs on important outcomes for patients such as...
quality of life and compliance.

A cross over randomized clinical study (NCT03551691) recruiting 24 participants with CF and pancreatic insufficiency >12 years of age is ongoing to evaluate changes in fat malabsorption using the coefficient of fat absorption (CFA) as the primary endpoint in subjects who are on and off treatment with a PPI in addition to PERT. Further duodenal power of hydrogen (pH) will be evaluated while on and off acid suppression, and the malabsorption blood test (MBT) will be used to characterize changes in fat absorption. Changes in nutritional status (weight, height, BMI), clinical GI symptoms, and quality of life in subjects treated with PPI vs. placebo will be registered.

**Keywords**

Failure to Thrive; Malabsorption; Malnutrition; Nutrition Disorders; Pancreas insufficiency; Pancreatic Enzyme Replacement Therapy; Supplementation;