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% of patients with Cystic Fibrosis (CF) 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, growth failure 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. The current therapy with exogenous pancreatic enzymes has been recently refined (Karnik NP, Ja, 2021). 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. In the past (Abu-El-Hajja M, 2012) 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 such as unavailability of preparations for infants and young children; side effects are occasionally described such as abdominal pain, perianal irritation, constipation, hyperuricemia and hyperuricosuria and fibrosing colonopathy when larger doses of PERT have been proposed.

Over the past years several objectives have been addressed:

- current gastric acid-protected porcine-derived products are designed to release enzymes in the upper small intestine to aid digestion and improve nutrient absorption;
- supplementation with PEPs at meals and snacks is the mainstay of therapy for EPI;
- the use of oral pancreatic enzyme products (PEPs) significantly improves the nutritional status of patients with CF;
- 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;
- PERT is closely linked to improvement in lung function, as well as to increased life expectancy.

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. On average the dosage is between either 500 to 2,500 lipase units/Kg/meal and 10,000 lipase units/Kg/day and 1500-3,000 lipase units/gram dietary fat/day.

More recently, consensus guidelines developed by an international multidisciplinary working group (Turk D et al, 2016), in accordance with officially accepted standards reviewed by ESPGHAN and ECFS, suggest supplementation with pancreatic enzyme lipase according to age and dietary fat.

There are several brands, strengths and preparations of PERT available (Ritvieu ME et al, 2023), no well-defined standard dose for PERT, and doses should be individualized. The international guidelines aim to keep lipase dose below 10,000 units/kg/day and correlate it with the meal’s fat content. Doses will be adjusted based on gastrointestinal symptoms, weight gain, and growth. Otherwise, PERT is considered effective and well-tolerated in children with CF.

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 including 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;
5. to evaluate impact of timing of PERT on gastrointestinal symptoms.
What is known

Regarding the last issue one CDSR evaluated timing of PERT.

1 CDSR (Ng C, et al 2021) found no studies that met the eligibility criteria to evaluate the timing of pancreatic enzyme replacement therapy (PERT) in CF. The excluded studies were either cross-over in design (but lacking a sufficient washout period between treatments) or did not assess the timing of PERT. The authors were unable to determine whether one dosing schedule for PERT is better than another since we identified no eligible RCTs. Further research is needed to fully evaluate the role of dosing schedules for PERT in fat absorption. Research should also establish reliable outcome measures and minimal clinically important differences. While RCTs with a cross-over design may have advantages over a parallel group design, an adequate washout period between intervention periods is essential.

1 CDSR (Somaraju UR, 2020) included 14 trials (641 children and adults with CF) with the aim of evaluating types and duration of PERT: two were parallel trials and 12 were cross-over trials. Interventions included different enteric and non-enteric coated preparations of varying formulations in comparison to each other. The number of participants in each trial varied between 14 and 129. 13 trials were for a duration of four weeks and one trial lasted seven weeks. The quality of the evidence ranged from moderate to very low. Authors could not combine results from the trials as they compared different formulations and the findings from individual trials provided insufficient evidence to determine the size and precision of the effects of different formulations. This review concluded for a limited evidence of benefit from enteric-coated microspheres when compared to non-enteric coated pancreatic enzyme preparations up to one month.

Regarding the second issue one CDSR was performed.

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 across the trial. Combined data from the same studies gave statistically significant results favouring enteric-coated microspheres over enteric-coated tablets on secondary outcomes as control on stool frequency, abdominal pain and fecal fat excretion.

A systematic Cochrane Review of the timing of pancreatic enzyme replacement therapy (PERT) in CF (Ng C, et al 2021) included 10 studies for eligibility of 269 references. Of these 10 studies, four cross-over studies had insufficient washout periods and five studies did not assess PERT timings RCTs. The aim was to compare PERT regimens pre-specifying different administration timings (e.g. before, during or after a meal) in any dosage (dose/kg body weight or dose/g ingested fat or any other strategy) or formulation to 'standard of care' or 'dietitian advice' in individuals of all ages with CF, with a confirmed diagnosis of CF by genotype or sweat chloride testing, with and without PI. Primary outcomes have been fat malabsorption (absolute CFA based on 72hour stool collection); nutritional status (change from baseline); weight in kg, % of predicted weight or z score; height in cm, % of predicted height or z score; BMI, % of predicted BMI or z score; adverse events. Mains results point out the large variations between different centres and treatment schedules.

An open randomised controlled cross-over trial (Raun AMT, 2022) has been performed in order to evaluate whether GI symptoms in CF could be related to the timing of pancreatic enzyme replacement therapy. 30 participants aged 0-17 years were randomised to four weeks of PERT prior to meals followed by four weeks of PERT after meals and vice versa. Subjects were divided in blocks of four and stratified by gender (male/female) and age (0-7; 6-11 years and 12-17 years). There was no wash-out period since the effect of PERT is expected to peak at 30 min after ingestion and tail off within two hours. Using the CF-specific validated CFAbd-Score, abdominal pain, dysfunctional bowel habits and Quality of Life (QoL) related to GI symptoms were assessed in relation to the timing of PERT. No significant difference regarding abdominal pain, bowel habits or QoL related to GI symptoms were registered when timing of PERT was changed from prior to after meals.

In order to assess correlation of PERT dose to GI symptoms in adult patients with CF in a cross-sectional study performed at the Copenhagen CF Centre, PERT intake, gastrointestinal (GI) symptoms and the use of concomitant treatments were registered by 120 participants (median age of 32.9 years, 46% women and 72% F508delta homozygote). Linear regression correlated PERT dose per kg body weight (U-lipase/kg). The PERT dose ranged from 0 to 6160 U-lipase/kg per main meal (mean 1828; SD 1115). The PERT dose was associated with participants’ sex (men vs. women: 661; 95% CI: 302; 1020 U-lipase/kg), age (-16; 95% CI: -31; -1 U-lipase/kg per kg), Participant with less frequent constipation and being lung transplanted assumed a higher PERT dose. A third of participants that did not take PERT for snacks, had increased diarrhoea. These findings indicate that PERT intake may be improved to reduce GI symptoms (Olsen MF, et al 2022).

A RCT (Stallings VA, 2020) investigated fat malabsorption and growth in children (n=66) with CF and EPI treated with a novel readily oral absorbable structured lipid supplement. At baseline and 3-month evaluations, CFA (72-hour stool, weighed food record) and height (HAT), weight (WAZ) and BMI (BMIZ) Z-scores were calculated. Fasting plasma fatty acid (FA) concentrations were also measured. Results after 3 months of treatment showed that subjects with CF, PI and more severe fat malabsorption experienced greater improvements in CFA, FA and growth after three months of treatment. This new oral supplement was safe, well-tolerated and efficacious in patients with CF and PI with residual fat malabsorption and improved dietary energy absorption, weight gain and FA status in this at-risk group.

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

[Refer to the original document for the full content]
● RCT study (NCT0432961) was 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 2019 et al, Graff GR et al. 2010) have been published related to the evaluation of efficacy and safety of new formulations of pancrelipase (MT20, Pancreaze, Pancrèpsiae MT);

● 1 trial (NCT00881000), 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 was conducted to evaluate the mode of administration and safety of EUR-1088 in infants 1 to 12 months of age with CF and PA was completed in 2011;

● a multicenter, explorative phase IIb study (NCT02880100) designed to assess the efficacy of UltraSeal 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 (NCT1641393) compared two pancreatic enzyme products (EUR-1088 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) performed for assessing the efficacy and tolerability of NM-BL (Burlulipase) 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 double-blind, randomized, multicenter, cross-over study to compare the effect of Creon N and Creon® on fat digestion in subjects ≥12 years of age with EPI due to CF (NCT02137382) has been completed;

● a phase II, multicenter, parallel-group, active-controlled, randomized, double-blind, dose-ranging study to evaluate the efficacy, 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;

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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 protocol 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 while suggest the potential benefit of educational and self-managerial tools to ensure adherence to therapies.

In a recent 24h-pilot study performed in 43 patients faecal pH has been used as a surrogate biomarker to monitor the efficacy of pancreatic enzyme replacement therapy in order to explain whether lower values of intestinal pH may justify why pancreatic enzyme replacement therapy is not completely effective in all patients with malabsorption related to CF (Calvo-Lerma J et al. 2021).

Recently a systematic search was performed in order to identify studies reporting measures of the exocrine pancreas in humans treated with CFTR modulators. Of 630 identified studies, 41 reported baseline and on-treatment assessments. CFTR modulators reduced acute pancreatitis events by 85% overall (rate ratio 0.15, 95% confidence interval (CI) 0.04, 0.52), with a greater effect registered in the subgroup with pancreas sufficient CF (PS-CP) (rate ratio 0.13 (95% CI 0.03, 0.53). Among 293 subjects with baseline and on-treatment evaluation of pancreas sufficiency, 253 were pancreas insufficient at baseline and 54 (21.3%) converted to pancreas sufficiency. Of 32 subjects with baseline FE-1 values <200 mcg/g, 16 (50%) increased to ≥200 mcg/g. Serum trypsin decreased by a mean of 565.9 ng/mL (standard deviation (SD) 311.8), amylase decreased by 38.2 U/L (SD 57.6), and lipase decreased by 232.3 U/L (SD 247.7) (Ramsey ML et al. 2023).

Unresolved questions

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. 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.

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.

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of enzymes needed for people with different levels of severity of pancreatic insufficiency, optimum time to start treatment and variations based on differences in meals and meal sizes. There is a need for a properly designed trial that can answer these questions.

In the new era of CFTR modulator therapies it has been hypothesized that timing of treatment initiation with modulators may prevent EPI and malnutrition allowing to advance in understanding pancreatic pathophysiology (Ritivosi ME et al., 2023) (Ramsey ML et al., 2023). Further clinical studies are needed.

Keywords

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