**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, delayed growth and loss in body weight in adults. In both children and adults with CF, persistent malnuritional 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 carboydrates 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. In the past, (Abu-El-Haija 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 such as abdominal pain, perianal irritation, constipation, hyperuricemia and hyperuricosuria and, occasionally, complications such as fibrosing colonoopathy when larger doses of PERT have been proposed.

Over the past years several objectives have been addressed:

- the use of oral pancreatic enzyme products (PEPs) significantly improves the nutritional status of patients with CF;
- 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, this is 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 (Perano SJ, 2014) 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 (Kalina D et al, 2012).

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.

**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.

**What is known**
1 CDSR (Somaraju UR, 2020) included 14 trials (641 children and adults with CF): 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 data 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. In the only comparison where combine any data were compared, the fact that these were cross-over trials is likely to underestimate the level of inconsistency between the results of the trials due to over-inflation of CIs from the individual trials. 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 pancreatic insufficiency, optimum time to start treatment and variations based on differences in meal and meal sizes. There is a need for a properly designed trial that can answer these questions.

An RCT (Stallings VA, 2020) investigated fat malabsorption and growth in children (n=66) with cystic fibrosis and pancreatic insufficiency (PI) 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 (HAZ), 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.

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 protocol (Yip C, 2019) is ongoing in order to revise dosing regimens for pancreatic enzyme replacement therapy (PERT) in C. It will include RCTs, also covering cross-over RCTs with a minimum washout period of two weeks, quasi-RCTs if baseline characteristics of intervention groups are similar. Participants will be individuals of all ages with CF, with a confirmed diagnosis of CF by genotype or sweat chloride testing, with and without PI. The following interventions will be evaluated: regimens prespecifying 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 of PERT. Primary outcomes will be fat malabsorption (absolute CFA based on 72-hour 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.

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 delivery 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 of PERT. Primary outcomes will be fat malabsorption (absolute CFA based on 72-hour 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.

- a RCT study ([CCT00432861](#)), conducted to compare the efficacy of enteric coated pancreatic lipase with bicarbonate (Pancrecarbi) 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 ([CCT01427725](#)) 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 ([Trappell BC et al, 2011](#), [Konstan MW 2010](#) et al, [Graft GR et al, 2010](#)) have been published related to the evaluation of efficacy and safety of new formulations of pancrelipase (MT20, Pancreaze, Pancrelipase MT);
- 1 trial ([CCT00980100](#)), ended in 2011, aimed to assess the efficacy of Panzytral™ 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-1008 in infants 1 to 12 months of age with CF and PA was completed in 2011;
- a multicenter, explorative phase IIb study ([CCT08880100](#)) designed to assess the efficacy of Ultrase MT12 in the control of steatorrhea and clinical signs and symptoms of malabsorption in CF children (2-6 years) with PI was completed in 2010;
- a completed randomised, double-blind, active-controlled, two-treatment, crossover, multinational, multicentre study ([CCT1641393](#)) 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) 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 parallel-study group (NCT022794988) 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 CFA in CF patients with EPI;
● 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 (NCT02137388) has been completed;
● a phase II, multicenter, parallel-group, active-controlled, randomized, double-blind, dose-ranging study to evaluate the efficacy and safety of different doses of Creon Immediate Release (IR) in subjects with EPI due to CF (NCT02415959) with the objective to assess the efficacy and safety of different doses of Creon IR in comparison to Creon® 25,000 Delayed Release/Gastro-Resistant (DR/GR) has been completed;
● a randomized double-blind (withdrawal) phase 3 study to evaluate the efficacy and tolerability of pancrelipase MT capsules compared with placebo in the treatment of subjects with CF (EUCTR2015-001219-11);
● a randomized, double-blind, multicentre, multinational, active-controlled, randomized, double-blind, dose-ranging study to evaluate the efficacy and safety of different doses of Creon in patients >12 years with CF was conducted. The primary efficacy endpoint was the coefficient of fat absorption over 72 hours at the end of each period. In 83/96 patients randomized into 2 treatment sequences (APT/KREON or KREON/APT) that completed the study APT demonstrated both non-inferiority and equivalence to KREON in fat absorption. APT demonstrated safety and tolerability similar to KREON.
● A phase 2 Trial to Assess the Safety & Efficacy of MS1819, a yeast-derived (non-porcine) lipase pancreatic enzyme replacement vs PERT (NCT03746483) in patients with EPI due to CF has been completed.

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.

More recently a retrospective analysis of the CFF Patient Registry using data from 2000 to 2012 for pediatric patients and from 2000 to 2013 for adults (Trapnell BC et al) indicates that a median annual PERT use rate of 87% in children, 80% increased BMI, and male sex were associated with fewer hospital admissions and annual hospital nights in CF patients.

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.

A phase 4 clinical trial (NCT03924947) will aim to compare US marketed pancrelipase drug product with drug product manufactured with a modernized process at an alternate manufacturing site, in participants (12 years and older) with EPI due to CF.

A phase 2 clinical trial (NCT04375878) will aim to assess the safety and efficacy of MS1819 in enteric capsules in adult patients with CF and pancreatic insufficiency.

Keywords

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