Safety and Efficacy of a Novel Microbial Lipase in Patients with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis: A Randomized Controlled Clinical Trial

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Objective To evaluate the safety and efficacy of a novel microbial lipase (NM-BL) in a liquid formulation for the treatment of exocrine pancreatic insufficiency (EPI) in patients with cystic fibrosis (CF) in a phase IIa proof-of-concept study.

Study design We conducted a double-blind, randomized, placebo controlled crossover study in patients with cystic fibrosis and exocrine pancreatic insufficiency. Adolescent and adult patients with CF were randomized to receive NM-BL or placebo for 1 week as replacement for their usual pancreatic enzyme formulation. They were subsequently crossed-over to the alternate study treatment. The coefficient of fat absorption was evaluated as the primary endpoint. Symptoms and adverse events were evaluated as secondary endpoints.

Results A total of 35 patients were randomized into the study and 22 patients completed both treatment periods. During treatment with NM-BL, the coefficient of fat absorption was significantly greater (72.7%) compared with placebo (53.8%) with a difference between groups of 18.8% ($P < .001$). Subjective assessment of stool fat and stool consistency also improved under treatment with NM-BL. Adverse events were mostly gastrointestinal in nature and were more common in the group receiving NM-BL.

Conclusions Currently available pancreatic enzyme products are limited because of the lack of liquid formulations and being largely porcine based. The novel microbial lipase NM-BL was safe and effective in this short term trial. The trial provided clinical proof-of-concept for this novel microbial lipase as a treatment for EPI in CF. A larger phase 2 dose ranging trial is warranted. *(J Pediatr 2016;176:156-61)*.

Trial Registration ClinicalTrials.gov: NCT01710644.

Exocrine pancreatic insufficiency (EPI) affects up to 90% of patients with cystic fibrosis (CF). In these patients, the pancreas fails to produce adequate amounts of digestive enzymes, leading to fat malabsorption and potential malnutrition. Untreated EPI results in steatorrhea, gastrointestinal symptoms (including abdominal pain, flatulence, diarrhea, and weight loss), and poor growth in infants and children.[1]

Current standard therapy for the treatment of EPI is pancreatic enzyme replacement therapy (PERT), which uses products that contain porcine pancreatin (pancrelipase in the US). These porcine pancreatic preparations, however, have several shortcomings. Most of the commercially available products are enteric coated to protect the lipase from irreversible inactivation by gastric acid and proteases. This protective coating requires the near-neutral pH in the duodenum for timely dissolution. Patients with CF often have more acidic duodenal contents as the result of impaired bicarbonate secretion, which has been shown to delay the release of the administered enzymes. In addition, because of their low specific activity, these animal-derived products require ingestion of relatively large number of capsules per meal. Finally, no existing porcine PERTs are available in a liquid form.[2]

The novel microbial lipase (NM-BL) contains only lipase (ie, no proteases), which may limit its use as the sole PERT used to treat patients with CF or other causes of pancreatic insufficiency. The main clinical consequence of EPI is fat

BMI	Body mass index
CF	Cystic fibrosis
CFA	Coefficient of fat absorption
CNA	Coefficient of nitrogen absorption
EPI	Exocrine pancreatic insufficiency
NM-BL	Novel microbial lipase
PERT	Pancreatic enzyme-replacement therapy
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

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maldigestion and steatorrhea. Lipase is the most unstable pancreatic enzyme, probably because of its high sensitivity to degradation by proteases and inactivation by acidic pH. Although reduced secretion of pancreatic amylase and protease can be compensated for by salivary amylase, intestinal glycosidase, colonic flora, gastric pepsin, and intestinal peptidases, the digestive action of pancreatic lipase is only minimally supplemented by extrapancreatic sources.[3,4] Consequently, steatorrhea occurs earlier and is more pronounced than azotorrhea in most cases and may even be the only clinical feature of malabsorption.[5,6] NM-BL is a novel bacterial lipase (INN: burlulipase) produced by a fermentative process that uses *Burkholderia plantarii*, a gram-negative bacterium that is not pathogenic to humans. NM-BL could overcome some of the shortcomings of porcine pancreatin formulations.

In contrast to commercially available PERTs, NM-BL is a liquid formulation that is administered in a cup of water with a meal. In vitro experiments have shown that NM-BL is more resistant to inactivation by gastric acid and proteases than conventional pancreatin products. In dogs with experimentally induced pancreatic insufficiency, the efficacy of NM-BL was comparable with conventional porcine products in reducing steatorrhea.[7] To further investigate use of NM-BL for pancreatic enzyme replacement, we conducted a placebo controlled phase IIa clinical study to investigate its safety and efficacy in patients with CF and EPI.

Methods

We conducted a multicenter, randomized, placebo controlled, double-blind, crossover study of the safety and efficacy of NM-BL in patients with CF and EPI ≥12 years of age (ClinicalTrials.gov: NCT01710644). The study protocol and informed consent forms were approved by the institutional review boards at each study institution. After verbal explanation of the study, all subjects/guardians signed an informed consent form. In the case of patients aged <18 years, assent was given.

The design of the study followed published expert recommendations.[8] Male and female subjects with CF followed at 1 of 9 CF Foundation-accredited centers were selected for this study. Subjects were eligible if they were ≥12 years of age, had a diagnosis of CF based on standard criteria,[9] and had documented EPI with a fecal elastase less than 50 μg/g. Subjects were required to be on treatment with PERT, had to be clinically and nutritionally stable with an acceptable body mass index (BMI; BMI percentile >10% for patients ≤20 years of age or a BMI >19.8 for male patients aged >20 years or a BMI >18.5 for female patients aged >20 years), and to be on stable treatment with acid-suppression therapy. Subjects were excluded if they had a history of fibrosing colonopathy, significant bowel resection, solid-organ transplant, being refractory to PERT, cirrhosis and portal hypertension, a history of distal intestinal obstruction syndrome or a current diagnosis of intestinal bacterial overgrowth, ileus or acute abdomen, or a requirement for tube feeding during the study. All subjects continued their other medications for treatment of CF, including proton pump inhibitors or H2 antagonists.

If patients met the criteria at the initial screening visit, eligible subjects continued on their usual PERT for up to 4 weeks and were randomized to 1 of 2 treatment arms: NM-BL then placebo or placebo then NM-BL. For each treatment period, patients were hospitalized at the site and the subject's prescribed PERT was discontinued. Patients were put on an individualized high-calorie and high-fat diet as recommended in CF Foundation nutrition guidelines,[10] consisting of 100 g of fat and at least 2 g of fat per kg body weight provided in 3 meals and 2 snacks. Fat and protein intake was recorded on the basis of the amount of food consumed. Patients received 90 mg of NM-BL protein per main meal and 45 mg of NM-BL protein per snack dissolved in approximately 50 mL of water to be consumed along with the respective meal.

On the evenings of days 2 and 5, the subjects received 400-500 mg of a blue stool marker (FD&C blue no. 2) to mark the start and end of the 72-hour stool collection period required for the coefficient of fat absorption (CFA) assessment. After the appearance of the second blue stool, the study drug and high-fat diet were discontinued, and patients were discharged and resumed their normal PERT for 1-4 weeks before they returned for the second treatment period (**Figure 1**; available at www.jpeds.com). The procedure used in the second period was identical to the first period. A follow-up visit occurred 4-10 days after the discharge from the second treatment period.

An independent data monitoring committee of the CF Foundation was set up before trial commencement. The board reviewed the trial design and an interim analysis of blinded safety data after 50% of the planned number of patients had completed the study.

Outcomes

The primary objective of the study was to evaluate the efficacy of NM-BL compared with placebo in improving fat absorption as determined by the CFA. The stool collection was performed from the first appearance of dyed stool to the second appearance of the dyed stool (day 6 or 7 of each treatment period depending on the subject's intestinal motility). The fat content of the stool was measured by a gravimetric method.[11] The CFA is considered the gold standard measure for the evaluation of fat absorption and is accepted by regulatory authorities as surrogate endpoint for EPI. The CFA was calculated from the fat intake and excretion according to the following formula:

$$\mathrm{CFA}(\%) = 100\,[\text{fat intake} - \text{fat excretion}]/\text{fat intake}.$$

Secondary efficacy outcomes included the coefficient of nitrogen absorption (CNA), representing the protein absorption and clinical symptoms (stool frequency, consistency, flatulence, and abdominal pain). The CNA was calculated similar to the CFA. Clinical symptomatology was determined from data recorded daily by subjects regarding the stool