

Treatment of Exocrine Pancreatic Insufficiency in Cystic Fibrosis Patients

a report by

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Cystic fibrosis (CF) is a disease that primarily affects the lungs; however, pancreatic insufficiency complicates the disease in most patients. This has a severe impact on both their quality of life and life expectancy. Successful management of gastrointestinal (GI) problems in CF is essential to maintain good health in these patients.

The exocrine pancreas is the most profoundly and commonly affected GI organ in CF. Approximately 85–90% of CF patients suffer from pancreatic insufficiency from birth.¹ Symptoms include steatorrhea, diarrhea, abdominal pain, passage of excess bowel gas, deficiency of fat-soluble vitamins, and failure to thrive. Untreated, pancreatic insufficiency can reduce fat absorption to just 40–50%.² Protein absorption is also impaired.³ It is well established that nutrition and lung function are closely linked in CF. Two studies demonstrated that both reduced height and reduced weight in CF patients can lead to early mortality.^{4,5} The primary objective in CF care is therefore to maintain normal growth into adulthood through pancreatic enzyme replacement therapy and other nutritional support.

Pancreatic insufficiency in CF patients is the result of an obstruction of the pancreatic ducts and, consequently, destruction of acinar tissue.⁶ The CF transmembrane regulator (CFTR) genotype has a strong correlation with pancreatic insufficiency.⁷ Analysis of the CFTR mutation in pancreatic phenotypes suggests that there are two categories of alleles: severe and mild.⁸ The mild allele is dominant and dictates pancreatic sufficiency; both alleles need to be severe in order for pancreatic function to be disrupted.

Diagnosis

The identification of the CFTR genotype allows for newborn screening to detect children with the two severe alleles and immediately identify them for treatment. Early diagnosis by neonatal screening leads to enhanced growth and weight gain through early nutritional intervention.⁹ Therefore, screening should be implemented to prevent malnutrition in infants with CF. Pancreatic insufficiency is generally recognized through failure to thrive of newborns on conventional formula.¹⁰

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Treatment

CF patients have 120–150% of the energy needs of healthy individuals with similar weight and height due to the lack of absorption of essential fats and proteins.¹¹ It is estimated that 90% of CF patients with pancreatic insufficiency rely on enzyme replacement therapy to maintain their nutrition.¹² Enzyme preparations are generally given in capsule form, but some are available in powders for younger children. They are swallowed with every meal or snack to ensure that fat and protein absorption from each meal or snack is optimized.

For the past 30 years, enteric-coated microspheres have been the treatment of choice for pancreatic insufficiency.¹³ The enteric coating protects enzymes from inactivation by stomach acid until they reach the small intestine. In the small intestine, the coating dissolves, releasing the active enzyme into the lumen of the small intestine to facilitate digestion. Enzyme preparations are derived from the porcine pancreas and predominantly include amylase, lipase, and protease. Pigs have a similar composition of pancreatic enzymes to humans and hence extracts also include additional enzymes such as colipase that aid fat digestion further. The extraction procedure is sophisticated, allowing a high level of enzyme activity per gram of extract.

Currently, pancreatic enzyme products are being designed that are derived from bacteria and yeast. This is an obvious advantage for achieving sterility of the enzyme and eradicating the risk of viral contamination. However, these preparations contain only amylase, lipase, and protease, and may not produce improvements on existing preparations derived from porcine pancreas. As mentioned previously, the pig-pancreas-derived products contain colipase, which is required for optimal activity of lipase, whereas the bacteria-derived preparations will not. This may account for the potentially lower rates of fat absorption seen with these products. Future enzyme replacement therapies will primarily be derived from porcine pancreas because it produces optimal results. Fat-soluble-vitamin deficiency is also a problem in CF patients with pancreatic insufficiency. Supplementation of vitamins A, D, K, and E are given routinely to maintain patient health.¹⁴ Vitamin K deficiency is rare in CF; however, due to fat malabsorption, bile acid deficiency, and liver disease, CF patients are at an increased risk.¹⁵ Thus, to avoid vitamin K deficiency problems, for example excessive bleeding, supplements are given to all patients.

Dosing

Response to enzyme preparation can vary between patients, hence specific doses are advised on an individual basis. It has been identified

that high doses of pancreatic enzymes, often in excess of 50,000 units of lipase per kilogram of bodyweight per day, caused an increased risk of developing fibrosing colonopathy.¹⁶ A UK study found that during the period 1999–2000, CF patients receiving standard strength (10,000 units lipase per capsule) and high-dose treatments (25,000 units lipase per capsule) commonly exceeded the recommended limits.¹⁷ This is of particular concern in children, who are at increased risk of fibrosing colonopathy. Patients consuming more than 50,000 units of lipase per kilogram of bodyweight per day are estimated to have a 0.38% risk of fibrosing colonopathy within a year.¹⁸ Guidelines have been developed that suggest limiting the intake to a maximum dose of 10,000 units of lipase per kilogram of bodyweight per day.

Measuring the Success of Treatment

There are both indirect and direct methods of measuring pancreatic function. The direct methods are invasive and involve passing a tube into the small intestine, stimulating the pancreas, and collecting the enzymes. This is extremely uncomfortable for the patient and hence indirect techniques are more widely used. Practitioners will most commonly use fecal elastase levels to confirm pancreatic insufficiency.¹⁹ Stools may also be collected over a 72-hour period to assess fat absorption efficiency and response to pancreatic enzyme supplements.

Breath tests have been studied as a more convenient way of measuring pancreatic insufficiency.²⁰ A ¹³C-mixed triglyceride breath test has been used to evaluate the success of enzyme replacement therapy in chronic pancreatic-insufficient patients.²¹ The breath test was able to detect fat absorption; however, it is still not as accurate as the gold standard—the 72-hour stool fat measurement. No breath test is currently available in the US.²²

Problems with Current Therapies

Pancreatic enzyme replacement preparations have varying success in CF patients with pancreatic insufficiency. In some cases, despite what appears to be appropriate weight-based dosing of enzymes, significant maldigestion persists. In healthy individuals, simultaneous secretion of enzymes, bicarbonate, and bile occur when nutrients enter the duodenum. The highest level of enzyme activity is found in the proximal intestine. In comparison, CF patients medicated with supplemental enzymes may have the highest enzyme activity in the jejunum and the ileum, indicating a delayed release of enzymes.²³ This may account for the lack of synchronization between the release of bile and intestinal enzymes causing malabsorption problems. This is one explanation for why enzyme therapy, in the best case scenario, restores fat absorption only to within 80–85% of that seen in healthy individuals.²⁴

Poor adherence to enzyme replacement therapy in adolescence and into adulthood accounts for some of the problems with treatment. Perception of body image has been identified as a reason for ceasing adherence to enzyme replacement.²⁵ Young women tend to overestimate their bodyweight in comparison with their actual bodyweight and hence take less supplementation. The opposite is true for men. Adherence to enzyme replacement therapy and nutritional supplementation is an important factor contributing to unexplained malnutrition, especially in young women with CF.

Additional and Alternative Therapies

Additional treatment may be provided to patients who do not respond adequately to enzyme replacement therapy. Proton pump inhibitors are used in a low percentage of cases alongside pancreatic enzymes to boost

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absorption in the small intestine. Patients with pancreatic insufficiency often have low pancreatic bicarbonate secretion, which may become insufficient for neutralizing the chime released from the stomach.²⁶ Lipase is released from enteric microspheres only at a pH over 5 and therefore may not be released until after the proximal intestine, thus reducing its efficacy. Inhibiting gastric acid secretion using proton pump inhibitors reduces the amount of gastric acid delivered to the duodenum and allows the enzyme supplementation capsules to be released in the proximal intestine. This may enhance the nutritional value patients receive from meals because of increased digestion efficiency. However, proton pump inhibitors provide no extra benefit to patients who already have an adequate response to enzyme replacement therapy alone. In selected cases, pancreatic enzyme supplementation fails to provide a normal nutritional profile in the patient, and enteral tube feeding may be employed to enhance caloric intake.²⁷ Most commonly, a gastrostomy tube is inserted surgically either with endoscopic guidance or by radiographic guidance. By providing access to the stomach via a gastrostomy tube, calories may be given as a supplement to oral feeds either during the day or at night. A firm conclusion cannot be made about the success of enteral tube feeding as no long-term studies have been performed. Shorter-duration trials have indicated that nutrition can be significantly improved using this method.

US Food and Drug Administration Guideline Changes

In 2004, the US Food and Drug Administration (FDA) published a notice in the Federal Registry stating that all existing pancreatic replacement enzymes must receive FDA approval in the next four years in order to remain on the market.²⁸ The FDA is seeking to improve both the effectiveness and safety of these therapies by standardizing dosing, manufacturing protocol, and formulation. Pancreatic enzyme replacement therapies were available by prescription before the introduction of the Federal Food, Drug, and Cosmetic Act in 1938, which stated that all drugs must go through a New Drug Application (NDA) process. Previously, these drugs were regulated only in terms of labeling and the manufacturing process. Over the years, the FDA has received complaints over adverse effects of overdosing and, more recently, concerns that supplemental enzymes do not provide a uniform therapeutic benefit. To overcome this shortfall, the FDA developed a policy regarding universal potency, stability, and consistency.²⁸

Historically, the FDA approved these products without the controlled trials that are necessary today. Most enzyme preparations are not stable, and

activity decreases over time. Manufacturers overfilled their preparations with the idea that toward the end of their shelf-life they would still contain the enzyme activity listed on the label. At the beginning of a new drug prescription, excess amounts of enzyme were present, and by the end of the shelf-life the supplements contained the amount shown on the label. This causes problems of adverse side effects from overdosing, such as fibrosing colonopathy, and the therapy being less effective near the expiration date. Next year, a new FDA guideline will be introduced that states that all enzymes should be stable throughout their shelf-life to ensure that patients have uniform application of the drug. This will inevitably aid patient care and reduce the occurrence of side effects from overdosing. Recently, zero-overfill products have been examined in phase III trials that successfully provide uniform drug delivery.²⁹

Products will not be recalled while manufacturers go through the NDA process. Patients will still be able to get prescriptions for enzymes not approved before the four-year period if they are applying for NDAs.

Future Research

Researchers are currently examining new methods of detecting fat absorption in order to evaluate the effectiveness of pancreatic enzyme replacement. Currently, fat absorption can reliably be tested only using 72-hour stool collection. This is not ideal, since patients find it cumbersome and impractical. Clinicians would benefit greatly from an improved method of accurately measuring the effectiveness of the enzyme replacement schedules of their patients. To date, breath tests are not robust enough to allow quantitative assessment of fat absorption that could be used to direct alterations to enzyme supplement dosing. Future research should concentrate on either improvements in the accuracy of the breath test or the development of a novel method of easily and inexpensively assessing fat absorption.

It is well documented that CF patients suffer from pancreatic insufficiency; however, other aspects of fat absorption may also be compromised. Recent research has suggested that abnormalities are

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present within the enterocyte of CF patients, which may alter fat absorption.³⁰ Additional research should be carried out in this area in order to fully understand why CF patients have malabsorption.

Summary

Pancreatic insufficiency affects 85–90% of all CF patients; therefore, effective treatment is essential to maintain adequate nutrition. Pancreatic enzyme replacement therapy is primarily used to increase absorption. However, enzyme supplements may not always be effective in all patients. Some patients require proton pump inhibitors alongside supplemental enzymes to increase efficacy. Currently, a 72-hour stool collection test for fat may be used to evaluate the success of enzyme therapy. This is cumbersome and unpleasant for patients, hence research is focusing on the development of a new method of testing fat absorption. The FDA has announced that all pancreatic enzyme replacement therapies must go through an NDA to ensure universal potency, stability, and consistent quality of drugs offered. ■

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