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Is Pancrelipase Delayed Release Capsule (Creon) Safe for Use in Patients' ≥ 7 Years Old Who Suffer From Pancreatic Insufficiency Due to Cystic Fibrosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Pancrelipase Delayed Release Capsule (Creon) is safe for use in patients' ≥ 7 years old who suffer from pancreatic insufficiency due to cystic fibrosis.

Study Design: Systemic review of 3 English language primary studies, published between 2000-2010.

Data Sources: Two double blind randomized controlled trials (RCTs) as well as an open label phase study with a double blind phase comparing the safety of Pancrelipase Delayed Release Capsule (Creon) in treating pancreatic insufficiency in those suffering from Cystic Fibrosis. These studies were found using Cochrane Systematic Reviews and PubMed.

Outcomes Measured: The outcomes of each study measured the safety and tolerability of Creon by monitoring vital signs, weight, BMI, safety laboratory values, and adverse events. Adverse events were tracked in all studies.

Results: Graff et al demonstrated that for every three participants who took Creon, there was one fewer incidence of Treatment Emergent Adverse Events (TEAE's) than in the group of participants taking the placebo. TEAE's were reported in 5 patients (29.4%) while taking Creon and in 9 patients (53.6%) while receiving the placebo. There were also no discontinuations due to treatment adverse events and no serious adverse events noted during the trial. Trapnell et al demonstrated that for every four participants who took Creon there was one fewer incidence of TEAE's than in the group of participants taking the placebo. Stern et al demonstrated that during the double blind phase in both the adult and pediatric/adolescent studies, higher percentages of placebo-treated patients (67% and 70% respectively) reported treatment emergent adverse events than Creon treated patients (39% and 61% respectively).

Conclusion: Creon does appear to be safe and tolerable for those over the age of 7 suffering from pancreatic insufficiency due to cystic fibrosis. The TEAE's reported in each study proved the tolerance of Creon to surpass that of other treatment modalities. These studies also address the other benefits of Creon in allowing for significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily stool frequency. Although these are promising results more RCTs must be conducted with wider age groups in order to compare the safety of Creon.

Key words: Creon, Cystic Fibrosis, Pancreatic Insufficiency

INTRODUCTION

Cystic fibrosis is a hereditary disorder affecting the exocrine glands causing the production of abnormally thick mucus, leading to the blockage of pancreatic ducts, intestines, and bronchi and often resulting in respiratory infections.¹ Exocrine pancreatic insufficiency (EPI) is defined as the lack of digestive enzymes secreted by the pancreas in association with diseases such as cystic fibrosis which leads to maldigestion, with resultant malabsorption of fat, protein, and fat soluble vitamins which ultimately leads to malnutrition.² Approximately 85% of patients diagnosed with cystic fibrosis also have EPI. The symptoms begin in newborns shortly after birth and increase throughout infancy.² Approximately 90% of patients with EPI are treated with pancreatic enzyme replacement therapy to maintain adequate nutrition.² If EPI is left untreated, the subsequent malnutrition and debilitating symptoms may lead to poor growth, poor weight gain, and failure to thrive especially for those with cystic fibrosis.²

Cystic fibrosis is the most common autosomal genetic disease among white persons and has a prevalence of 1 in 2,500 newborn infants.³ The only risk factor for cystic fibrosis is a family history of the condition. The mean annual healthcare cost for treating cystic fibrosis in the United States is \$48,098 which is more than 22 times the average of \$2,172 for people without cystic fibrosis.⁴ Medical expenditures for people with cystic fibrosis increase with age through childhood and plateau during and after the teenage years.⁴

A study shows that adults with cystic fibrosis average about 12 office visits per year. Despite the monthly contact with physicians, 33% of patients have at least one inpatient stay per year.⁵ Individuals with cystic fibrosis have mean annual expenditures for inpatient care that are 35 times higher (\$16, 545 vs. \$467) than those for people without cystic fibrosis.⁴ This was due

primarily to the greater number of inpatient admissions among those in the cystic fibrosis group. The average expenditure for outpatient visits are 10 times higher (\$13,092 vs. \$1,267) for those with cystic fibrosis than individual's without.⁴ Not only are hospital admissions and healthcare costs higher for those with cystic fibrosis, but one of the biggest monetary burdens is prescribed medications. The average annual expenditures for prescribed medications were 42 times higher (\$18,461 vs. \$437) among those with cystic fibrosis.⁴

Cystic fibrosis is an autosomal recessive disease caused by abnormalities of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride conductance channel and affects the function of the exocrine glands in multiple organs, including the lungs, liver, pancreas, intestines, and skin.⁵ The disease is characterized by malabsorption, gastrointestinal abnormalities, infertility, and severe progressive sinopulmonary disease.⁵ Differences in disease patterns seen in individuals and families probably result from the combined effects of the particular mutation and various, but still unknown, factors in the patient and his or her environment.⁶ Despite the great advances in research, there is still no cure for cystic fibrosis due to these genetic changes and mutations.

There are numerous treatment options for individuals suffering from cystic fibrosis, each of which targets a different symptomology caused by the disease. The main treatments for lung problems in people with cystic fibrosis focus on antibiotics for infections of the airways, chest physical therapy, and exercise. The antibiotics used are: Tobramycin, Colistin, and Azithromycin.⁷ Chest physical therapy requires the individual to pound their chest and back over and over in order to dislodge the mucus within their lungs. Patients are encouraged to perform aerobic exercise in order to loosen their mucus and encourage coughing to clear the mucus build up in the lungs. Surgeries are a common occurrence for those suffering from cystic fibrosis and

range from nasal polyp removal to lung transplants. One of the hardest components of the disease to treat are digestive complications. Patients are treated with oral pancreatic enzymes to help them digest fats and proteins and to assist in the absorption of vitamins.

Although there are several drugs that aid those with EPI, Creon has been approved for those with cystic fibrosis. Pancreatic enzyme replacement therapy is critical for adequate nutrition in patients with cystic fibrosis with EPI. Thus far, numerous studies have been conducted and results show that Creon is a safe treatment for EPI due to cystic fibrosis. Creon allows patients significant improvements in stool fat, weight gain, and absorption of nutrients due to its ability to break down fats, proteins, and carbohydrates.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is Pancrelipase Delayed Release Capsule (Creon) safe for use in patients’ ≥ 7 years old who suffer from pancreatic insufficiency due to cystic fibrosis.”

METHODS

The criteria used for the selection of the 3 studies included that patients be either male or female over the age of 7 with cystic fibrosis causing exocrine pancreatic insufficiency. The studies involved the interventional use of either Creon 12,000 Units or 24,000 units. The comparison groups in the two RCTs received either Creon or a visually matched placebo. In the double blind phase study a group was given Creon while a subgroup was given either Creon or a placebo. The outcomes measured in the 3 studies included the safety and tolerability of Creon for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis using the incidence of

treatment emergent adverse events (TEAEs) for statistical analysis. The three studies included consist of two randomized, double blind, placebo controlled studies, two period crossover clinical trials (RCTs) and one open label phase study with a double blind phase.

Keywords used to search for the articles included “cystic fibrosis”, “Creon”, and “pancreatic insufficiency”. All articles were originally published in peer-reviewed journals in the English language. Data was researched and collected by the author using articles from 2000-2010 in PubMed and the Cochrane library. Articles were selected based on relevance to the clinical question and whether they included patient oriented evidence that matters (POEMS). All articles chosen for this review were peer-reviewed and published in well-known journals such as Journal of Clinical Therapeutics, The American Journal of Gastroenterology, and the Journal of Cystic Fibrosis. Inclusion criteria consisted of the requirement that studies that were RCTs or clinical trials published after 1996 in which no other systematic reviews, meta-analysis, or review article was found on the Cochrane database answering the same question with additional criteria found in Table 1. Exclusion criteria included studies in which patients under 7 years old were utilized. The statistics used to evaluate patient outcomes included p values, RRI, ARI, CI, and NNH. The demographics and characteristics of the individuals included in these studies are displayed in table 1.

Table 1 - Demographics & Characteristics of included studies (Table 1)

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Graff, 2010 (2)	RCT	17	7 to 11 years old	-confirmed diagnosis of CF 2 positive sweat tests and/or disease causing mutations detected on CF transmembrane conductance regulator gene analysis -confirmed diagnosis of enzymatic pancreatic insufficiency (EPI) defined as a coefficient of fat absorption (CFA) <70% without pancreatic enzyme supplementation or as human fecal elastase <50ug/g (measured within the past 12 months) -must have been receiving treatment with a commercially available PERT product as a stable dose for >3 months	-if patient had severe medical conditions that limit participation -if they had undergone any recent major surgery -Ileus or acute abdomen malignancy of the digestive tract (excluding pancreatic cancer), HIV, celiac/ Chron's disease -known allergy to Pancrelipase or the inactive ingredients in Pancrelipase delayed release capsules, or exposure to an experimental drug within 30 days of the start of the study	1	Creon 12,000 units
Stern, 2000 (8)	Open label	97	>18 years of age and between 7 and 18 years of age	-a diagnosis of CF documented by sweat chloride results (>70) and clinical symptoms of exocrine pancreatic insufficiency with a history of steatorrhea -patients must have been stabilized on a diet and dose of pancreatic enzyme supplementation	-if a patient had extreme cachexia, severe acute or chronic pulmonary disease, or were using other gastrointestinal medications or medications affecting the gastrointestinal tract other than oral pancreatic enzymes	21	Creon and high fat diet
Trapnell, 2009 (9)	RCT	34	12 years of age and older	- a diagnosis of CF (confirmed by 2 positive chloride sweat tests and/or CFTR gene analysis) and EPI (confirmed by either a coefficient of fat absorption (CFA) <70% without supplementation or fecal elastase <50 ub/g stool within the past 12 months) -receiving treatment with a commercially available pancreatic enzyme product	-if they had an ileus or acute abdomen, distal ileal obstruction syndrome within 6 months of enrolment, gastrointestinal malignancy within 5 years of enrollment, a history of pancreatitis or fibrosing colonopathy or known infection with HIV	2	Creon 24,000 units

OUTCOMES MEASURED

All of the outcomes measured were POEMS related to the safety and tolerability of Creon for the treatment of pancreatic insufficiency in those with cystic fibrosis. Outcomes were measured in a variety of ways and included vital signs, physical examination, weight, BMI, safety laboratory values, and adverse events.^{2, 8, 9} The safety of Creon was measured by treatment emergent adverse events (TEAEs) reported by the patients.^{8, 9, 10} The TEAEs monitored were gastrointestinal disorders, nervous system disorders, respiratory disorders, and skin/subcutaneous tissue disorders.^{2, 8, 9} Secondary efficacy outcomes were also assessed. These include the coefficient of nitrogen absorption (CAN), stool fat, stool weight, and clinical symptomatology.^{2, 8, 9} Laboratory analyses using standard procedures were performed at Mayo Clinical Trial Services.^{2, 8, 9}

RESULTS

The three studies chosen evaluated the safety of Creon for the treatment of pancreatic insufficiency in individuals ≥ 7 years old suffering from cystic fibrosis. Two double blind randomized controlled trials (RCTs) as well as an open label phase study with a double blind phase were chosen for analysis.

The study conducted by Graff et al consisted of twenty three individuals, sixteen of whom completed the study. Inclusion and exclusion criteria for the study can be found in Table 1. Each period during the 2-period crossover consisted of the patients receiving either Creon 12,000 units or the identical placebo capsules for a total of five days. A variety of safety measures were monitored during the study. These included: vital signs, physical examinations, standard laboratory safety tests (hematology and biochemistry), and adverse events. Treatment

emergent adverse events were reported in 5 patients (29.4%) during receipt of Creon and in 9 patients (56.3%) during receipt of placebo; these were predominantly gastrointestinal events. There were no discontinuations due to treatment emergent adverse events and no serious adverse events. Creon was also shown to provide significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily stool frequency as compared with the placebo ($p < 0.001$). The NNH was calculated to be -3 (Table 2) which indicates that for every three participants who took Creon, there was one fewer incidence of TEAE's than in the group of participants taking the placebo.²

Table 2. Analysis of Numbers Needed to Harm for Creon Use

Graff (2010)	CER	EER	RRI	ARI	NNH
	56.3%	29.4%	-48%	-26.9%	-3

The study conducted by Trapnell et al consisted of thirty four individuals, thirty two of whom completed the study. Inclusion and exclusion criteria for the study can be found in Table 1. Each period during the 2-period crossover each period consisted of the patients receiving either Creon 24,000 units or the identical placebo capsules for a total of five days. A variety of safety measures were monitored during the study. These included: vital signs, physical examinations, standard laboratory safety tests (hematology and biochemistry), and adverse events. Physical examinations were performed during screening and at the end of each crossover period. Laboratory safety tests were performed during screening, at the end of the first crossover period, and at the beginning and end of the second crossover period. Treatment emergent adverse events and treatment related TEAEs had a lower overall incidence during Creon treatment than during placebo treatment (43.8% vs. 64.5%). Analysis of adverse events did not reveal any

TEAEs with a greater clinically meaningful incidence in the Creon group compared with the placebo group, and no cases of hypersensitivity were reported. Creon was also shown to provide significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily stool frequency as compared with the placebo ($p < 0.001$ for all). The NNH was calculated to be -4 (Table 3) which indicates that for every four participants who took Creon, there was one fewer incidence of TEAE's than in the group of participants taking the placebo.⁹

Table 3. Analysis of Numbers Needed to Harm for Creon Use

Trapnell (2009)	CER	EER	RRI	ARI	NNH
	64.5%	43.8%	-32.1%	-20.7%	-4

The study conducted by Stern et al consisted of ninety seven individuals, seventy four of whom completed the study. Of those seventy four patients, thirty six were adults and thirty eight were pediatrics/adolescents. Inclusion and exclusion criteria for the study can be found in Table 1. During the open label phase study and the double blind phase study patients received either Creon or the identical placebo capsules for a total of five to seven days. Tolerance was assessed by physical examination, adverse events, vital signs, urinalysis, and serum biochemistry and hematology evaluations. During the open label phase, 52% of the adult patients and 64% of the pediatric/adolescent patients reported at least one treatment emergent adverse event. During the double blind phase in both the adult and pediatric/adolescent studies, higher percentages of placebo-treated patients (67% and 70% respectively) reported treatment emergent adverse events than Creon treated patients (39% and 61% respectively). Creon was also shown to provide significant improvements in stool fat, weight, and nitrogen and a significant reduction in daily

stool frequency as compared with the placebo ($p < 0.001$ for all). The NNH could not be calculated for this study due to the lack of control throughout the duration of the trial.⁸

DISCUSSION

The results from these studies demonstrate that Creon therapy is a safe and effective treatment for exocrine pancreatic insufficiency in patients with cystic fibrosis. Although none of the studies compared Creon to any other EPI drug, these early studies show promising results in terms of efficacy and safety. In all three studies the adverse events were minimal and the reported TEAE's proved to be minuscule. Creon treated patients demonstrated significantly superior results compared with placebo treated patients for coefficient of fat absorption, stool frequency, stool consistency, and coefficient of nitrogen absorption.^{2, 8, 9}

Although these studies yielded important results, there were limitations that need to be addressed. The number of patients employed in each study was very low. By enrolling more participants results gathered are more efficacious. In addition, trials need to be completed with individuals suffering from cystic fibrosis who are under the age of seven. This will allow for the investigation of the efficacy of Creon in pediatric and neonatal patients. Another limitation that can be addressed is the duration of the studies. All three studies lasted only five to seven days. In order to gain better results, longitudinal analyses must be conducted.

Creon is also used for other conditions that cause pancreatic insufficiency. These conditions include chronic pancreatitis, cystic fibrosis, pancreatic cancer, post pancreatectomy, and post- gastrointestinal bypass surgery.¹⁰ Due to the wide use of Creon, it is commonly covered by most insurance companies. There are also Patient Assistance Programs that help supply the drug for free or at a reduced cost for its customers. However, for those individuals

without insurance the cost of 90 capsules of Creon totals about \$500.¹¹ Such an elevated cost can truly hinder a patient's ability to afford a vital medication for their wellbeing.

CONCLUSION

This review and chosen studies show that Creon is a safe treatment for pancreatic insufficiency in individuals with cystic fibrosis who are ≥ 7 years of age. No serious or life threatening adverse events were reported related to the use of Creon during these studies. None of the studies reported any deaths when the use of Creon even when extremely high doses (24,000 Units).

Due to the limited amount of studies, small sample sizes, and very few comparison studies, future studies are needed to directly compare Creon with other EPI drugs in order to test efficacy and safety. Also, future research should include longer treatment durations to more definitively evaluate the benefits and risks of treating cystic fibrosis patients with Creon.

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