CLINICAL TRIALS OF PANCREATIC ENZYME REPLACEMENT FOR PAINFUL CHRONIC PANCREATITIS — A REVIEW

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Background

Painful chronic pancreatitis is a frustrating problem both for patients and clinicians, and affects between 0.4 and 5% of the adult population. The condition is typified by recurrent bouts of severe abdominal pain, particularly after eating, and the pain is often accompanied by nausea and vomiting. Because of exocrine insufficiency, severe weight loss and malnutrition often coexist. A variety of etiologies for chronic pancreatitis exist — toxic-metabolic (alcohol, prescription and illicit drugs, hypercalcemia, and hypertriglyceridemia), idiopathic, genetic, autoimmune, recurrent severe-acute pancreatitis-related, and obstructive (strictures, gallstones or pancreatic duct stones) [1]. However, in adults, most cases are due to alcohol abuse.

The multiple possible etiologies of painful chronic pancreatitis combined with the likelihood that many patients with the condition are addicted to alcohol (and possibly continue to abuse alcohol) make clinical research in this field particularly challenging. Additionally, the biologic basis of pain in chronic pancreatitis remains somewhat controversial. Multiple other etiologies have been proposed and are reviewed elsewhere [2]; some experts have postulated that pain in chronic pancreatitis may actually be centrally mediated, rather than mediated by inflammation of the pancreas itself [3].

It has been proposed that administering supplemental porcine pancreatic extracts to patients with painful chronic pancreatitis stimulates receptors in the proximal small intestine and triggers a negative-feedback loop which suppresses baseline pancreatic enzyme secretion, decreasing ductal pressures, thereby decreasing pain [4, 5]. It should be noted, however, that other proposed pathophysiological mechanisms for pain exist, including chronic perineural inflammation and fibrosis [6], uninhibited cholinergic stimulation of pancreatic secretion [7] and colonic hypermotility due to malabsorption and steatorrhea [8]. Of these alternative proposed etiologies, only colonic hypermotility due to steatorrhea and malabsorption would potentially respond to pancreatic enzyme supplementation.

Published Studies and Guidelines

In 1998, a technical review published by the American Gastroenterological Association (AGA) found that '[the] role of pancreatic enzymes in reducing pain in chronic pancreatitis ... remains unclear' [9]. However, an AGA medical position statement appearing in the same issue of *Gastroenterology* recommended routine use of pancreatic enzyme supplements for painful chronic pancreatitis [10]. Further recommendations also included avoidance of narcotic pain medication until after consideration of invasive endoscopic therapy because of a 'risk of addiction', despite evidence that alcoholics with chronic pain do not have a significantly increased risk of either addiction or problematic narcotic use [11, 12]. The AGA medical position statement does advocate the routine use of a quality-of-life (QOL) questionnaire though the AGA makes no specific recommendation as to which one.

We searched PubMed for available studies on pancreatic enzyme supplementation for treatment of pain in chronic pancreatitis from 1980 to present. When needed, we contacted authors of studies for additional information. We searched the terms 'chronic pancreatitis'; 'pancreatitis'; 'pain'; and 'pancreatic enzymes'. We also searched relevant citations of identified studies.

Nine studies (6 articles and 3 abstracts) of pancreatic enzyme supplementation for the treatment of pain in chronic pancreatitis have been undertaken or reported, with widely varying results (table 1) [4, 8, 13-19].

Table 1. Studies of pancreatic enzyme supplementation for the treatment of pain in chronic pancreatitis

Article	Study design	Study duration	n (M/F)	Coated/ uncoated	Acid suppression?	Total daily dose of enzymes	Pain measurement	Outcomes
Slaff et al. [4]	single center double-masked RCT with crossover	60 days, 30 days in each arm, no washout period	20 (9/11)	uncoated	no	192,000 USP lipase, 720,000 USP amylase, 720,000 USP protease	pain score (rated 1–4) and analgesic consumption	reduction in pain score in 9 patients with mild to moderate disease ($p < 0.01$)
Halgreen et al. [8]	double-masked RCT with crossover	4 weeks, 2 weeks in each arm, no washout period	20 (12/8)	coated	no	32,000 USP lipase, 160,000 USP amylase, 200,000 USP protease	10 cm VAS, analgesic consumption, and number of pain attacks	NS
Isaksson and Ihse [13]	double-masked RCT with crossover	3 weeks, 1 week in each arm with 1 week of washout	19 (11/8)	uncoated	no	Pankreon granules 7.5 ml 5 times daily	10 cm VAS, examiner's assessment, and analgesic consumption	reduction in patient's opinion ($p < 0.01$) and examiner's opinion ($p < 0.05$) of pain
Larvin et al. [14]	single center double-masked RCT with crossover	4 weeks, 2 weeks in each arm, no washout period	65 (40/25)	coated	no	96,000 USP lipase, 448,200 USP amylase, 337,500 USP protease	pain severity, frequency scores, analgesic consumption, patient preference	NS
Campbell et al. [15]	multicenter double-masked RCT with crossover	8 weeks, 4 weeks in each arm, no washout period	52 (not stated)	coated	no	96,000 USP lipase, 448,200 USP amylase, 337,500 USP protease	pain score and analgesic consumption	NS
Mössner et al. [16]	multicenter double-masked RCT with crossover	4 weeks, 2 weeks in each arm, no washout period	47 (41/6)	coated	no	200,000 USP lipase, 747,000 USP amylase, 625,000 USP protease	pain diary and analgesic use	NS
Malesci et al. [17]	single center double-masked RCT with crossover	8 months, 4 months in each arm, no washout period	26 (not stated)	coated	no	208,000 USP lipase, 697,120 USP amylase, 390,000 USP protease	10 cm VAS multiplied by number of hours of pain	NS
Czakó et al. [18]	prospective, multicenter observational study, no placebo	mean follow-up not specified	group 1: patients with newly diagnosed chronic pancreatitis, 31 (29/2) group 2: patients with 'older' disease (mean duration 3.4 years), 39 (37/2)	coated	no	without exocrine insufficiency: 30,000 USP lipase, 99,600 USP amylase, 112,500 USP protease; With exocrine insufficiency: 75,000 USP lipase, 224,100 USP amylase, 187,500 USP protease	EORTC QLQ-C30 with two additional questions relating to steatorrhea	reductions in pain in groups 1 and 2
Kahl et al. [19]	prospective, single center observational study, no placebo	mean follow-up not specified	231 (not stated)	not specified	not specified	not specified	EORTC QLQ-C30 and PAN-26	decreased pain ($p < 0.01$)

Shortcomings of Published Studies

The published clinical trials of enzyme replacement for pain relief in painful chronic pancreatitis are plagued by a number of methodological and design flaws. These include, but are not limited to, lack of a priori power analysis, failure to use validated instruments to assess pain or health-related quality of life, use of crossover designs, selection of study populations which are not generalizable to clinical patient populations, and use of coated pancreatic enzymes rather than uncoated forms (only 2 studies have evaluated uncoated enzymes [4, 13]).

There are 9 published clinical trials on the use of pancreatic enzyme supplements for painful chronic pancreatitis in the English-language medical literature (6 were

published as full papers and 3 are abstracts). Five of these studies [8, 14, 15, 16, 17] noted no improvement in pain with treatment, but all failed to report whether an a priori power analysis was done, raising the possibility of type 2 error — sufficient numbers of patients may not have been studied to detect a significant difference. Further, even though 4 of the 9 published studies [4, 13, 18, 19] reported improvement in pain (statistically significant p values) with pancreatic enzyme supplements, they also failed to report having done an a priori power analysis. This is not necessarily a fault, but may indicate a lack of planning in conducting the study. All studies reported significant placebo responses.

Failure to use validated instruments or to systematically assess health-related quality of life (HRQOL) is another common problem with the published studies. Only 2 of the 9 studies assessed HRQOL in a systematic fashion, using published, validated instruments [18, 19]. These studies were both published after the 1998 AGA position statement advocating the systematic use of HRQOL measures in the treatment of chronic pancreatitis. Six of the 9 studies evaluated the frequency of use of rescue pain medications as an endpoint [4, 8, 13, 14, 15, 16], which is potentially clinically useful. This assessment certainly possesses face validity, but it has not been systematically validated for content to the authors' knowledge. One of the 9 studies included a subjective assessment by an examiner of the patients' pain status [13], which introduces a potential for bias [13] and discordance [20].

Seven of the 9 published clinical trials also made use of crossover designs [4, 8, 13, 14, 15, 16, 17]. Crossover designs are beneficial in reducing confounding because each patient serves as his own control and they reduce the required number of participants. However, numerous problems exist with crossover designs — carryover effects, assignment sequence, and dropouts in particular [21, 22]. Dropouts were not overly common in the studies, but carryover effects certainly may exist. Only 1 published study included a washout period [13]. Since the pathophysiology of painful chronic pancreatitis remains poorly understood, a mandatory washout period should be included in order to attempt to get pancreatic secretion and pain levels back to the

patient's baseline between drug and placebo (and vice versa). Chronic pancreatitis is not a rare disease so in general the use of crossover designs is probably not ideal.

Finally, selection of patients in the published studies is nonuniform and is poorly described, particularly with regard to rigorous screening for alcohol abuse, a potential confounder. One of the most important issues in the treatment of patients with painful and nonpainful chronic pancreatitis is alcohol abstinence [23]. Achieving alcohol abstinence is difficult in the best circumstances and may be made more complicated by a chronic pain condition such as painful chronic pancreatitis. Unfortunately, only 1 publication makes mention of a systematic attempt to document whether patients were using or abusing alcohol while on the study protocol [17]. A variety of validated instruments and questions for assessing alcohol abuse [24] are available as well as inexpensive biologic markers [25] for active alcohol use. It would seem clear that either or both could be employed to assess compliance with alcohol abstinence on a study protocol. What is not clear, however, is what to do with patients who continue to abuse alcohol or relapse during treatment. In particular, a decision must be made as to whether or not they should be included in the final analysis. In the 'real world', it is likely that patients undergoing treatment for painful chronic pancreatitis will continue to abuse alcohol or relapse. In order to make a study generalizable to clinic populations, patients should probably be continued in the protocol even if they do abuse alcohol and the temptation to perform compliers-only analyses should be avoided. Consideration should be given to making alcoholism treatment a part of future proposed protocols.

Overview of Individual Studies

The first trial of pancreatic enzyme replacement was published by Isaksson and Ihse [13] in 1983. They enrolled 19 patients in a double-blind placebo-controlled crossover trial comparing Pankreon granules (an un- coated preparation available in Europe, but not in the United States) 5 times daily with placebo. The study was performed with a crossover design and after 1 week, patients received a 1-week washout period and then changed groups. The etiologies of chronic pancreatitis were idiopathic (18 patients) and alcohol (1 patient). It was noted that 3 patients may have been drinking during the study. They reported a '30% reduction' in pain at a

significance level of $p < 0.05$, but pain scores were not reported except in graph form. They also reported decreased frequency of pain by self-report of patients. Frequency of narcotic usage was unchanged between the groups.

In 1984, Slaff et al. [4] reported a double-blind, randomized, placebo-controlled crossover trial of uncoated pancreatic enzymes designed to measure pain as an outcome, in addition to measuring pancreatic secretion in patients receiving pancreatic enzyme replacement. This study randomized 29 patients. The etiologies of chronic pancreatitis were alcohol (10 patients) and idiopathic (10 patients). Patients were also stratified according to degree of pancreatic exocrine insufficiency. Patients were treated with either a regimen of Ilozyme 4 times daily or placebo for 30 days and then crossed over without a washout period. Pain scores were not reported in aggregate, but a significant improvement was noted in patients with mild to moderate pancreatic insufficiency when on pancreatic enzymes. It is unclear from the paper whether this subgroup analysis was planned a priori.

Halgreen et al. [8] reported their experience with coated pancreatic enzymes in 1986, comparing them to placebo. They enrolled 20 patients in a double-blind placebo-controlled crossover trial. The etiology of chronic pancreatitis was alcohol in 11, idiopathic in 4, gallstone in 3, hyperparathyroidism in 1 and hyperlipidemia in 1. Nine of the 20 patients had steatorrhea. Patients were treated with Pancrease, 2 capsules at meals and 1 with snacks. Pain was assessed after each meal and each time analgesics were needed. No change was noted in treatment versus placebo arms in any of the outcome variables. Subgroup analysis was also performed comparing outcomes in patients with steatorrhea versus those without. No difference was noted in any of the subgroup analyses.

Larvin et al. [14] published a report as an abstract in 1991 comparing Creon 3 times daily with placebo. They performed a randomized, controlled crossover trial with 4 weeks in each arm without a washout period. They enrolled 78 patients, 65 of whom completed the protocol. Twenty-nine males and 7 females had a history of heavy alcohol use. No significant benefit of Creon over placebo was noted in any of the pain endpoints.

In 1992, Campbell et al. [15] presented their research in abstract form. They performed a multicenter, randomized, placebo-controlled crossover trial comparing 4 weeks of coated enzymes 4 times daily with placebo. No washout period was included. No significant differences were noted between the treatment and control groups.

Mossner et al. [16] published a report of their experience with coated enzymes in 1992. They performed a multicenter, double-blind, randomized controlled crossover trial comparing a coated enzyme preparation with placebo. Groups were treated for 2 weeks and then crossed over without a washout period. They enrolled 47 patients, of whom 43 completed the protocol. Unlike others, they included both patients with chronic pancreatitis and patients with 'possible acute relapse'. Etiologies of chronic pancreatitis were not well described. No significant change was noted in the treatment versus the placebo group. Though pain medication use was proposed as a primary outcome, these data were not reported.

Malesci et al. [17] published a report in 1995 of a double-blind, randomized, placebo-controlled crossover study comparing coated enzymes to placebo. They studied 26 patients; 22 completed the trial — 2 went to surgery and 2 were noncompliant with treatment and were excluded from analysis. Etiologies were alcohol in 15, idiopathic in 10, and hereditary in 1. Patients were excluded if they had severe steatorrhea or advanced ductal changes on endoscopic retrograde cholangiopancreatography. Patients were treated for 4 months in each arm. It is important to note that 4 patients drank alcohol daily in the trial and 2 patients drank alcohol occasionally during the trial. In the final analysis, no difference was noted between the treatment and control groups.

In 2003, Czako et al. [18] reported a multicenter, prospective follow-up study of coated pancreatic enzyme replacement. They enrolled 75 patients, 70 of whom completed the trial. Patients were analyzed in 2 groups, those with newly diagnosed chronic pancreatitis and those with longer disease duration (mean 3.4 years). Etiologies in the new-disease group were alcohol in 22 and unstated in 9. Etiologies in the older-disease group were alcohol in 28 and unstated in the remaining 9 patients. As this was a follow-up study, there was no comparison or control group. In the final analysis, there was a

significant reduction in pain in both the newly diagnosed and older-disease patients ($p=0.001$ and $p=0.008$, respectively).

Kahl et al. [19] reported their experience in the medical management of a large cohort of patients with alcoholic chronic pancreatitis. They reported improvements in pain and HRQOL in patients receiving medical management. However, few details of their medical management strategy were explained.

A meta-analysis was published in 1997 by Brown et al. [26]. They analyzed the available studies and concluded that there was no significant benefit of pancreatic enzymes for pain relief in painful chronic pancreatitis. Given the heterogeneity of outcome measurements between published studies, their meta-analysis focused on patients' preference of enzymes or placebo. They acknowledge that this may have biased the final results of their meta-analysis.

Proposals for Future Studies

It is clear that the current published studies have not definitively answered the question of whether or not pancreatic enzyme supplementation is useful in painful chronic pancreatitis. In fact, few studies address the use of uncoated enzymes — the recommended treatment strategy. What is clear, however, is how future studies should be structured.

First, patients enrolled in clinical trials of pancreatic enzyme supplements should be classified as to the etiology of their chronic pancreatitis using the recognized classification system proposed by Etemad and Whitcomb [1]. They should also be rigorously screened for alcohol abuse. This will allow clinicians to make a reasonable assessment of the generalizability of the results of any given trial. It would also be helpful to classify patients according to the morphology of their pancreas, i.e., dilated ducts, small duct disease, calcifications, strictures. This would further aid in generalizability.

Second, a systematic assessment of HRQOL must be made prior to initiation of therapy and at regular intervals throughout the study. HRQOL in chronic pancreatitis patients is associated with increased pain, but other factors appear to be important as well [27] [Use of validated pain instruments such as the Brief Pain Inventory [28], the

McGill Pain Questionnaire [29], or others, would be useful. In fact, an instrument designed specifically for chronic pancreatitis, the QLQ-PAN(CP)28, exists, and would be useful in comparing potential interventions against one another [30]. Screenings for ongoing alcohol use and abuse either via validated instruments, available biologic markers, or both must be performed. As noted previously, consideration should be given to including treatment for substance abuse in any protocols.

Third, a priori power analysis must be done, estimating a placebo response rate of at least 25% [31] and possibly higher. Conservatively, one would have to estimate a treatment effect of 20% improvement over placebo, which would require a sample size of about 125 patients. This sample size, while large, would not be overly difficult at a tertiary care referral center or in a multicenter study.

Fourth, a placebo-controlled randomized trial must be performed, as crossover designs are not ideal for the reasons outlined previously. Avoidance of narcotics is also impractical and possibly unethical. Narcotic pain medication should be used both in the active treatment and placebo arms. Quantity of narcotic use and frequency of use would both be useful surrogate and/or secondary outcomes.

Finally, multiple planned subgroup analyses should be performed to determine whether certain etiologies of painful chronic pancreatitis are more amenable to treatment with enzyme replacement than others. This would further aid in the generalizability of future studies of this difficult-to-treat condition. However, one must consider the utility of these subgroup analyses and their potential impact on the sample size required for the study.

Recommendations for Clinicians

Based upon the published studies, the authors would recommend that clinicians follow the general guidelines proposed by the AGA [10]. They would, however, add the following caveats for the use of pancreatic enzymes in painful chronic pancreatitis:

- Pain should be assessed in a standardized and repeat- able fashion prior to initiating a therapeutic trial of pancreatic enzymes. This could be as simple as using a 10-cm visual-analog pain scale which is widely available and takes just seconds for a patient to fill out.

- Therapeutic trials should be limited in time to 6 weeks with uncoated enzymes and concurrent acid suppression, at which point another standardized pain measurement questionnaire should be filled out. With the currently available literature, we would suggest that not one group of patients is more likely to benefit from this intervention than another; however, there is a suggestion that it may be more effective for women with nonalcoholic chronic pancreatitis.
- Uncoated pancreatic enzymes are usually available in the USA as a tablet with 16,000 USP of lipase, and 60,000 USP each of amylase and protease (Viokase 16® and generics). The suggested dose for painful chronic pancreatitis is a total of 12 tablets per day, split with meals and snacks.
- If the clinician feels that narcotics should be a part of the pain management strategy for a patient, pill counts should be part of routine pain assessment at clinic visits.
- Alcohol rehabilitation should be considered for any patient with ongoing alcohol abuse — before beginning therapy with enzyme supplements. This can be as simple as printing out a list of Alcoholics Anonymous meetings in the local area to give to the patient — these can be found online at http://www.alcoholics-anony- mous.org.
- Since only 1 study has shown significant reductions in pain with coated pancreatic enzymes [18], we would not recommend their use in painful chronic pancreatitis in general. Specific cases, however, may represent exceptions to this suggestion.

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Painful chronic pancreatitis is a challenging problem for clinicians and patients. Many patients receive a therapeutic trial of pancreatic enzyme supplementation at some point in the course of their disease, but it is unclear what the expected outcome of such a trial should be and whether or not all patients should receive a trial of pancreatic enzymes. We searched PubMed for all studies of pancreatic enzyme supplementation for painful chronic pancreatitis from 1980 to the present. We also searched the references of identified manuscripts and requested additional information from study authors when necessary. Manuscripts were assessed for study design, bias, pain assessment, and pain management protocol. The results are described in full.