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ORIGINAL ARTICLE

A Pilot Study of Octreotide LAR® *vs.* Octreotide *tid* for Pain and Quality of Life in Chronic Pancreatitis

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ABSTRACT

Context Chronic abdominal pain is the most difficult management issue in patients with chronic pancreatitis. Recently, a long-acting depo-formulated version of octreotide has been developed that can be given as a once monthly intramuscular injection, Octreotide LAR® (O-LAR) rather than as a thrice daily subcutaneous injection (octreotide short-acting, O-SA). **Objective** To see if O-LAR is similar in efficacy to O-SA in the treatment of painful chronic pancreatitis in a small open-label, unblinded pilot study. **Patients** Seven advanced chronic pancreatitis patients with daily, severe abdominal pain who had previously responded to O-SA were recruited from the pancreas clinics of the University of Florida and monitored for one month on O-SA and for four months while on O-LAR. Each patient served as his/her own control as this was a paired data set. **Main outcome measures** 1) Daily VAS scores; 2) daily morphine equivalents; 3) monthly health related quality of life chronic pancreatitis surveys; 4) daily diaries of work/pleasurable activities missed or hospitalization/Emergency Department visits. **Results** Average daily VAS scores for patients during O-SA therapy were 4.50±2.28 and during the fourth month of O-LAR therapy, 3.86±2.11, difference -0.64±0.80 (P=0.078). Average daily morphine equivalents were not dissimilar at 124.3±177.3 mg during O-SA therapy and 131.6±194.3 mg during O-LAR therapy; difference 7.3±17.5 mg P=0.310. Health related quality of life chronic pancreatitis scores were not significantly changed when moving from O-SA to O-LAR. Adverse events were rare. **Conclusions** Octreotide LAR® may be a reasonable substitute for *tid* octreotide in treating chronic pancreatitis pain. Further, larger studies would be useful to better characterize the role of Octreotide LAR® in the management of chronic pancreatitis pain.

INTRODUCTION

Chronic abdominal pain is the most difficult management issue in patients with chronic pancreatitis, causes the majority of the 90,000 admissions annually in the U.S. for chronic pancreatitis [1], leads to narcotic dependence and disability, and is a major detriment to quality of life.

For patients with chronic pancreatitis that fail pancreatic enzymes and neuromodulatory agents, few medical options are available other than narcotics. One agent, short-acting octreotide (O-SA) may hold some promise but is controversial in chronic pancreatitis pain. Octreotide is a longer acting synthetic analogue of the hormone somatostatin [2].

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Abbreviations HRQoL: health related quality of life; O-LAR: long-acting release octreotide; O-SA short-acting octreotide; QoL: quality of life

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Some pre-clinical data suggests octreotide may benefit chronic pancreatitis patients. Octreotide potently inhibits pancreatic secretion directly and also indirectly by blocking CCK and secretin release [3]. Other theoretical mechanisms that might help octreotide improve pancreatitis pain are that it may be anti-inflammatory, may alter the cytokine milieu, and may protect pancreatic cells in experimental models of acute pancreatitis. Octreotide may also decrease proteolysis, reduce intraductal pressure, and can be effectively administered subcutaneously (unlike somatostatin which requires continuous i.v. infusion) [4].

Our previous clinical work indicated that subcutaneous octreotide injections gave remarkable pain relief to a subset of patients with severe, painful chronic pancreatitis. In a placebo-controlled, double blind, dose ranging pilot study of 91 patients for 4 weeks with a 25% reduction in pain considered the primary end point, a dose response curve (40, 100, 200 µg *tid*) was seen with the greatest relief seen in those on 200 µg subcutaneously *tid* (65% *vs.* 35% for placebo) [5]. Even greater pain relief was seen in the subgroup of patients with constant daily pain (75%). Although the P value was slightly above 0.05, it should be recognized that this study was not powered to show a difference

between octreotide and placebo. Rather, the original intent of the study was to find the appropriate dose to use in a large multicenter trial. It is quite likely that a trend towards improved pain over placebo exists. Sixty-one of these patients continued in an open label trial of octreotide for 6 more weeks in which pain was recorded daily by patients and biweekly by investigators. Thirty one percent of patients in this study had complete abolition of pain. By 4 more weeks, 64% still had at least a 25% reduction in pain and by 6 more weeks, 50% still had similar pain relief. Gallstones or sludge developed in 13% of patients receiving octreotide *vs*. none for placebo, but no adverse events occurred [6]. The manufacturer at the time, (Sandoz Corp, East Hanover, NJ, USA), never funded the appropriately powered follow up randomized controlled trial for 200 *tid*.

A study in the Russian literature of 15 chronic pancreatitis patients given octreotide found 8 had a complete pain response and 6 a partial response with one non-responder. Insulin levels did not change. They also performed studies in dogs showing decreased trypsin activity after octreotide therapy and greater activity of trypsin inhibitors [7].

Another independent small study out of the Medical College of Wisconsin, not funded by pharmaceutical manufacturer, showed that in 6 patients (4 women, 2 men) with a mean age of 49 years with daily pain from chronic pancreatitis as evidenced by calcifications or ERCP findings or an abnormal secretin stimulation test (though steatorrhea over 13 g/24 h or insulin requiring diabetes were exclusions), average visual analogue scale (VAS) scores (0-10) were 3 with a peak pain of about 4 while on octreotide acetate (Sandostatin®, Novartis, East Hanover, NJ, USA) for 3 weeks versus 3.5 and 4.5 for the one-week placebo run-in and 4 and 5.4 for the 3-week drug free follow up. Analgesic use was also lower during the octreotide phase versus the placebo and drug free follow up periods. All of these results were statistically significant [8].

These results have remained controversial in the pancreas world. A small, very short duration, but perhaps better publicized study did not reveal pain relief. In this double blind placebo controlled crossover study, 10 patients with alcohol induced chronic pancreatitis were randomized to placebo or octreotide, with only a two day washout (which may be insufficient) and only three days on drug and placebo. VAS scores, fecal chymotrypsin, and analgesic use were recorded while the patients were hospitalized for the study. Although pancreatic secretion, measured by fecal chymotrypsin was reduced by octreotide, there were no differences in pain control or analgesic use. However, it should be noted that four of the patients had pancreatic duct stones. Furthermore, it was not entirely clear when the patients had quit alcohol. Two patients were still drinking in the two-week run-in before the trial, though the authors state that as inpatients, none of the patients had access to alcohol [9].

One of the disadvantages of octreotide therapy in patients with painful chronic pancreatitis is the need for subcutaneous injections three times daily. Recently a long-acting depo-formulated version of octreotide has been developed that can be given as an once monthly intramuscular injection. If extrapolated from the carcinoid and acromegaly literature the equivalent dose to 200 µg *tid* of short-acting octreotide (O-SA) would be 20-30 mg of Octreotide LAR® (O-LAR) (Novartis, East Hanover, NJ, USA) [10, 11, 12, 13, 14]. A steady state is usually achieved after 3 injections (3 months). The role of O-LAR in chronic pancreatitis pain has even less supporting data than O-SA.

Therefore we aimed to see if O-LAR is similar in efficacy to O-SA in the treatment of painful chronic pancreatitis in a small open-label, unblinded pilot study. This study compares pain relief, quality of life (QoL), and narcotic usage in advanced chronic pancreatitis patients who had previously responded to, and were on, O-SA, who were transitioned to O-LAR, given i.m. 60 mg every 28 days.

MATERIALS AND METHODS

Patients

Patients were included from the pancreas clinics at the University of Florida if they had chronic pancreatitis as evidenced by calcifications, atrophy, or main duct dilation on CT, 5 or more diffuse EUS criteria with sufficient supporting clinical history including dilation of the main pancreatic duct, or serum trypsin less than 20 ng/mL with appropriate clinical history and a proven steatorrhea on a 72 h fecal fat collection. In other words, these patients were all candidates for the Puestow procedure yet still had recalcitrant pain. Only one patient had actually undergone a Puestow prior to the study. None had undergone a therapeutic endoscopic procedure. All of these patients had to have been followed by the principal investigator's clinic for the diagnosis of chronic pancreatitis for at least one year. Patients were included only if they had constant daily pain rather than cyclical pain patterns.

Patients were excluded if they were pregnant or lactating females, females of child bearing age not on contraception, children under the age of 18 years, if they had recent documented acute pancreatitis by CT scan or laboratory findings in the last 6 months, if they had evidence of recidivism within the last 4 months (as evidenced by repeated follow up, abstinence, and compliance in the clinic of the principal investigator), if they had a pain pattern of only pain attacks with no daily pain, or if they had evidence of pancreatic duct stricture, large obstructing pancreatic duct stone, pseudocyst, or cancer.

Experimental Design

Seven advanced chronic pancreatitis patients with daily, severe abdominal pain who responded to O-SA subcutaneous 200 µg *tid* were monitored for one month while taking O-SA. One other patient was enrolled but

Table 1. Differences in pain scores and morphine equivalents used (values are mean±SD; n=7).

Outcome	Month 1 (O-SA)	Month 5 (O-LAR)	Difference (month 5-1)	P value
Daily VAS pain score (0-10)	4.50±2.28	3.86±2.11	-0.64±0.80	0.078
Daily morphine equivalent used (mg)	124.3±177.3	131.6±194.3	7.3±17.5	0.314

was unable to keep a diary and she was dismissed from the study. The etiology of the patients' advanced chronic pancreatitis was: alcohol (n=2); idiopathic (n=3); biliary (n=1); hereditary (n=1). Average age was 48.6±18.1 years. Three women and four men were included.

Their O-SA was abruptly stopped with the first i.m. injection of 60 mg O-LAR, which was continued monthly for four months. All patients were maintained on a standardized enzyme, pancrelipase (Ultrase MT 20®, Axcan Pharma, Mont-Saint-Hilaire, Quebec, Canada), two tablets with meals.

Each patient served as his/her own control as this was a paired data set.

On month one (O-SA) and months 2-5 (O-LAR), the following data were collected: 1) daily pancreatic VAS scores (marked by patient with a hash on a 10 cm line), maximum score 10, minimum score 0; 2) daily diaries of morphine equivalents taken for pancreatic pain; 3) monthly health related quality of life surveys (HRQoL-CP: a validated, 4 part, chronic pancreatitis specific survey) [15] were made. This quality of life index has physical, psychological, economic, and social scores on a 1-7 integer scale for each question (there are 7 physical questions for a total possible score in that section of 49; there are 4 psychological questions for again a total possible maximum score of 28; there are 4 economic questions for a total possible score of 28; there are 6 social questions for a total possible maximum score of 42; maximum total score is 147); 4) liver function tests and TSH were monitored monthly; 5) daily diaries of work/pleasurable activities missed or hospitalization/Emergency Department visits; 6) if the patient had been hospitalized the records were queried to obtain the dose of morphine equivalents taken during the hospitalization; 7) morphine equivalents were calculated in the standard fashion [16]; 8) right upper quadrant ultrasound performed at the start of the study and then during the third month of O-LAR therapy to monitor for the development of gallbladder stones.

STATISTICS

Comparisons between month 1 and month 5, when a steady state was most likely to have been obtained on O-LAR were made by paired t-tests, all two-sided. For each subject, a personal slope of total VAS score as the dependent variable *vs*. day number was obtained for all months of O-LAR therapy. These were compared for a mean slope of zero via a one-sample, two-sided t-test. The t-test was used as it is generally fairly robust even in non-normal data as long as no outliers are present [17]. No *a priori* sample size was calculated as this was intended to be a pilot study. Data are reported as mean±SD. Data were analyzed by means of the SAS software (SAS Institute Inc., Cary, NC, USA).

ETHICS

Approval was obtained from the University of Florida Internal Review Board prior to the commencement of the study. Treatment of patients was in accordance with all patient protection codes of ethics. Written informed consent was obtained from each patient.

RESULTS

On average, patients who had previously had a response to short-acting octreotide (O-SA), did well when transitioned to long-acting octreotide (O-LAR).

On average, VAS pain scores nearly achieved a significant drop without a significant increase in morphine equivalents used. Average daily VAS scores for patients during O-SA therapy were 4.50±2.28 and during the fourth month of O-LAR therapy, 3.86±2.11, difference -0.64±0.80 P=0.078. Average daily morphine equivalents were not dissimilar at 124.3±177.3 mg during O-SA therapy and 131.6±194.3 mg during O-LAR therapy, difference 7.3±17.5 P=0.314. (Table 1). There was no significant linear association between VAS scores and days on O-LAR: fitted mean slope 0.0034±0.0128 per day, P=0.500.

HRQoL-CP scores were not significantly changed when moving from O-SA to O-LAR (Table 2).

Although more patients on O-SA missed more work and pleasure from pancreatitis pain (27 and 51 days, respectively) than while on O-LAR (10 and 5 days, respectively), not every patient kept track of pleasurable activities missed and one patient was retired, one disabled, and one a student, so that the overall small number of patients makes reaching conclusions about missed work/pleasure difficult.

Table 2. Health related QoL chronic pancreatitis survey results (HRQoL-CP; values are mean±SD; n=7 except where noted).

Sub-scales (possible range score)	Month 1 (O-SA)	Month 5 (O-LAR)	Difference (Month 5-1)	P value
Physical (0-49)	28.64±13.67	28.86±12.56	0.21±4.90	0.912
Psychological (0-28)	12.71±5.59	12.86±5.31	0.14±1.68	0.829
Economic (0-28)	14.71±6.87	14.17±7.11 [a]	1.17±3.60 [a]	0.463
Social (0-42)	28.57±5.94	26.29±4.68	-2.29±3.04	0.094
Total (0-147)	**84.64±29.59**	**74.17±9.97** [a]	**-0.08±9.03** [a]	**0.983**

[a] n=6

The same issue can be said of hospitalizations (one patient was hospitalized during the study and this was during therapy with O-SA).

Adverse Events

Adverse events were rare. One patient had worsening diabetes while on O-LAR and required insulin. However, she has since remained on insulin 2 years after cessation of the octreotide. Diarrhea scores on the two agents were not dissimilar (data not shown). Patient weights were similar (data not shown). One patient developed new asymptomatic gallbladder sludge while on O-LAR, based on "before and after" right upper quadrant ultrasounds, but there were no differences in liver function tests in patients on O-LAR *vs*. on O-SA (data not shown).

DISCUSSION

On average, in this pilot study, advanced chronic pancreatitis patients with severe, daily pain who had previously demonstrated a response to short-acting octreotide (O-SA) maintained their pain control and quality of life when transitioned to octreotide long-acting (O-LAR). Although not significant, there was a slight trend toward improved pain control while on O-LAR. Furthermore, patients' use of narcotics remained about the same throughout the study on either agent. After having tried once monthly O-LAR injections, all patients except one have chosen to remain on O-LAR, insurance permitting. Quality of life remained about the same while on O-LAR. One might even find a trend of better VAS scores and less work and pleasurable activities missed while on the O-LAR treatment; however, there are not enough data in this small study to draw any definitive conclusions about work and pleasurable activities.

Although one patient's diabetes became insulin-requiring while on O-LAR, she remains insulin-requiring 2 years after the O-LAR was stopped. This makes it difficult to conclude that the O-LAR alone caused the worsening diabetes. Although asymptomatic sludge was detected in one patient on O-LAR, this likely would not have been picked up without the use of routine ultrasound in this study.

One area of controversy is in excluding patients with obstructive, large pancreatic duct stones and strictures. We did this to minimize the effect octreotide might have in reducing intraparenchymal pressure and stimulation as a cause for pain reduction, and to better standardize the patient population. On the other hand, neither did we obtain pre-study endoscopic retrograde pancreatograms on these patients. We felt that the benefit in standardization this would provide would be overshadowed by the increased risk of the endoscopic retrograde pancreatogram. We also felt somewhat confident in the ability of our radiologists to rule out pancreatic duct strictures, masses and cysts by CT scan.

Another area of controversy is in our choice of quality of life surveys. The HRQoL-CP was the only disease specific QoL index available at the time of this study. More recently, the SF-12 and others have been more widely publicized in the application to chronic pancreatitis patients, but this was not as universally accepted at the time of the inception of this study. Nevertheless, the HRQoL-CP was validated in a small study published in abstract form.

The limitations of this study include small size. Also the dose of O-LAR was chosen without any previous pilot data but a double dose was given to more rapidly achieve steady state. It is possible that smaller doses of O-LAR such as that given for carcinoid at 20 mg/month may not be sufficient. It is also possible that weight based dosing may achieve different results. One possibility to standardize opiates before the start of the trial may have given more accurate morphine equivalents, but in practice this might prohibit many patients from entering the study.

It is not clear why the length of time on O-LAR did not have a major effect on VAS scores. It is possible that a steady state was achieved fairly early due to the high dose of O-LAR that was given or that a greater sample size might show a difference of pain response with time on O-LAR.

The follow up was fairly long compared to other octreotide trials.

CONCLUSION

Once monthly Octreotide LAR® may be a useful substitute for *tid* short-acting octreotide in the management of pain in chronic pancreatitis, a disease with few other medical options. Further, larger studies would be useful to better characterize the role of Octreotide LAR® in the management of chronic pancreatitis pain.

Conflict of interest The authors have no potential conflicts of interest

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