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ORIGINAL ARTICLE

Prospective Study

Continuing episodes of pain in recurrent acute pancreatitis: Prospective follow up on a standardised protocol with drugs and pancreatic endotherapy

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Abstract

AIM

To assess the outcomes of drug therapy (DT) followed by pancreatic endotherapy for continuing painful episodes in recurrent acute pancreatitis.

METHODS

DT comprised of pancreatic enzymes and anti-oxidants failing which, endotherapy (ET; pancreatic sphincterotomy and stent placement) was done. The frequency of pain, its visual analogue score (VAS), quality of life (QoL), serum C peptide and faecal elastase were compared between baseline and after 1 year of follow up in all patients and in the two subgroups on DT and ET. Response was defined as at least 50% reduction in the severity of pain to below a score of 5.

RESULTS

Of the thirty nine patients analysed, 21 (53.9%) responded to DT and 18 (46.1%) underwent ET. The VAS for pain (7.0 ± 2.0 *vs* 1.3 ± 2.5, $P < 0.001$) and the number of days with pain per month decreased [1.0 (1.0, 2.0) *vs* 1.0 (0.0, 1.0), $P < 0.001$], and the QoL scores [55.0 (44.0, 66.0) *vs* 38.0 (32.00, 51.00), $P < 0.01$] improved significantly during follow up. Similar

significant improvements were seen in patients in the subgroups of DT and ET except for QoL in ET. The serum C-peptide (P = 0.001) and FE (P < 0.001) levels improved significantly in the entire group and in the two subgroups of patients except for the C peptide levels in patients on DT.

CONCLUSION

A standardised protocol of DT, followed by ET decreased the intensity and frequency of pain in recurrent acute pancreatitis, enhanced QoL and improved pancreatic function.

Key words: Drug therapy; Endoscopy; Exocrine insufficiency; Pancreatic diabetes; Pancreatic duct stents; Quality of life; Recurrent acute pancreatitis; Surgery

Core tip: This prospective case series provides evidence for the efficacy of a sequential approach to the treatment of patients with recurrent acute pancreatitis in whom painful episodes persisted after initial aetiological work up and appropriate interventions if any, with drugs and endoscopic therapy. Along with improvements in the intensity and average number of days with pain, the protocol also improved the quality of life, C-peptide levels and faecal elastase in these patients. The significance of our results needs to be explored in future studies on the effect of these interventions in preventing the progression of recurrent acute pancreatitis to chronic pancreatitis.

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INTRODUCTION

Recurrent acute pancreatitis (RAP) is an important cause of morbidity and mortality in gastroenterology practice[1,2]. Many aetiological factors underlie RAP and a variable proportion of patients exhibit multiple causative factors. Up to a third of patients may have no cause evident and these have been variably designated as unexplained, idiopathic, or true idiopathic disease[3-5]. Identifying the cause helps in unravelling the underlying patho-mechanisms and also directs therapy. Current recommendations on the treatment of RAP focus on the cause. However, the causative or therapeutic significance of some of these factors continue to be controversial. Biliary sludge, crystals and microcalculi provide examples[6,7]. Identifying some causative factors such as genetic mutations may not convert to effective therapy as of today. Similarly, while endoscopic sphincterotomy at the minor papilla appears to improve pain in patients with pancreas divisum presenting with RAP the very cause-effect relationship between these two conditions has been questioned[8-10]. Patients may continue to smoke and drink despite advice to the contrary and even when they comply with such advice, painful episodes may continue to occur. Continuing attacks of pancreatitis even after an identified cause has been corrected suggest that other unrecognized or unknown factors may be operative in such patients. No therapy short of total pancreatectomy and islet cell transplantation is available for such patients who continue to have recurrent episodes of pancreatic pain[7].

The natural history of acute pancreatitis (AP) and RAP progressing to chronic pancreatitis (CP) and the overlap in the causative factors of these three conditions suggest a continuum in their disease spectrum[11]. The lack of definitive therapy in patients with idiopathic RAP and the continuing symptoms in some of those in whom the cause has been corrected means that these patients are potentially at risk of progression to CP with the consequent risks of developing pancreatic diabetes, steatorrhea and pancreatic cancer over time.

The mechanisms underlying inflammation and pain in RAP are poorly understand but are likely to overlap with those of CP[12]. Supplementation of pancreatic enzymes and anti-oxidants, though controversial, are routinely recommended for the treatment of CP, but have not been tried in RAP[13-15]. Endoscopic pancreatic sphincterotomy, an accepted therapy in CP has been used with variable success and attendant controversies, especially in the subgroups with pancreas divisum and sphincter of Oddi dysfunction[5,8,16]. Most centers manage the pain of CP in a stepwise fashion once the underlying causative factors have been addressed - drug therapy with anti-oxidants and/or enzyme supplementation initially followed by endoscopic therapy and finally surgery for those who fail the former approaches[17,18]. We hypothesized that patients with unexplained RAP and those in whom painful inflammatory episodes continue despite treatment of the identified causative factors may benefit from supplementation of pancreatic enzymes and anti-oxidants or endoscopic pancreatic sphincterotomy and temporary stent placement. This prospective case series was designed to assess the role of a standardized protocol of initial drug therapy (DT) followed by endoscopic therapy (ET) in those failing the former, in patients with continuing painful episodes of RAP even after initial work up for definite causative factors and treatment directed at any of these detected.

MATERIALS AND METHODS

Patients with RAP seen in the Department of Gastroenterology and Hepatology, Kasturba Hospital, Manipal University, Manipal, India between January 2013 and June 2014 were eligible for the study. An episode of pancreatitis was defined by any two of typical upper abdominal pain, elevation of serum amylase and lipase above three times the upper limit of normal and changes of pancreatitis on abdominal imaging. RAP was defined as 2 or more episodes of pancreatitis with complete resolution of symptoms in between in the absence of imaging changes of CP on at least two of the following imaging studies - abdominal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography or endoscopic ultrasound (EUS). The patients underwent aetiological evaluation as per current standard of care[3,4]. Sphincter of Oddi manometry and genetic testing were not routinely done. Patients with pancreatic or periampullary carcinoma were excluded. Those undergoing therapy specifically for pseudocysts, pancreatic ascites or pleural effusion were included only if they had recurrence of pancreatic pain after the fluid collections had been tackled. Patients with treatable causes such as bile duct stones, gall bladder microcalculi, hypercalcaemia, serum triglyceride levels more than 500 mg/dL were treated appropriately and included only if recurrent episodes of pancreatitis continued to occur[19]. Those with alcoholic RAP underwent assessment and de-addiction therapy by a psychiatrist. Tobacco smokers were advised to discontinue smoking. Those with recurrence of an acute episode of pancreatitis after any treatable cause had been corrected and those in whom no treatable cause was evident were included.

Interventions

DT comprised of supplementation of pancreatic enzymes as 3 tablets (Digimax tablets, Shreya Life Sciences, Mumbai, containing protease activity of 93750 USP units per tablet) with meals per day and anti-oxidant capsules (Antoxid, Dr Reddy's Pharma, Hyderabad) three times a day. ET involved an initial pancreatogram for defining the ductal anatomy, a 3-4 mm long pancreatic sphincterotomy and the placement of a 5 cm long, 5 French pancreatic stent with multiple side holes and a single flange at the duodenal end. Biliary sphincterotomy was done only if the initial cannulation happened to be in the bile duct or if the pancreatic duct could not accessed after repeated attempts[20]. The stents were checked for spontaneous passage and removed if still seen *in situ* between 3 and 6 wk after placement. Response to therapy was defined as at least 50% reduction in the severity of pain [as defined by the visual analogue score (VAS)] to a score below 5. Failure of DT, either as at entry to the study or after initiation into the study qualified the patient for ET. Those with no response to pain after initial ET were offered repeat endotherapy which involved sphincterotomy if stenosis of the pancreatic opening was encountered, and pancreatic stent placement since total pancreatectomy with islet cell transplantation is rarely performed in our country. Patients were explained the study protocol at entry, and written informed consent was obtained from all before enrollment. The protocol was approved by the Ethics Committee of Kasturba Hospital, Manipal.

Follow up

The patients were followed up at intervals of 6-12 wk or more frequently as clinically indicated. Follow up was continued for a minimum of 1 year on either of the two therapies. Abdominal pain was assessed at baseline and at each follow up visit for its severity using a VAS scale with a maximum score of 10[21]. The number of days with pain since the last follow up was assessed at each visit and averaged to the number of days with pain per month for the entire period of follow up. Quality of life was assessed in all patients aged 18 years and above using the EORTC C 30 questionnaire at baseline, when there was a change of therapy and at the end of 1 year of follow on a given therapy. The EORTC C 30 questionnaire is a validated, self-administered questionnaire with 30 questions, available in the three languages spoken by our patients[22].

Exocrine and endocrine function

Exocrine and endocrine functions were evaluated at baseline, when there was a change of therapy and at the end of 1 year of follow on a given therapy. Fasting plasma glucose and glycosylated haemoglobin (G-Hb) were used to diagnose diabetes mellitus as per the American Diabetes Association criteria[23]. Serum C peptide levels were estimated in fasting morning samples by Enzyme Immunoassay (EIA) (Human C-Peptide EIA kit RayBio Norcross, United States) and values between 1.3-5.2 ng/mL was considered normal[24]. Faecal elastase (FE) was estimated by enzyme-linked immunosorbent assay (ELISA) (Faecal Elastase 1 ELISA kit, ScheBo Biotech, Giessen, Germany) and a value less than 200 μg FE1/g was classified as exocrine insufficiency. All these tests were done at baseline, when there was a change of treatment and at the end of 1 year of follow up on a given treatment.

Statistical analysis

All study parameters were compared between two time points - at entry to either of the two therapies (DT or ET) and at the end of 1 year on the same therapy. The results are provided for all patients as a group and also separately in the two subgroups on DT and

Table 1 Characteristics of patients with recurrent acute pancreatitis completing the study *n* (%)

Number	39
Age in years, median (range)	26 (9-55)
Male:female	32 (82):7 (18)
Alcohol abuse	11 (28.2)
Smokers	10 (25.6)
Number of pain episodes (yr), median (range)	3.00 (1-30)
Duration of symptoms (mo), median (range)	12.00 (1-48)
Family history of pancreatitis	0
Drug therapy alone/endotherapy	21 (53.9)/18 (46.1)
Duration of follow up, median (range)	13 (12-24)

Table 2 Visual analogue score and average number of days with pain per month all patients with recurrent acute pancreatitis and in the subgroups

	Baseline	1 yr	*P* value
All patients (*n* = 39)			
VAS	7.7 (5.5, 8.3)	0 (0, 2)	< 0.001
Average number of days with pain per month	1.0 (1.0, 2.0)	1.0 (0, 1.0)	< 0.001
Patients on DT (*n* = 21)			
VAS	7.3 (5.1, 8.3)	0 (0, 2.4)	< 0.001
Average number of days with pain per month	2.0 (1.0, 2.0)	1.0 (0.0, 1.0)	< 0.01
Patients on ET (*n* = 18)			
VAS	7.1 (5.8, 8.4)	0 (0, 7.5)	< 0.01
Average number of days with pain per month	1.0 (1.0, 3.5)	1.0 (0.0, 1.0)	< 0.05

Data expressed as median (quartiles). VAS: Visual analogue scale.

ET. Continuous variables were expressed as median (quartiles) or as mean ± SD and Wilcoxon Signed Rank Test or paired *t*-test were used as appropriate for comparison as appropriate. The package SPSS 16.0 was used for statistical analysis. The statistical review was performed by a biomedical statistician.

RESULTS

Patients

Forty five patients with RAP were enrolled of whom 39 (86.7%) who completed at least one year of follow up on either of the two therapies were analysed; the remaining 6 (13.3%) were lost to follow up. Eight (20.5%) of these were aged below 18 years. None had a family history of CP. The other characteristics of these patients are shown in Table 1.

Interventions

Twenty-one (53.9%) responded to drug therapy and did not undergo any further interventions. The other 18 (46.1%) underwent endoscopic therapy, 8 (20.5%) having already failed drug therapy at entry, and the rest failing drug therapy during the course of the study. The latter patients did not respond to DT over a median (quartiles) 3 (2.0, 5.0) mo, as evidenced by no improvement in the VAS 8.0 (5.9, 8.5) *vs* 6.6 (4.1, 8.0), $P \geqslant 0.05$). All 18 in the endotherapy group underwent successful pancreatic sphincterotomy and stent placement. one (5.5%) patient had pancreas divisum and the sphincterotomy and stent placement were done at the minor papilla. Three (16.7%) patients on ET needed 1 additional endoscopic procedure and 1 (5.5%) needed 2 additional procedures during the one year follow up.

Pain

The VAS and the average number of days with pain per month decreased significantly in all patients with RAP at the end of follow up. Similar significant improvements were seen in the subgroups on DT and ET (Table 2).

Eleven (28.2%; 8 on DT and 3 on ET) patients had no recurrence of pain with appropriate therapy during the 1 year of follow up. Twenty one (53.9%, 13 on DT and 8 on ET) had partial relief of pain. None of these 32 patients needed re-admissions to the hospital for the control of pain. The remaining 7 (17.9%) failed both therapies. Four of these needed between 1 and 7 (median 2) re-admissions to the hospital for the control of acute episodes of pain.

Quality of life

The QoL scores improved significantly at the end of follow up in patients aged above 18 years (*n* = 31, 79.5%) and in the subgroup on DT (Table 3). However, the decrease seen in patients on ET alone did not reach statistical significance.

Pancreatic functions

No patient had diabetes mellitus or steatorrhea at baseline and none developed these sequelae during follow up. All patients had normal serum C peptide and FE levels at baseline. These parameters improved significantly in the entire group and in the two sub-groups of patients except for the C peptide levels in patients on DT (Table 4).

Adverse events

Patients tolerated DT well and none discontinued drugs due to adverse events. Following ET, 3 (16.7%) patients developed acute exacerbation of pancreatitis, which subsided with conservative management. No other complications were encountered following ET.

DISCUSSION

By following up patients with RAP in whom painful episodes continued to occur after common, treatable causes had been ruled out or corrected, we have shown that more than three quarters of them improved on a standardized protocol of oral pancreatic enzyme replacement along with anti-oxidant supplementation followed by selective use of endoscopic pancreatic sphincterotomy and stent placement in non-responders

Table 3 Quality of life scores in patients with recurrent acute pancreatitis above the age of 18 years and in the subgroups on drug therapy and endoscopic therapy

	Baseline	1 yr	*P* value
All patients (n = 31)	55.0 (44.0, 66.0)	38.0 (32.00, 51.00)	< 0.01
Patients on DT (n = 22)	55.0 (47.0, 64.0)	40.00 (31.50, 54.00)	< 0.01
Patients on ET (n = 9)	59.5 (47.5, 67.5)	36.0 (32.50, 54.3)	0.084

Data expressed as median (quartiles). DT: Drug therapy; ET: Endoscopic therapy.

to the former therapy. The improvement in the pain was evidenced by a reduction in the VAS and the average number of days with pain per month, avoidance of hospitalisation for the control of pain in the responders and also an attendant improvement in the QOL. Such a stepwise approach to the management of pain has been previously described in patients with CP[17,18,20]. However, this is the first time a similar approach has been shown to be effective in the treatment of the pain of RAP. This is also probably the first report on the response to the use of pancreatic enzymes and anti-oxidants in the treatment of RAP. Controversies surround the significance of the entity of sphincter of Oddi dysfunction (SOD) and the usefulness of endoscopic therapy for RAP with or without concomitant SOD[16,25,26]. Given such controversies our results show that a difficult to manage subgroup of patients with RAP can be treated successfully using the protocol we used.

Pancreatic enzymes and anti-oxidants are often used for the treatment of pain in CP though their exact role remains controversial. A Cochrane review concluded that the former therapy is no better than placebo[13]. The conflicting results of two recent, large trials on anti-oxidant therapy for CP appears to translate into only a small benefit in a meta-analysis[14,15,27]. Nonetheless, our results indicate that randomised controlled studies with these drugs for the management of RAP are warranted in the future.

The role of endoscopic pancreatic sphincterotomy in the treatment of RAP is controversial. The response to pancreatic sphincterotomy or stent placement have been variably reported in 50%-100% of patients with idiopathic RAP irrespective of whether they had SOD or not in various case series[4,5,28]. In a recent randomised trial, combined pancreatic and biliary sphincterotomy was no better than biliary sphincterotomy alone in patients with RAP and SOD, either treatment relieving pain in about half the patients[16]. However, patients without SOD underwent only biliary but not pancreatic sphincterotomy in this study. Some of the differences in the outcomes of pancreatic endotherapy in RAP in different studies could be because of the differences in the patients enrolled. The patients who qualified for our study had few therapeutic options available to them short of total pancreatectomy and islet cell transplantation.

RAP is a condition with diverse aetiologies and consequently one with variable natural history. The mechanisms underlying the pain in RAP are complex and not fully understood, but are likely to be similar to those in CP[21,29,30]. Being those in whom painful episodes continued after an initial evaluation for causative factors and their treatment, the patients in the present study were uniform in one sense. No clear cut recommendations are available as to how to treat these patients short of total pancreatectomy and islet cell transplantation, a procedure available only in a few centres. On the other hand the age range of the patients was wide and the proved or presumed causative factors such as alcohol abuse, tobacco smoking or pancreas divisum were seen in varying proportions thereby suggesting that the group was diverse. The fact that more than 80% of the patients showed a complete or partial response during follow up suggests however that the treatment approach we followed is effective. The reason for this could be that the therapies we used targeted specific common pathways leading to recurrent episodes of pain in RAP irrespective of the etiology. For example the negative feedback induced by the enzyme supplementation and the reduction in the pancreatico-duodenal pressure gradient brought about by the pancreatic sphincterotomy could both have acted by decreasing the pancreatic ductal pressure irrespective of whether SOD was present in our patients or not[21,31].

Admittedly, the small numbers included in our study and the lack of a control group are its obvious limitations, especially because long, pain free intervals can occur spontaneously in RAP. Also, it is possible that some of the response seen could be attributed to the rigorous follow up and also the resultant close monitoring of compliance with abstinence from alcohol and tobacco use. Nonetheless, it cannot be forgotten that the type of patients studied have almost no treatment options left and in this sense form a particularly difficult-to-treat group. An example is the group of patients with alcohol or smoking as causative factors who continued to have painful episodes of pancreatitis despite initial interventions such as alcohol deaddiction therapy and advice on tobacco abuse. Nonetheless, the relative role of abstinence from alcohol or smoking, pancreatic enzyme supplementation and anti-oxidant therapy can only be teased out in larger, randomised controlled trials which, for obvious reasons, are not easy to conduct.

The significant improvement in serum C peptide and FE levels we have shown on follow up compared to baseline are probably being reported for the first time in RAP. Their significance can be questioned since none of the patients in the present study had pancreatic insufficiency to begin with, which is on expected lines. But these results are also interesting because

Table 4 Comparison of serum C peptide and faecal elastase levels at baseline and end of follow up

	Baseline	1 yr	*P* value
All patients (n = 39)			
C Peptide (35)	3.2 (2.8, 4.3)	6.4 (2.6, 11.5)	0.001
F Elastase (38)	401.94 (215.5, 484.8)	559.6 (411.3, 597.4)	< 0.001
Patients on DT (n = 21)			
C Peptide (21)	4.13 (3.11, 4.35)	4.47 (2.55, 11.65)	0.079
F Elastase (24)	406.18 (220, 496.43)	559.55 (442.24, 597.30)	0.002
Patients on ET (n = 14)			
C Peptide (14)	2.85 (2.15, 3.53)	7.52 (2.33,10.35)	0.004
F Elastase (14)	335.87 (207.3, 481.41)	562.70 (265.47, 597.35)	0.006

Data expressed as median (quartiles). DT: Drug therapy; ET: Endoscopic therapy.

it is reasonable to attribute such improvements to the reduction in the repeated episodes of pain and the associated inflammation within the pancreatic parenchyma. Mild, transient exocrine and endocrine dysfunction are known following acute episodes of pancreatitis and progression of RAP to CP has been attributed to recurrent episodes of inflammation[18,32,33]. Also, progression of pancreatic insufficiency has been associated with recurrent painful episodes in patients with CP[34]. Such data from these diverse studies taken together raise the possibility that interventions which decrease the painful episodes in RAP could possibly also prevent its progression to CP. Our results should provide the impetus for undertaking such long term studies to evaluate the effect of successful interventions that decrease pain and inflammation in RAP on its progression to CP.

In conclusion, a standardised protocol of DT with pancreatic enzymes and anti-oxidant supplementation followed by ET with pancreatic sphincterotomy and temporary stent placement in the non-responders to the former decreases the intensity and average number of days with pain per month, avoids repeated hospitalisations in those who respond, improves pancreatic exocrine and endocrine functions and enhances QoL. Our results pave the way for larger, randomised trials that can evaluate the effect of these therapeutic interventions on the progression of RAP to CP.

ACKNOWLEDGMENTS

The authors of this study thank Ms. Melissa Glenda Lewis, Department of Statistics, Manipal University, Manipal for inputs on statistics.

COMMENTS

Background

Recurrent acute pancreatitis (RAP) is an important cause of morbidity and mortality in gastroenterology practice. Continuing attacks of pancreatitis even after an identified cause has been corrected suggest that other unrecognized or unknown factors may be operative in such patients. No therapy short of total pancreatectomy and islet cell transplantation is available for such patients who continue to have recurrent episodes of pancreatic pain.

Research frontiers

Many aetiological factors underlie RAP and a variable proportion of patients exhibit multiple causative factors. Up to a third of patients may have no cause evident and these have been variably designated as unexplained, idiopathic, or true idiopathic disease. Current recommendations on the treatment of RAP focus on the cause. However, the causative or therapeutic significance of some of these factors continues to be controversial. So it is important to understand the role of standardized therapy in patients suffering due to RAP.

Innovations and breakthroughs

This study focussed on the role of a standardized protocol of initial drug therapy (DT) followed by endoscopic therapy (ET) in those failing the former, in patients with continuing painful episodes of RAP even after initial work up and treatment of definite causative factors. In this study, they have shown that more than three quarters of them improved on a standardized protocol of oral pancreatic enzyme replacement along with anti-oxidant supplementation followed by selective use of endoscopic pancreatic sphincterotomy and stent placement in non-responders to the former therapy. The improvement in the pain was evidenced by a reduction in the pain scores and the average number of days with pain per month, avoidance of hospitalisation for the control of pain in the responders and also an attendant improvement in the quality of life (QoL). Such a stepwise approach to the management of pain has been previously described in patients with chronic pancreatitis (CP). However, this is the first time a similar approach has been shown to be effective in the treatment of the pain of RAP. This is also probably the first report on the response to the use of pancreatic enzymes and anti-oxidants in the treatment of RAP.

Applications

A standardised protocol of DT with pancreatic enzymes and anti-oxidant supplementation followed by ET with pancreatic sphincterotomy and temporary stent placement in the non-responders to the former decreases the intensity and average number of days with pain per month, avoids repeated hospitalisations for those in pain who respond, improves pancreatic exocrine and endocrine functions and enhances QoL. The results pave the way for larger, randomised trials that can evaluate the effect of these therapeutic interventions on the progression of RAP to CP.

Terminology

DT in this study comprised of supplementation of pancreatic enzymes as 3 Tablets (Digimax tablets, containing protease activity of 93750 USP units per tablet) with meals per day and anti-oxidant capsules (Antoxid) three times a day. ET involved an initial pancreatogram for defining the ductal anatomy, a 3 mm - 4 mm long pancreatic sphincterotomy and the placement of a 5 cm long 5 French pancreatic stent with multiple side holes and a single flange at the duodenal end. Biliary sphincterotomy was done only if the initial cannulation happened to be in the bile duct or the pancreatic duct could not accessed after repeated attempts. The stents were checked for spontaneous passage and removed if still seen in situ between 3 and 6 wk after placement. Response to therapy was defined as at least 50% reduction in the severity of pain (as defined by visual analogue score) to a score below 5. Failure of DT, either as at entry to the study or after initiation into the study qualified the patient for ET.

Those with no response to pain after initial ET were offered repeat endotherapy which involved sphincterotomy if stenosis of the pancreatic opening was encountered and pancreatic stent placement since total pancreatectomy with islet cell transplantation is rarely performed in our country.

Peer-review

This article is unique since it emphasises on the use of a standardised protocol of DT followed by ET for those suffering in recurrent pain due to RAP. The results show that DT and/or ET helps to improve the pancreatic exocrine and endocrine functions and enhance the QoL of these patients.

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