Original Article

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Early Clinical Experience with Simvastatin for Treating Pain in Patients with Idiopathic Chronic Pancreatitis

Internal Medicine Section

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ABSTRACT

Introduction: Chronic Pancreatitis (CP) is a progressive inflammatory disorder characterised by recurrent episodes of severe abdominal pain. Experimental studies demonstrated protective effects of statins in pancreatic fibrosis.

Aim: To assess impact of simvastatin therapy on the severity of pain in patients with idiopathic CP or recurrent acute pancreatitis.

Materials and Methods: This prospective, single centre and open-label study included patients with idiopathic CP and recurrent acute pancreatitis, depending upon inclusion and exclusion criteria. Patients were treated with either simvastatin (40 mg per day) (Group-A; n=25) or standard therapy (proton-pump inhibitor and antioxidant therapy) (Group-B; n=25). Severity of the pain was assessed using a Visual Analogue Score (VAS) at the start of treatment and at 12-month of treatment.

Results: Between June 2017 and August 2017, a total of 50 patients, age ranging from 18 years to 54 years, were included in the study. The study population predominantly included male patients (n=38). The intensity of pain in patients of Group-A reduced significantly (p=0.0001) from 8 (range 6-10) at baseline to 2 (range 0-9) after 12 months of the treatment. There was significant reduction in the intensity of pain in Group-B also {7 (range 6-10) at baseline vs. 5 (range 0-7); p=0.0001}. However, the reduction of VAS score was significantly higher in Group-A as compared to Group-B at 12-month follow-up {6 (range-1-8) vs. 3 (range 0-6); p=0.032}.

Conclusion: Simvastatin treatment improved severity of pain in patients with CP or recurrent acute pancreatitis at 12-month follow-up. However, large randomised trials are needed to replicate these findings.

Keywords: Abdominal pain, Acute recurrent pancreatitis, HMG Co-A reductase inhibitors, Statins

INTRODUCTION

Chronic Pancreatitis (CP), a progressive inflammatory condition of the pancreas, is histologically characterised by loss of normal pancreatic parenchymal architecture with varying degrees of fibrosis and inflammatory infiltrate [1]. The natural history of CP is characterised by recurrent acute exacerbations of pancreatitis in the early stage followed by loss of functional capacity of pancreas in the late stage [2,3]. As a result of persistent damage to the endocrine and exocrine tissues of the pancreas due to recurrent episodes of acute pancreatitis and chronic inflammation, the disease leads to clinical manifestations of endocrine (diabetes mellitus) and exocrine insufficiencies (steatorrhea, mal-digestion).

Pain is a well recognised and debilitating symptom for which patients with CP seek medical assistance. Among all the complications of CP, abdominal pain was found to be strongest predictor of poor Quality of Life (QoL) and disability [4]. Even though endoscopic and surgical treatments are often performed to relieve pain, these invasive therapies provide beneficial effects in a subset of patients with CP [5]. A combination of analgesics, pancreatic enzymes, adequate nutrition and antioxidants (and if applicable cessation of smoking and alcohol) are currently used medical therapy in CP [5,6]. However, till date, none of the medical therapies are ascertained to achieve sustained pain relief in CP [7]. Hence, there is an unmet need for therapeutic alternative.

Statins are widely used for both primary and secondary prevention of atherosclerotic disease. Apart from their efficacy in improving plasma lipid profiles, the protective effects of the statins in acute pancreatitis have been documented in several observational studies [8-11]. However, there is a scarcity of evidences which demonstrated beneficial effects of statins in CP. Moreover, except one retrospective observational study, the evidences are confined to experimental studies (animal models) [12-15]. Hence, it is necessary to assess the role of statins in patients with CP. We thus, designed this study to assess the role of simvastatin therapy in reduction of pain in patients with idiopathic CP or recurrent acute pancreatitis. Hence, we hypothesised that simvastatin therapy decreases pain in patients with CP and in patients with recurrent acute pancreatitis.

MATERIALS AND METHODS

Study Design and Patient Population

This prospective, single centre and open-label study was conducted at Surat Institute of Digestive Sciences, Surat, Gujarat, India, between June 2017 and August 2017. All consecutive patients with idiopathic CP and recurrent acute pancreatitis who had acute inflammatory episodes or abdominal pain of pancreatic origin were included in the study as per inclusion and exclusion criteria.

Patients were diagnosed with CP based on the occurrence of episodes of abdominal pain along with morphological alterations of the pancreatic duct as per Cambridge criteria [16]. Patients who had recurrent episodes of acute pancreatitis (as per Atlanta classification) with resolution of symptoms between each episode, and absence of morphological criteria for CP were diagnosed with recurrent acute pancreatitis.

Inclusion criteria: 1) age between 18 years and 70 years; 2) if there was at least one episode of pain every month requiring analgesics during the preceding three months, or at least one episode of severe pain requiring hospitalisation in the preceding three months, the patient was considered to have significant pain; 3) if the patient provided written informed consent.

Exclusion criteria: 1) patients having reversible aetiologies of pancreatitis, for example, alcohol, hypercalcaemia and hypertriglyceridemia, presence of complications of CP for example, pancreatic pseudoaneurysm, inflammatory head mass or distal bile

duct stricture; 2) having received earlier or taking at present HMG-CoA reductase inhibitors; 3) evidence of pancreas divisum either by magnetic resonance cholangio-pancreatography or contrast-enhanced computed tomography; 4) family history of pancreatitis or pancreatic cancer; 5) pseudocyst >5 cm in size or pancreatic ascites; 6) narcotic addicts; 7) previous pancreatic surgery; 8) pancreatic cancer.

The study was conducted according to good clinical practice and Declaration of Helsinki. The study was approved by institutional ethics committee (SIDS/SIMVA_JUN/2016-17). All the patients provided written informed consent for participation prior to enrolment in the study.

Methodology

At the time of enrolment, all patients were treated with standard therapy including micronutrient antioxidants (A tablet containing β carotene: 3000 IU, methionine: 550 mg, selenium: 200 μg, vitamin C 40 mg, vitamin E 10 mg; once a daily) and proton-pump inhibitor. Patients and their caregiver were thoroughly explained, the availability of treatments for CP as well as inadequate evidences of safety and efficacy of simvastatin for treatment of CP. The decision to opt simvastatin therapy was left upon the discretion of the patient. If the patient agreed to initiate simvastatin therapy, he was prescribed simvastatin 40 mg per oral or else was treated with the standard therapy [1,2].

All the patients were followed annually (or as and when required). Severity of the pain was assessed using a VAS, where 0 is absence of pain and 10 is intolerable pain (scale 0-10) at baseline and at 12-month of the treatment.

STATISTICAL ANALYSIS

Continuous variables were presented as median (range) and categorical variables were presented as frequency (percentage). Mann-Whitney or Wilcoxan-rank test were used to assess statistically significant difference. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS® statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 50 patients, age ranging from 18 years to 54 years, were included in the study [Table/Fig-1]. The study population predominantly included male patients (n=38). Of the 50 patients included in the study, 25 patients received simvastatin therapy (Group-A) and 25 patients received standard therapy (Group-B). There was no statistically significant difference in baseline clinical characteristics between Group-A and Group-B.

Clinical characteristics	Overall N=50	Group-A n=25	Group-B n=25	p-value
Age (years), median (Range)	33 (18-54)	35 (21-54)	37 (18-48)	0.43
Male: Female	38:12	18:7	20:5	0.95
BMI[1], median (Range)	23 (21.5-24.2)	22.4 (21.5-23.8)	24.2 (22-24.2)	0.34
Current smoker, n (%)	10 (20%)	6 (24%)	4 (16%)	0.65
Duration of pancreatitis (months), median (Range)	12 (8-60)	08 (8-48)	10 (10-60)	1.3
No of patients with underlying DM[2], n (%)	18 (36%)	8 (32%)	10 (40%)	0.54

[Table/Fig-1]: Baseline clinical characteristics of the study population.
BMI: Body mass index; DM: Diabetes mellitus

The intensity of pain in patients of Group-A reduced significantly (p=0.0001) from 8 (6-10) at baseline to 2 (0-9) after 12 months of the treatment [Table/Fig-2]. Similarly, there was significant reduction in the intensity of pain in Group-B (7 (6-10) at baseline vs. 5 (0-7); p=0.0001). However, it is noteworthy that the reduction of VAS score is significantly higher in Group-A as compared to Group-B at 12-month follow-up {6 (1-8) vs. 3 (0-6); p=0.032}.

	Visual analogue score		p-value	Reduction of visual analogue score at 12 month from baseline median (Range)	p-value
	At baseline median (Range)	At 12-month follow-up median (Range)			
Group-A	8 (6-10)	2 (0-9)	0.0001	6 (1-8)	0.032
Group-B	7 (6-10)	5 (0-7)	0.0001	3 (0-6)	

[Table/Fig-2]: Visual analogue score at baseline and at 12-month of treatment.

DISCUSSION

The current baseline study reports short-term outcomes of pain as measured by VAS score in patients treated with simvastatin (40mg/day) for CP as compared to patients treated with standard therapy. The major finding of the study is that there was a significant improvement in the intensity of pain among patients treated with simvastatin at 12-month of follow-up.

Otani M et al., assessed long-term treatment with pravastatin on the development of diabetes mellitus and pancreatic fibrosis in diabetes mellitus-prone Otsuka–Long–Evans–Tokushima Fatty (OLETF) rats [14]. The results of the studies demonstrated down-regulated levels of expression of TNF-α and TGF-β1 mRNA [14]. These observations were reiterated in the study conducted by Wei L et al., [13-15]. TNF-α, a pro-inflammatory cytokine, is found to be involved in the onset of pancreatitis and TGF-β1 plays an essential role in the induction of fibrosis [17,18]. TGF-β1 is inhibited by antioxidant treatment in CP (having oxidative stress as underlying pathophysiology). Hence, it has been presumed that statin (pravastatin) suppresses progression of pancreatic inflammation and fibrosis by attenuating oxidative stress. The production of IL-10 (anti-inflammatory cytokines which inhibit production of TNF-α and IL-6) was also found to be increased in pancreas with statin therapy [13,19]. Pancreatic stellate cells produce extracellular matrix with expression of α-SMA-positive cells which is considered as an important step in the development of pancreatic fibrosis [20,21]. Statin treatment inhibits activation of pancreatic stellate cells through decreased expression of α-SMA-positive cells [13]. More recently, Bang UC et al., designed case-control study using Danish National Patient Registry and evaluated the association of statins (in patients with CP) with mortality, severity of CP, and pancreatic cancer. Results of the study showed that the use of statins was associated with reduced all-cause mortality (hazard ratio 0.64 (95% confidence interval: 0.49-0.83)), reduced progression of CP (hazard ratio 0.21 (95% confidence interval: 0.17-0.26)), and reduced risk of pancreatic cancer {hazard ratio 0.21 (95% confidence interval: 0.06-0.70)} [12]. In a nut-cell, statin can be considered as a therapeutic alternative owing to its anti-oxidant, anti-inflammatory and anti-fibrotic effects in CP.

The results of the study showed that both treatments (simvastatin and standard therapy) reduced the intensity of the pain. However, there was statistically significant higher reduction of VAS score in patients receiving simvastatin as compared to patients receiving standard therapy.

LIMITATION

These results need careful interpretation in view of inherent limitations of the study. Important potential source of errors in this study could include the small sample size, use of only VAS score for pain (to assess of efficacy of treatment as it is unable to measure pain character, frequency, pattern or pain interference) and short-duration of follow-up. Hence, further large randomised control trials using validated, disease-specific questionnaires (to assess QoL)

and long-term follow-up are required.

CONCLUSION

The findings of the study demonstrate that both treatments (simvastatin and standard therapy) improved severity of pain in patients with CP or recurrent acute pancreatitis at 12-month follow-up. However, there was significantly more reduction in the intensity of pain among patients receiving simvastatin as compared to patients receiving standard therapy.

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