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Cystic fibrosis transmembrane conductance regulator modulators reduce the risk of recurrent acute pancreatitis among adult patients with pancreas sufficient cystic fibrosis

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ABSTRACT

Background: Approximately 1 in 5 patients with pancreas sufficient cystic fibrosis (PS-CF) will develop acute pancreatitis (AP). It is not known whether ivacaftor alone or in combination with other CFTR (cystic transmembrane regulator) modulators (tezacaftor or lumacaftor) can reduce the risk of AP in patients with PS-CF and AP history.
Methods: We retrospectively queried the CF registry at our institution for adult patients with PS-CF, a documented history of AP and initiation of CFTR modulators for pulmonary indications. Patient characteristics including demographics, CFTR genotype, pancreatitis risk factors, pancreatic exocrine function and other relevant laboratory, imaging parameters were obtained from the time of the sentinel AP episode through the follow-up period.
Results: A total of 15 adult CF patients were identified with mean age of 44.1 years (SD ± 13.8). In the 24 months preceding CFTR modulator initiation, six of these patients had at least 1 episode of AP with median of 2 episodes [1.75, 2.5]. None of the patients had evidence of pancreatic calcifications or exocrine pancreas insufficiency at the time of CFTR modulator initiation. The mean duration of follow-up after CFTR modulator initiation was 36.7 months (SD ± 21.5). None of the patients who remained on CFTR modulators developed an episode of AP or required hospitalization for AP related abdominal pain during follow-up.
Conclusions: CFTR modulators, alone or in combination, substantially reduce the risk of recurrent AP over a mean follow-up period of 3 years in adult patients with PS-CF and a history of prior AP. These data suggest that any augmentation of CFTR function can reduce the risk of pancreatitis.

Introduction

Approximately 1 in 5 patients with pancreas sufficient cystic fibrosis (PS-CF) will develop acute pancreatitis (AP) and have an increased risk of developing AP when compared to CF patients with pancreas insufficiency (PI-CF) [1]. The cystic fibrosis transmembrane conductance regulator (CFTR) modulator, ivacaftor, was shown in a recent case series of 6 patients with PS-CF and AP to reduce the risk of recurrent AP over a 12 month follow-up period [2]. However, all 6 of these patients had at least one ivacaftor responsive mutation. It is not known whether ivacaftor alone or in combination with other CFTR modulators (tezacaftor or lumacaftor) can reduce the risk of recurrent AP in patients with PS-CF and AP.

Methods

We retrospectively collected data on all adult PS-CF patients at our institution enrolled in the CF registry with a documented history of AP. There was no restriction placed on which CFTR

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mutations were included. We recorded the use of any CFTR modulator(s) including ivacaftor alone or in combination with lumacaftor or tezacaftor for pulmonary indications. Patient characteristics including demographics, CFTR genotype, pancreatitis risk factors and number of AP episodes, pancreatic exocrine function and other relevant laboratories as well as imaging parameters were recorded. The results from pulmonary function tests were obtained from the time of CF diagnosis to follow-up after initiation of a CFTR modulator. Patients without documented evidence of AP and those with other etiologies of pancreatitis were excluded. The primary outcome of interest was the number of AP events prior to and after CFTR modulator initiation. We also separately collected information on PS-CF patients with a documented history of AP, but not on treatment with a CFTR modulator for comparison as controls. Given the limited sample size, statistical comparison of event rates was avoided to preclude interpretation errors from type II statistical error.

Results

A total of 15 adult PS-CF patients with documented evidence of AP and on treatment with CFTR modulators were identified (Table 1). Seven of these patients were female and the mean age was 44.1 years (SD ± 13.8). The mean age at the time of first acute pancreatitis episode was 32.2 years (SD ± 17.1), while the mean age at the time of CFTR modulator initiation was 42.5 years (SD ± 14.1). Eight of the 15 patients had a ΔF508 as one of their CFTR mutations. Prior to CFTR modulator initiation, the frequency of AP events ranged from 1 to 10 (Fig. 1). In 24 months preceding CFTR modulator initiation, six of these patients had at least 1 episode of AP, with a median of 2 episodes [1.75, 2.5] (Table 1). None of the patients had CT imaging evidence of pancreatic calcifications or had low fecal pancreatic elastase (<200 μg/g) at the time of CFTR modulator initiation. The mean duration of follow-up after CFTR modulator initiation was 36.7 months (SD ± 21.5) (range 19.2–95 months). None of the patients who remained on CFTR modulators developed any episode(s) of AP or required hospitalization for abdominal pain during the follow up period. However, there was one patient (ID# 12) who developed AP only during times when she had to discontinue CFTR modulator use due to problems with insurance coverage**.** The majority of the patients had improved percent-predicted forced expiratory volume in 1 s ($PPFEV_1$) on PFTs following CFTR modulator initiation, during follow-up at 3–6 month interval. $PPFEV_1$ was fluctuating and was not suitable for formal statistical analyses due to the limited sample size. Another 8 adult PS-CF patients were identified with evidence of AP and who were not initiated on CFTR modulators (Fig. 1). These patients had a median of 3 AP episodes [2, 5.25] and have continued to have AP related hospitalizations in the past year.

Discussion

CFTR modulators are a new class of drugs that act by improving production, intracellular processing, and/or function of the defective CFTR protein [3]. While CFTR modulators have been developed and used primarily to treat the pulmonary manifestations of CF, limited data exists on the efficacy of CFTR modulators in preventing AP [2,4]. Animal disease models demonstrated elimination of tissue inflammation and damage in pancreata when CFTR expression is rescued [5]. Among PS-CF patients who develop AP, 60% are known

Table 1
Patient demographics, CF genotype and CF modulator used and acute pancreatitis characteristics.

Patient ID	Age	Gender	CFTR Mutation #1	CFTR Mutation #2	CFTR Modulator Regimen	Number of AP episodes in 24 months prior to CFTR modulator initiation	Number of AP episodes documented after CFTR modulator initiation	Duration of follow-up since CFTR modulator initiation (in months)
1	38	M	F508del	2789+5G- > A	Ivacaftor transitioned to tezacaftor/ivacaftor combination	2	**0**	19
2	39	F	R1162X	2789+2insA	Ivacaftor	2	**0**	29
3	44	F	F508del	G551S	Ivacaftor	0	**0**	26
4	47	F	F508del	3849 + 10kbC- > T	Tezacaftor/ivacaftor combination	0	**0**	24
5	47	M	F508del	2789+5G- > A	Ivacaftor transitioned to tezacaftor/ivacaftor combination	0	**0**	25
6	30	M	2183AA- > G	S945L	Ivacaftor transitioned to tezacaftor/ivacaftor combination	1	**0**	36
7	32	M	2789+5G- > A	duplication exons 8-10	Tezacaftor/ivacaftor combination	0	**0**	20
8	38	F	F508del	R352Q	Tezacaftor/ivacaftor combination	0	**0**	35
9	76	F	R117H	TG12/T5	Ivacaftor	2	**0**	25
10	59	M	F508del	3272-26A- > G	Ivacaftor transitioned to tezacaftor/ivacaftor combination	0	**0**	27
11	50	F	F508del	R352Q	Ivacaftor transitioned to tezacaftor/ivacaftor combination	0	**0**	64
12	29	F	4251delA	G551D	Ivacaftor	4*	**5***	95
13	64	M	3849 + 10kbC- > T	3849 + 10kbC- > T	Ivacaftor transitioned to tezacaftor/ivacaftor combination	0	**0**	31
14	27	M	2789+5G- > A	E60X	Tezacaftor/ivacaftor combination	0	**0**	24
15	41	M	F508del	R117H	Ivacaftor	2	**0**	64

(M = Male, F = Female, CF = cystic fibrosis, CFTR = Cystic fibrosis transmembrane conductance regulator, AP = Acute pancreatitis) * Patient # 12 discontinued CFTR modulator after initiation intermittently and developed AP only during times when she was not using CFTR modulator.

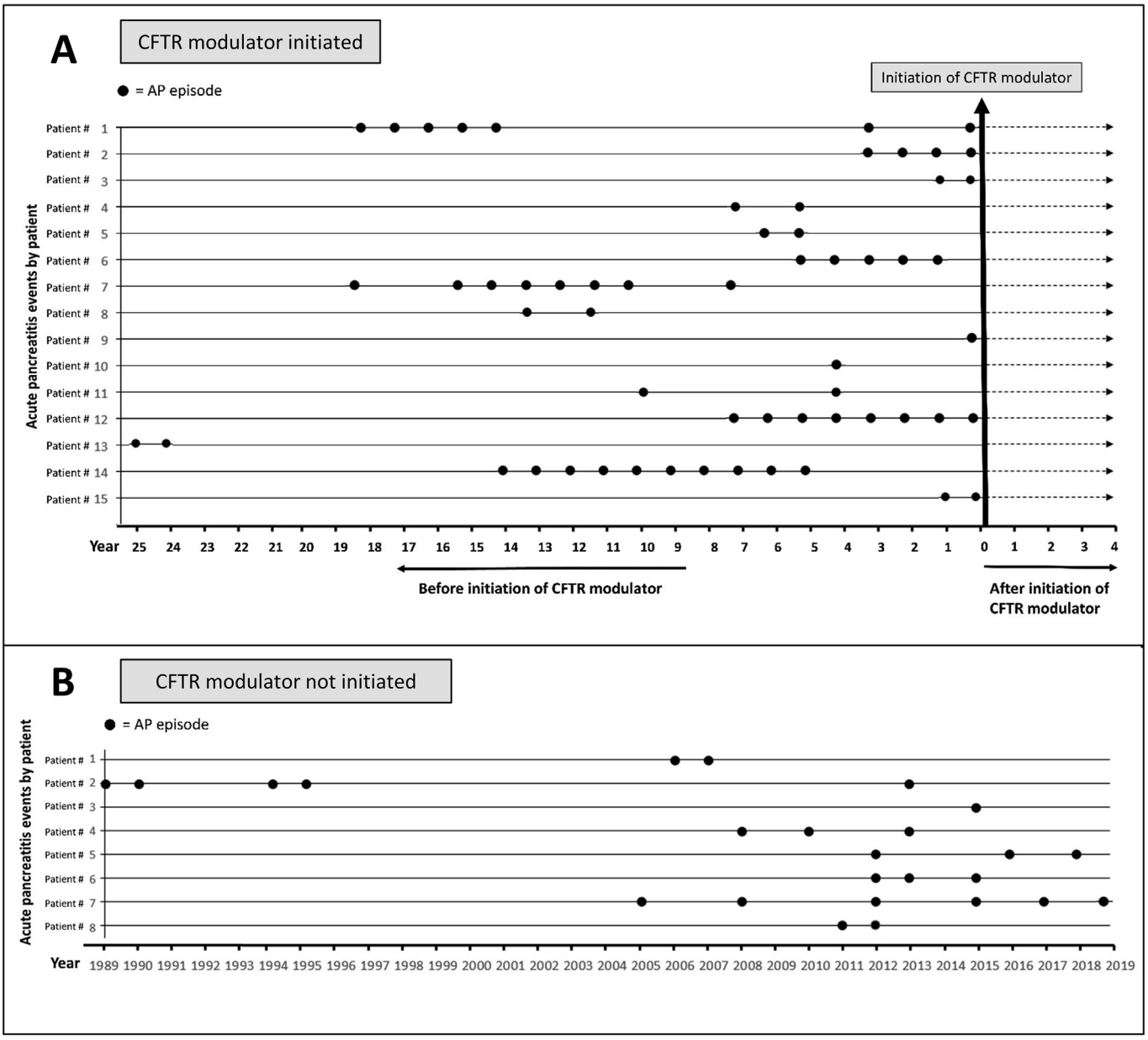

Fig. 1. (A) Frequency of acute pancreatitis (AP) episodes over time in a patient cohort initiated on CFTR modulator(s). Each row represents an individual patient and each dot represents an AP episode in that year. The solid vertical line represents initiation of CFTR modulator(s). X-axis represents years before or after initiation of CFTR modulator(s). (B) Frequency of AP episodes over time in patient cohort that was not initiated on CFTR modulator(s). Each row represents an individual patient and each dot represents an AP episode in that year. X-axis represents time as year.

to have a recurrence of AP and 20% have >10 AP episodes [6]. Recurrent AP is associated with a significant impairment in the quality of life and can accelerate the progression to chronic pancreatitis as well as exocrine pancreatic insufficiency and diabetes [7]. This case series suggests a potential role for CFTR modulators in preventing AP episodes among PS-CF patients with a wide spectrum of CFTR mutations, not limited to ΔF508, over a mean follow-up period of 3 years. These data suggest that any augmentation of CFTR function can reduce the risk of acute pancreatitis. In this series, the majority of patients initiated on CFTR modulators had an overall improvement of $PPFEV_1$ but this was affected by recurrent pulmonary infections in some patients.

Limitations of this study include the small sample size, inability to perform a formal statistical comparison with a matched control group not on CFTR modulators. However, our data serves only as a proof of concept in support of a trial to evaluate the efficacy of CFTR modulators for the secondary prevention of AP. Since only 40% of the patients initiated on CFTR modulators had an episode of AP in 24 months preceding CFTR modulator initiation, one may theorize that the other 60% of patients have progressed to CP and the resulting fibrosis would prevent additional episodes of AP regardless of whether they were on CFTR modulators. However, none of the patients in our cohort had clinical or laboratory evidence of pancreas insufficiency at the time of CFTR modulator initiation and their imaging studies did not reveal clear morphologic changes of CP. These patients initiated on CFTR modulators; therefore, continue to be at risk of developing AP.

More than 10 million Americans are asymptomatic carriers of defective CFTR variant(s). The majority of CFTR variants are not associated with functional consequences [8]. AP is a complex

disease that results from an interplay of several genetic and environmental risk factors. Recent evidence suggests a role of environmental factors such as alcohol and smoking in the disruption of CFTR expression and localization [9,10]. With such a high prevalence of CFTR variants, therapies that augment CFTR function may reduce the risk of AP, which is especially relevant for the prevention of recurrent AP. Interestingly, a recent case report demonstrated the complete reversal of pancreatic exocrine insufficiency with the use of CFTR modulators. This was hypothesized to be due to enhanced ductal ion conductance and resumption of partial pancreatic acinar cell function [11]. While CFTR modulators potentially lead to resumption of acinar cell function, it has been hypothesized that this may result in recurrence of AP episodes as the balance between acinar function and ductal obstruction is tilted towards the former. However, this has not been noted in our cohort and larger studies are warranted to explore this phenomenon.

Among those developing AP in a cohort of PS-CF patients, the onset of AP preceded the diagnosis of CF in 24% [6]. In addition, we are increasingly identifying patients with idiopathic recurrent AP who have undergone an extensive diagnostic evaluation that only reveals mild CFTR mutation(s) with normal sweat chloride concentration which is consistent with CFTR-RD (related disease) [12]. Some of these CFTR-RD functional variants impair bicarbonate conductance-permeability in the pancreatic ductal cells, which result in alteration of luminal pH and increase risk of AP [13]. It is conceivable that the early initiation of CFTR modulators in the larger population of CFTR-RD patients could also prevent the long-term sequelae of IRAP. This was recently demonstrated in a case report [14]. We believe our data provides additional support for a trial of CFTR modulators for the secondary prevention of recurrent AP among PS-CF patients, regardless of mutation class. While one may argue about the cost-effectiveness in recommending such an expensive preventive strategy vis-à-vis CFTR modulators for secondary prevention of AP, we should also not only consider the cost but also the quality adjusted life years saved by potentially preventing progression of AP to chronic pancreatitis, associated chronic pain and possible malignant transformation. A larger prospective study and eventually a controlled trial is therefore warranted to further investigate the findings of the current study.

Author contributions

Venkata S. Akshintala - study concept and design; acquisition of data; interpretation and analysis of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Ayesha Kamal - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Mahya Faghih - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Garry R. Cutting - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Liudmila Cebotaru - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Natalie E. West - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Mark T. Jenning - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Rebecca Dezube - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

David C. Whitcomb - study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Noah Lechtzin - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Christian A. Merlo - drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Vikesh K. Singh - study concept and design; interpretation and analysis of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Declaration of competing interest

Vikesh K. Singh: Consultant to Abbvie, Ariel Precision Medicine, and Akcea Therapeutics. Advisory board participant for Orgenesis.

David C. Whitcomb: Serves as a consultant for AbbVie, Regeneron and Ariel Precision Medicine and may have equity in Ariel Precision Medicine.

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Ayesha Kamal: No relevant conflicts to declare.

Mahya Faghih: No relevant conflicts to declare.

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Christian A. Merlo: No relevant conflicts to declare.

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