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Therapeutic hopes for CFTR-related recurrent pancreatitis: a case-series

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ABSTRACT

The presence of *CFTR* variants increases the risk of pancreatitis in pancreatic sufficient people with cystic fibrosis (pwCF) or with CFTR-related disorder (pwCFTR-RD). Modulators have been showed to decrease pancreatitis episodes in pwCF presenting recurrent pancreatitis. Whether CFTR modulators are efficient to prevent recurrent episodes of pancreatitis in pwCFTR-RD is not known. We collected clinical, biological, imaging and CFTR functional data in 4 patients with recurrent pancreatitis and CFTR-RD, treated with CFTR modulators and assessed the efficacy of the treatment. With a follow-up of minimum 9 months, we found that ETI and ivacaftor reduced or even resolved the number of acute pancreatitis episodes

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by 2 pathogenic variants *in trans* in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene, leading to a multisystem disease mainly affecting the lungs and digestive system [1]. In recent years, increasing recognition has been given to CFTR–related disorders (CFTR-RD), describing individuals with CFTR dysfunction who do not meet full diagnostic criteria for classic CF [2]. These individuals may present with isolated or milder organ involvement, often making diagnosis challenging and contributing to delays in targeted management [3]. Unlike people with CF (pwCF) and no residual CFTR function, who frequently develop pancreatic insufficiency early in life, patients with residual CFTR function are more prone to pancreatitis, as partially functional pancreatic ductal cells may still produce water and electrolytes albeit not in appropriate amounts so that ducts become obstructed, triggering intrapancreatic enzyme activation and inflammation [4].

Pancreatitis in the context of CFTR-RD remains underrecognized. Early identification of CFTR dysfunction in this setting carries important implications not only for diagnosis and genetic counseling but also for emerging therapeutic strategies. In recent years, CFTR modulators have shown promise in improving pancreatic ductal function in pwCF with residual CFTR activity, suggesting a potential role in reducing pancreatitis frequency and severity (reviewed in [5]). Various published clinical cases have confirmed this pancreatic CFTR function restoration of modulators in real life [6,7]. To date, it is unknown if improving CFTR dysfunction translates into a reduction in the number of pancreatitis episodes in pwCFTR-RD presenting recurrent pancreatitis (RP). This case-series describes the story of 4 pwCFTR-RD and RP and the therapeutic impact of CFTR-modulating therapy in altering the disease

Abbreviations: ARP, acute recurrent pancreatitis; CF, Cystic fibrosis; pwCF, people with CF; ETI, elexacaftor-tezacaftor-ivacaftor; FEV1, forced expiratory volume in one second; BMI, body mass index; NPD, Nasal potential difference; BAST, β-adrenergic sweat test.

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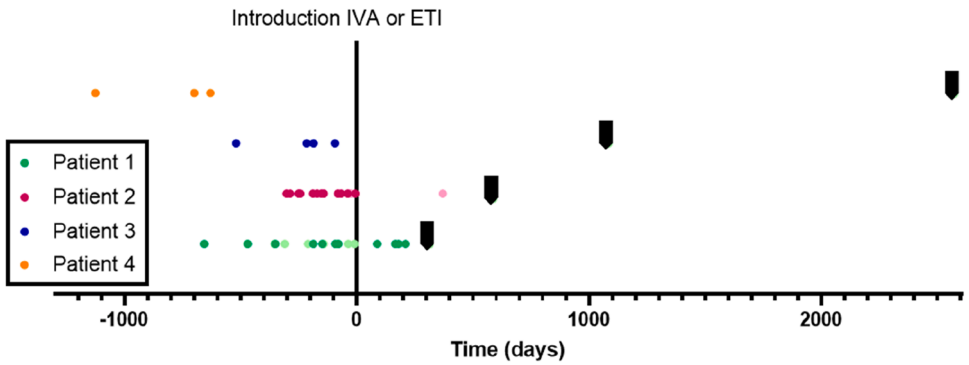

Fig. 1. Pancreatitis episodes in the 4 patients before and after modulator initiation. The dark-colored dots represent the pancreatitis episodes defined by at least 2 of the following signs or symptoms: abdominal pain, elevated lipase above 3 times the upper limit of normal and compatible abdominal ultrasonography/CT scan. The light-colored dots represent abdominal pain suggestive for pancreatitis without elevated lipase and compatible abdominal imaging. Black arrows represent the end of the follow up.

course.

2. Case report 1

A Moroccan 21-year-old woman was assessed at the CF reference center for RP (5/year) since the age of 12. She reported chronic productive morning cough, but lung function and chest CT were normal. Fecal elastase and sweat chloride concentration (SCC) were in the normal range. One F508del CF causing variant was found in *trans* with F1166C, only described in one Tunisian child with CF [8]. There were no other pathogenic variants in genes for chronic pancreatitis such as *CTRC, SPINK1, PRSS1, CaSR, CPA1* or *CLDN2*. MRI showed a reverse pancreas divisum. Nasal potential difference (NPD) showed some abnormalities however not meeting the criteria for CF, as well as β-adrenergic sweat test (BAST) by evaporimetry. She was treated with elexacaftor-tezacaftor-ivacaftor (ETI) for 9 months, presenting only 2 episodes of pancreatitis, a decrease of chronic abdominal pain. On ETI, BAST shifted to values comparable to those in healthy subjects (β-adrenergic peak pre-ETI of 0.38 versus on-ETI of 59 g/h.m^2; CF range <4.5 g/h.m^2 and healthy 30–60 g/h.m^2) [9] and by bubble test (pre-ETI of 0.04 versus on-ETI of 0.27 nl/min; normal value above 0.16 nl/min) (Fig. 1 and Table 1).

3. Case report 2

A Caucasian 12-year-old boy presented in clinic for RP since the age of 10 (12 episodes in 2 years) (Fig. 1). He had no unusual respiratory symptoms. His lung function, fecal elastase and SCC were within normal ranges. Two CFTR variants, one with varying consequences (R117H;7T) and another, non-CF causing in CFTR2 [10] but CFTR-RD-causing in CFTR France [11] (5T;TG11) were found in *trans*. There were no variants in other causal or risk factor genes for chronic pancreatitis such as *CTRC, SPINK1, PRSS1, CaSR, CPA1* or *CLDN2*. MRI evidenced a partial pancreas divisum. NPD showed some abnormalities, not meeting the CF range and rectal organoid morphology was in the intermediate zone (Table 1). RNA analysis performed on the organoids did not demonstrate additional intronic variants causing splicing defects. He was then treated with ivacaftor and didn't present new episodes of pancreatitis over a period of 19 months, although he presented one episode of abdominal pain evocative of pancreatitis but with normal lipase and pancreas imaging. NPD reverted to normal values on ivacaftor (Table 1).

4. Case report 3

A Caucasian 11-years-old girl presented in clinic after 3 episodes of pancreatitis over a 9 months period. Her past medical history was remarkable for a tetralogy of Fallot. She denied any unusual respiratory symptom. SCC was twice in the intermediate range (30 and 36mmol/L). Genetic testing evidenced two *CFTR* variants in *trans*, one CF causing variant (F508del) and one variant of unknown significance (R1438W), only described in complex alleles [12,13], predicted as benign-moderate or causing splicing defects by *in silico* prediction [14]. There were no pathogenic variants in other causal or risk factor genes for RP (*CTRC, SPINK1, PRSS1,* CASR*, CPA1* or *CLDN2)* and pancreas imaging didn't evidence an obstructive etiology. She was treated with ETI and didn't present new episodes of pancreatitis after a follow-up of 37 months (Fig. 1).

5. Case report 4

A Moroccan 15-years-old boy presented RP since the age of 3 years (3 episodes in 16 months) and one episode of distal intestinal occlusion syndrome. He complained about cough but had no bronchiectasis on chest CT and lung function was normal. The SCC was normal (20mmol/L). One CF causing variant (G551D) and one CFTR-RD causing variant (L997F, non-CF causing in CFTR2 and CFTR-RD-causing in CFTR France) were found *in trans*. At the NPD, basal potential difference was within the normal range with a high response to amiloride, evocative of eNaC hyperactivity, chloride secretion was difficult to interpret. Intestinal current measurements (ICM) were within the normal range (Table 1). He started ivacaftor at the age of 7 years and didn't present any new episode of pancreatitis after a follow up of 8 years. After one year of ivacaftor, NPD didn't show any ENaC hyperactivity. Regarding ICM, values remained within the normal range after one and two years of treatment. BAST assessed by evaporimetry, performed after two years of ivacaftor therapy, showed values in the range of those observed in heterozygous subjects (β-adrenergic peak: 9.8 g/h.m^2; CF range <4.5 g/h.m^2 and healthy 30–60 g/h.m^2).

None of the patients presented unwanted effects of modulators during follow-up. Table 1 summarizes CFTR functional testing (NPD, BAST, ICM and rectal organoids) performed before modulator therapy in the patients.

Informed consent was obtained from the patient before publication.

6. Discussion

This case series illustrates the notable reduction of recurrent episodes of pancreatitis after initiating CFTR modulators in four patients with indications of some degree of CFTR dysfunction but without CF. Improvement was strikingly temporally related to the initiation of modulators and sustained over time except for patient 1. However, it has to be noted that this patient also carried an anatomical variant that could explain the persisting episodes of RP although no recurrence was noted in patient 2 also presenting an anatomical abnormality.

Table 1
Summary of functional tests performed before modulator initiation.

Patient	Diagnosis	CFTR genotype		SCC (mmol/L)	NPD						BAST		ROMA	ICM
		Allele 1	Allele 2		Basal PD (mV)	Amiloride (mV)	Delta amiloride (mV)	Delta total chloride (mV)	Delta ATP (mV)	Wilschanski index	Sermet index	β-adrenergic peak (g/h.m^2)	bubble test (nl/min)		
1	CFTR-RD	F508del	F1166C	12	Right: **−52** Left: −31	Right: −16 Left: −13	Right: **36** Left: −18	Right: −26 Left: −9	Right: **−19** Left: −7.8	Right: 0.49 Left: −0.6	Right: 1.03 Left: **0.1**	0.38	0.04	NA	NA
2	CFTR-RD	R117H;7T	5T; TG11	12	Right: −20 Left: −26	Right: −14 Left: −17	Right: 6 Left: 9	Right: **−4** Left: **−4**	NA	Right: 0.51 Left: 0.64	Right: **0164** Left: 0	NA	NA	Close to non-CF pattern, but **high magnitude of swelling**	NL
3	CFTR-RD	G551D	L997F	**30** and **36**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4	CFTR-RD	F508del	R1438W	20	Right: 3	NA	Right: 21.8	Right 6.3	Right: −5.1	0.908	**−0.859**	NA	NA	NA	NL

CFTR-RD: CFTR-related disorder, BAST: β-adrenergic sweat test, ICM: intestinal current measurement, NA: not available, NL: normal, NPD: nasal potential difference, ROMA: rectal organoid morphology analysis, SCC: sweat chloride concentration. Diagnostic criteria for CF: Delta total chloride <10 mV, Sermet index <0.27, Wilschanski index: >0.7. **BOLD** are indicated as "not normal".

Table 2
Arguments for and against the use of modulators in pwCFTR-RD and pancreatitis.

Pros
-Reducing the number of pancreatitis episodes
-Preservation of pancreatic exocrine function
-Improving quality of life
-Improving non-pancreatic symptoms (sino-pulmonary symptoms)
Cons
-Modulators have an exorbitant cost
-Exposure to side effects of medication
-Limited clinical evidence
-Efficacy related to genotype

Compound heterozygous genotypes involving either a severe and a mild CFTR variant or two mild variants are described risk factors for RP [3], though evidence for the latter remains limited [15]. The pathophysiologic relationship between CFTR dysfunction and the development of pancreatitis is complex and only partially understood.

Pancreatitis is a severe debilitating disease with a significant morbidity and mortality [16]. Its management is mainly supportive and very few specific treatments exist impacting a limited number of patients. In this context, CFTR modulators could represent an interesting therapeutic tool for a broader patient's group to prevent further pancreatitis episodes and progressive decline in pancreatic function [17] (Table 2). It is however difficult to perform clinical trials in pwRP in the context of CFTR-RD, as the duration of the active treatment necessary to reach the clinical endpoint is difficult to define and may be too long to demonstrate statistically significant differences in the treatment group compared to controls [18]. Whether CFTR modulators would also benefit to patients with alcoholic chronic or RP which demonstrated mislocalization of CFTR remains to be further studied [19].

Despite soliciting patients from 8 western European expert CF centers, our sample is limited by size and variable follow-up duration. This is, at least in part, attributable to the exorbitant costs, the subsequent limited access to these medications and the absence of EMA approval to treat pwCFTR-RD with modulators (Table 2). Moreover, interpreting advanced CFTR functional tests in the grey zone remains challenging. Nevertheless, we believe that this data suggests the benefit of modulators in at least some patients with RP associated to CFTR dysfunction and warrants further trials. Access to drugs in rare diseases is a major issue. The pharmaceutical industry should have a duty to make medicines available at an acceptable price for investigator-initiated trials, or to ensure that drug-repurposing commercial trials can take place.

In conclusion, our findings in this small patient group hints towards a possible therapeutic role of ivacaftor or ETI in patients with RP as part of a CFTR-RD designation, warranting a prospective trial to demonstrate the efficacy in pwCFTR-RD.

Author contributions

SG and IS realized the conception and design of the article; SG, IS, AL and FV collected clinical data; SG and IS drafted manuscript; SG, AL, ISG, ED, AL, FV and IS edited and revised manuscript; all authors approved final version.

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Declaration of competing interest

SG, EDW, FV, IS and AL are PI's of Vertex studies, received speaking

fees and/or performed advisory boards for Vertex industry. Others author state no conflict of interest.

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