CLINICAL EVIDENCE OF PANCREATIC RECOVERY IN CHILDREN WITH CYSTIC FIBROSIS ON IVACAFTOR

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November 20, 2023

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To the Editor,

Pediatric research has shown that young children with cystic fibrosis (CF) and treated with ivacaftor have seen improvements in pancreatic function. KIWI was a 24-week safety and efficacy trial of ivacaftor in children aged 2-5 years with CF (1). KLIMB was an 84-week open label extension of KIWI (2). Patients enrolled in KIWI revealed an average increase of 99.8 ug/g in fecal elastase (FE). Before beginning ivacaftor, 26 of 27 patients were pancreatic insufficient. After 24 weeks, 25% of these 26 patients had FE results demonstrating pancreatic sufficiency (>200 ug/g) (1). These improvements in FE were maintained during the 84-week KLIMB extension (2).

In the ARRIVAL Study, a younger population was studied. Infants aged 12-24 months previously diagnosed with pancreatic insufficiency were assessed (3). After 24 weeks post ivacaftor initiation, six of nine, or 67%, of the infants had repeat FE values of >200 ug/g, consistent with pancreatic sufficiency, as well as evidence of decreased pancreatic inflammation noted with reduction in immunoreactive trypsinogen.

Based on this data we instituted a new protocol for repeat FE monitoring in all patients with pancreatic insufficiency who started on ivacaftor by the age of two years. If FE is normal (>200 ug/g), discontinuation of pancreatic enzyme replacement therapy (PERT) is considered along with ongoing monitoring of clinical symptoms and adjustments to vitamin and diet recommendations as indicated.

Below is a review of our cohort of pediatric patients who were currently, had been consistently treated with ivacaftor, and were assessed for current pancreatic function by repeat FE testing. All FE values were collected prior to initiation of elexacaftor/tezacaftor/ivacaftor (ETI) in those newly eligible. Nine patients at our CF center who were on PERT have started ivacaftor in the last 6 years with a mean current age of 4.9 years (SD 1.7). The median age of ivacaftor initiation was 1.1 years (range 0.4 - 2). The mean duration of treatment is 3.9 years (SD 1.3).

Seven patients had a repeat FE result >200 ug/g. Six of the seven pancreatic insufficient patients presented as newly pancreatic sufficient as evidenced by a FE result of >200 ug/g compared to previous result of <200 ug/g. Patient I was included in this cohort as he was treated with PERT for clinical symptoms of pancreatic insufficiency even though his baseline FE values were above 200 ug/g.

The six newly pancreatic sufficient patients started ivacaftor between 0.4 and 1.1 years of age. Our recovery data of 75% is close to the rate seen in the ARRIVAL study. We calculated binomial probability for pancreatic recovery in this small case control series using 0.67 factor based on previous data in ARRIVAL (4). This resulted in a 28% favorability of success.

Unsurprisingly, the rate of recovery was higher in the younger age of initiation of ivacaftor than that seen in the older 2–5 year-old cohort in KIWI. A correlation between pancreatic recovery and younger age of initiation was also noted in a recently published multi-center retrospective study of all available CFTR modulators and PE recovery (5). In this study, of the 15 patients with FE results of 200 or greater, 10 had been treated with ivacaftor as their initial modulator therapy. Based on the demographic data, 62.5% of those treated with ivacaftor had pancreatic recovery, which is similar to our cohort data.

We urge CF Centers to institute clinical protocols to recheck pancreatic elastase to assess for restoration of pancreatic function in all pediatric patients treated with PERT on ivacaftor. Subsequently, CF Centers should establish processes for discontinuing PERT, monitoring fat soluble vitamins, and adjusting diet as indicated. Resulting medication adjustments will significantly impact the treatment burden and cost for these children and their families. Those with pancreatic restoration should be monitored for symptoms of pancreatic insufficiency as well as growth trends at routine intervals and pursue repeat FE as indicated based on clinical assessment.

This study was approved by the Oregon Health and Science University Institutional Review Board (IRB#26442).

Patient	Current Age (years)	Ivacaftor Initiation	Age of Initiation (years)	Ivacaftor Duration (years)	Initial FE Result (ug/g)*ˆ	Repeat FE Result (ug/g)¥	Repeat FE Result (ug/g) ¥	Repeat Result 2 (ug/g)ˆ
A	4.5	8/2019	1.1	3.4	<15			392
B	5.0	6/2019	1.1	3.9	57			>800
C	5.7	3/2018	0.5	5.2	95			453
D	2.3	7/2021	0.4	1.9	58			>800
E	5.4	2/2019	1.1	4.3	212		<15	21
F	8.3	3/2017	2	6.3	<50			98
G	3.3	8/2020	0.5	2.8	151			375
H	4.0	1/2020	0.6	3.4	43			>500
I	5.6	4/2019	1.4	4.2	485	488	243	606

Figure 1. Individual Fecal Elastase results

FE=Fecal elastase

*Initial FE result (testing completed shortly after birth), ¥repeat FE results if available, Δ testing completed 05/2023-06/2023 and prior to ETI initiation if applicable

for upper and lower limits are different

Shaded boxes represent pediatric patients who appear newly pancreatic sufficient based on FE result >200ug/g (6) and clinical assessment of symptoms.

Result	**Interpretation**
Less than 100 ug/g	Severe insufficiency
100-199 ug/g	Moderate insufficiency
200 ug/g or greater	Normal

Figure 2. Reference range for Pancreatic Fecal Elastase by Immunoassay (6)

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