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Case Report

Severe Abdominal Pain and Acne Vulgaris after the Initiation of Elexacaftor / Tezacaftor/Ivacaftor (ELX/TEZ/IVA)

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Abstract

The development of CF transmembrane conductance regulator (CFTR) modulators especially Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), has led to significant improvement in CF care. However, as increasing number of patients are started on (ELX/TEZ/IVA), side effects that have not been described in clinical trials are now being reported. In this case report we describe a CF patient with mild disease and remarkable complications once ELX/TEZ/IVA was started.

Keywords: Cystic fibrosis; CF transmembrane conductance regulator modulators; Elexacaftor/tezacaftor/ivacaftor; Severe constipation; Acne Vulgaris

Abbreviations: CF: Cystic Fibrosis; CFTR: CF transmembrane conductance regulator; ELX/TEZ/IVA: Elexacaftor/tezacaftor/ivacaftor; ED: Emergency Department

Introduction

Cystic Fibrosis (CF) is an autosomal recessive disease caused by a defective CF Transmembrane conductance Regulator (CFTR) gene. [1] Mutations in the CFTR gene leads to thick viscous mucus in lungs, pancreas, and gastrointestinal tract. [1] Chronic thick mucus accumulating in the lugs will lead to irreversible airway damage and progressive lung function decline. [1] CF complications secondary to thick secretion build up leads to malabsorption, bowel obstruction and hepatobiliary disease in the pancreas, gastrointestinal tract, and biliary ducts, respectively. [1,2] Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a CFTR corrector/potentiator triple combination therapy, which has demonstrated efficacy in patients who are F508del homozygous or heterozygous with minimal function mutations in the CFTR gene. [3,4]. Since the release of ELX/TEZ/IVA there has been significant improvement in lung function and quality of life in CF patients. [2] However, observational studies have shown higher rates of side effects and complications that were rarely observed or not described in the clinical trial setting [2].

This case report describes a patient with severe complications shortly after starting ELX/TEZ/IVA necessitating its discontinuation several times with final resolution of the complications and resumption of ELX/TEZ/IVA.

Case Presentation

CP is an 18 years old young man with pancreatic insufficient cystic fibrosis (sweat test: 109 mEq/L and homozygous delF508). He has a mild course of CF with significant history of sinusitis and polyposis requiring several surgeries. He was treated with Tezacaftor/Ivacaftor (TEZ/IVA) and was switched to Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA) on 11/21/2019. While on TEZ/IVA he had experienced headache and abdominal pain which were managed with a bowel regimen of MiraLAX. Nonetheless, shortly after starting ELX/TEZ/IVA he began to experience increasing abdominal pain and headaches that were significantly worse than prior episodes. A few bowel cleanouts with MiraLAX was done, however; CP continued with worsening abdominal pain and ELX/TEZ/IVA was stopped. He was taken to the local Emergency Department (ED). In the ED, he complained of severe sharp abdominal pain since the start of ELX/TEZ/IVA. His physical exam was unremarkable except for abdominal distension, generalized abdominal tenderness. All labs were within normal limits including liver enzymes. Abdominal x-ray revealed large volume stool burden in the left upper quadrant. Abdominal ultrasound demonstrated stable gallbladder sludge without features of cholecystitis. In the ED, CP was given milk and molasses enema and discharged with MiraLAX, Colace, Senna and GoLytly. He was recommended to restart ursodiol. ELX/TEZ/IVA was restarted on 12/2/2019 after cleanout was completed. On 12/12/19 he developed otitis media, acute sinusitis and conjunctivitis at the same time and was treated with antibiotics and he continued on ELX/TEZ/IVA. On 2/22/2020, he reported worsening abdominal pain and distention, therefore; discontinued ELX/TEZ/IVA and presented to urgent care for worsening abdominal pain that required another bowel clean out. Complete work up by GI was done and was negative. He

restarted ELX/TEZ/IVA mid-March 2020. Since then he tolerated ELX/TEZ/IVA and abdominal pain resolved with daily MiraLax. On 08/12/2020, he stopped ELX/TEZ/IVA due to the development of painful cystic acne and "stye's". He had deep cysts on face, axilla and neck. He denied any abdominal pain at that time. Since discontinuation of ELX/TEZ/IVA his acne cleared up with no other interventions. He restarted ELX/TEZ/IVA again six days after resolution of his acne. Since that time there was no further reports of abdominal pain or cystic acne flares.

CP has had previous history of acne vulgaris diagnosed February 26, 2018 and he completed a course of isotretinoin in 08/2018 with complete resolution of his acne. In addition, prior to starting ELX/TEZ/IVA, his constipation was well controlled on daily MiraLAX. He did not need to visit the ED or urgent care for this complaint prior to the use of ELX/TEZ/IVA.

Discussion

Shortly after our patient started ELX/TEZ/IVA, he developed severe episodes of abdominal pain and constipation that lead to recurrent discontinuation of ELX/TEZ/IVA and repeated ED visits. Moreover, he experienced otitis media, acute sinusitis and conjunctivitis simultaneously, and severe acne vulgaris while on ELX/TEZ/IVA. There was a notable correlation between cessation of ELX/TEZ/IVA and resolution of our patient's symptoms. Most of these complications were not reported in the clinical trials. [3,4]. It is unclear the mechanism of action that incited his symptoms. However, they could be due to restoration of CFTR function in different organs.

Chronic constipation is not uncommon in CF, with viscous intestinal mucus and gastrointestinal dysmotility resulting in undigested food adhering to intestinal walls [5]. Theoretically, with initiation of a highly effective CFTR modulator and resultant hydration of sticky intestinal mucus, fecal matter may detach from the luminal wall and begin to move along the bowels simultaneously, increasing the potential for the symptom of abdominal pain suggestive of DIOS and constipation [5]. Therefore, abdominal pain reported in real-world studies, particularly cases that were severe and/or warranted interruption or discontinuation of therapy, may have been in relation to sudden increased fecal transit. Thus, more information about location and quality of abdominal pain, and expected onset along with findings on physical assessment and imaging, would be necessary to evaluate this theory further [4].

Other adverse events reported after the initiation of ELX/TEZ/IVA included: rash, testicular pain and discomfort, RUQ and epigastric pain, elevated liver enzymes, and biliary colic with some patients necessitating cholecystectomy. Also, worsening depression and anxiety were reported [2].

In conclusion, CF patients on ELX/TEZ/IVA should continue to be closely monitored for unreported side effects. Further studies are needed for examining pulmonary and extra-pulmonary complications of ELX/TEZ/IVA.

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