JPPT | Case Report

New Tic Disorder in a Child With Cystic Fibrosis Treated With Elexacaftor/Tezacaftor/Ivacaftor

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The widespread use of highly effective cystic fibrosis transmembrane-conductance regulator modulator therapy has dramatically altered the lives of individuals with cystic fibrosis. Clinical trials leading to modulator approval by the US Food and Drug Administration demonstrated improvements in major outcome measures including pulmonary function, gastrointestinal symptoms, and quality of life. Subsequent clinical experience has confirmed significant improvement across these domains. Adverse effects reported during clinical trials included headache and dizziness amongst others including upper respiratory infections, abdominal pain, diarrhea, rash, and elevated serum transaminases. Post marketing clinical experience has suggested that there may be additional central nervous system adverse effects resulting from modulator therapy. Reported events after initiation of cystic fibrosis transmembrane-conductance regulator modulator treatment include headaches and increased prevalence of mental health concerns including anxiety and depression. We report a new tic disorder in a 7-year-old girl with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor.

ABBREVIATIONS CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane-conductance regulator; CNS, central nervous system; ETI, elexacaftor/tezacaftor/ivacaftor; FAERS, US Food and Drug Administration Adverse Event Reporting System; HEMT, highly effective modulator therapy

KEYWORDS adverse event; CFTR modulator; cystic fibrosis; elexacaftor/tezacaftor/ivacaftor; tics

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene, *CFTR*. Mutations in *CFTR* may result in decreased amounts of or function of the cystic fibrosis transmembrane conductance regulator protein (CFTR) expressed on epithelial surfaces throughout the body. Although CFTR is widely expressed in many organ systems, the primary clinical manifestations of CF are chronic airway infection leading to loss of pulmonary function and gastrointestinal manifestations including pancreatic insufficiency leading to malnutrition.[1] Historically, therapies for CF were aimed at mitigating the downstream effects of CFTR dysfunction. Over the past 2 decades, CFTR modulator therapies, which improve the quantity or function of CFTR, have been developed.[2]

Highly effective modulator therapy (HEMT) includes CFTR modulators, which demonstrated significant improvement in multiple domains evaluated during clinical trials and sustained benefit in post-approval observational studies. Ivacaftor and elexacaftor/tezacaftor/ivacaftor (ETI) are considered HEMT for people with cystic fibrosis meeting specific age and *CFTR* mutation label requirements.[3] ETI was approved on 21 October 2019 and is currently labeled for use in people with CF who are heterozygous for *F508del* or 1 of 177 other specified mutations.[4] In the clinical trials leading to US Food and Drug Administration (FDA) approval, neurological adverse events reported included headache in 17% of subjects receiving ETI versus 15% in subjects receiving placebo.[2] Anxiety and depression were not outcome measures monitored or reported in the clinical trials. Post-marketing clinical experiences suggest an increased incidence of headache, mental health concerns, tics, and seizures among people with CF initiating therapy with ETI.[5,6] The Cystic Fibrosis Care Center at Children's Mercy Kansas City reports the development of a new tic disorder in a child with CF treated with ETI.

Patient Case

A 7-year-old female who is heterozygous for *F508del* and *R1162X* mutations was born at term and diagnosed with CF secondary to meconium ileus and abnormal newborn screening. Overall, she did well clinically and did not have significant symptomatology. ETI therapy was initiated at age 6.5 years; she received 2 tablets of elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg by mouth in the morning and 1 tablet of ivacaftor 75 mg by mouth in the evening. At that time, pulmonary function was normal (force expiratory volume during the first second = 95% of

Table. Central Nervous System Adverse Effects Reported by FAERS (All Reports Received As of December 31, 2022)

Adverse Effect	Ivacaftor (4925 treated) N (%)	ETI (7004 treated) N (%)
Headache	148 (3.01)	617 (8.81)
Anxiety	40 (0.81)	247 (3.53)
Depression	39 (0.81)	199 (2.84)
Dizziness	53 (1.08)	176 (2.51)
Mental disorder	21 (0.43)	76 (1.09)
Migraine	19 (0.39)	62 (0.89)
Seizure	18 (0.37)	35 (0.50)
Eye irritation	1 (0.02)	16 (0.23)
Eye pain	7 (0.14)	9 (0.13)
Tic disorder	3 (0.006)	7 (0.10)

ETI, elexacaftor/tezacaftor/ivacaftor; FAERS, US Food and Drug Administration Adverse Event Reporting System

predicted), as was nutrition (body mass index = 89th percentile). Other medications prescribed at the time of ETI initiation included albuterol twice daily with airway clearance, 7% sodium chloride inhalation, pancreatic enzyme replacement therapy with each meal, and fat-soluble vitamin supplementation.

Patient's mother contacted Cystic Fibrosis Care Center at Children's Mercy Kansas City 2 months after initiating therapy with ETI regarding concerns for possible adverse effects. Mother reported that patient developed an eye-rolling tic shortly after initiation of the medication. The frequency of the tic increased to the point that it was "constant" and the patient then developed eye pain. She was evaluated by an optometrist who reported no findings which would explain pain or the tic. ETI was discontinued by mother, with resolution of symptoms within 2 weeks. Approximately 1 month after discontinuation, ETI was resumed at a decreased dose of only 1 tablet of elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg by mouth in the morning and no tablets in the evening. Mother reported a return of the same symptoms within 2 days of re-starting the medication. Mother immediately discontinued ETI, symptoms resolved, and the child's mother is unwilling to resume therapy at this time. The Naranjo Adverse Drug Reaction Probability Scale was applied to this case and received a score of 6/10 (see Supplementary Table), indicating this adverse drug reaction is probably related to ETI.[7]

Discussion

Clinical trials leading to FDA approval of ETI reported a slight increase in headaches among individuals treated with ETI compared with those treated with placebo. Dizziness was also reported uncommonly but at a slightly higher rate than in the placebo group. Other central nervous systems (CNS) adverse effects, including anxiety and depression, were not reported. Subsequent case reports and communication through professional organizations suggest that ETI may be associated with significant adverse CNS events. Cases of behavioral tics, seizures, anxiety, depression, tremors, and dementia-like symptoms have been reported and are thought to correlate with ETI initiation. Additionally, the FDA Adverse Event Reporting System (FAERS) Public Dashboard describes significant CNS-related adverse events summarized in the Table. Although these data support a not insignificant incidence of adverse CNS events reported among people with CF treated with HEMT, they may underestimate the actual incidence as "minor" adverse effects are often not reported by clinicians.

The reasons for CNS adverse effects among people with CF treated with ETI are not entirely clear, as the function of CFTR in the CNS remains poorly understood and there do not appear to be clinically significant manifestations of abnormal CFTR function in the CNS among most people with CF. However, CFTR is known to be diffusely expressed in the peripheral and central nervous systems of healthy individuals and people with CF and a number of structural and functional CNS abnormalities have been reported in animal models and among people with CF.[8] How HEMT alters the function of CFTR in the CNS is completely unknown. It is plausible, if not expected, that improvement in CFTR expression and function at cell surfaces in the CNS would lead to CNS effects by altering electrolyte and fluid homeostasis. This could result in increased cerebrospinal fluid and transient headaches as a new equilibrium is developed. Direct effects on the areas of the CNS where CFTR is heavily expressed are also considerations. The increased prevalence of headache and mental health issues reported in post-marketing clinical experience may support this hypothesis.

The case above, in which there is a clear temporal relationship between initiation of ETI and the onset of tics, discontinuation of therapy and resolution of symptoms, and return of symptoms with resuming therapy along with the Naranjo score are compelling that the newly developed tics were related to ETI. This is consistent with FAERS reporting which includes eye irritation, eye pain, and new tic disorders.

Although HEMT has been in use among people with CF for 10 years, ETI has only been used in a majority of people with CF for approximately 3 years. Efficacy data from clinical trials and subsequent clinical experiences indicate that HEMT is life changing for people with CF. Overall, safety data from trials has been reassuring, but the CF care community is rapidly accumulating data suggesting that there may be significant and previously

unrecognized CNS adverse effects associated with HEMT. This case strongly suggests ETI as the causative agent for this child's new tic disorder. Given this and other reports, a systematic approach must be taken to document CNS adverse effects of HEMT and conversations regarding potential risks must occur before initiation of therapy. A high index of suspicion regarding new neurological symptoms must be maintained after starting HEMT and therapy should be adjusted or stopped pending a thorough evaluation.

Article Information

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