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BRIEF REPORT

Incidence of transaminitis in adults with cystic fibrosis taking elexacaftor/tezacaftor/ivacaftor

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ABSTRACT

Background: Cystic fibrosis (CF) transmembrane conductance regulator modulators are a cornerstone of CF treatment. However, many patients develop CF liver disease (CFLD) over time, and previous data indicate a risk for transaminase elevation with modulator use. Elexacaftor/tezacaftor/ivacaftor is a commonly prescribed modulator with broad efficacy among CF genomic profiles. Theoretically, elexacaftor/tezacaftor/ivacaftor drug-induced liver injury could exacerbate and further worsen CFLD, but holding modulators can cause a decline in clinical status.

Objectives: This study was designed to determine the real-world incidence of transaminase elevations in adult patients with CF taking elexacaftor/tezacaftor/ivacaftor.

Methods: This exploratory, retrospective descriptive study included all adults with CF-prescribed elexacaftor/tezacaftor/ivacaftor at our institution's outpatient CF clinic. We explored transaminase elevations in 2 separate outcomes: incidence of transaminase elevations of more than 3 times the upper limit of normal (ULN), and transaminase elevations of 25% or more above baseline.

Results: 83 patients were prescribed elexacaftor/tezacaftor/ivacaftor. Nine patients (11%) experienced an elevation of more than 3 times ULN and 62 (75%) experienced an elevation of 25% or more above baseline. The median days to transaminase elevation were 108 and 135 days, respectively. Therapy was not discontinued due to transaminase elevations in any of the patients.

Conclusion: Transaminase elevations among adults taking elexacaftor/tezacaftor/ivacaftor were common but did not result in discontinuation of therapy. Pharmacists should be reassured of the liver safety profile of this important medication for patients with CF.

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Background

Cystic fibrosis (CF) is an autosomal, recessive disease that involves multiorgan dysfunction. CF is caused by altered epithelial chloride ion transport via mutations in the CF transmembrane conductance regulator (CFTR) membrane protein.[1,2] The liver is one of the many organs affected by altered chloride ion transport.[2-4] CF liver disease (CFLD) can have a heterogeneous clinical presentation and is the third most frequent cause of death in CF.[4]

Significant advancements in CF research have improved patient care, including the development of small molecules to restore CFTR function.[5,6] CFTR modulators target the causative defect of specific genetic mutations to improve the functioning of the CFTR membrane protein and facilitate normal chloride ion transport.[1,5-7] Ivacaftor is a potentiator that helps open the CFTR channel and is available alone (Kalydeco-Vertex) or in combination with correctors that ensure correct folding of the CFTR protein: lumacaftor/ivacaftor (Orkambi-Vertex), tezacaftor/ivacaftor (Symdeko-Vertex), and elexacaftor/tezacaftor/ivacaftor (Trikafta-Vertex).[7-11]

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Elexacaftor/tezacaftor/ivacaftor is the first triple therapy oral agent indicated for patients with CF who are 6 years or older with at least 1 F508del mutation in the CFTR gene or a mutation that is responsive to this combination; a majority of patients are eligible to take elexacaftor/tezacaftor/ivacaftor once they meet the age requirement.[11] It was Food and Drug Administration approved in 2019 after 2 randomized controlled trials demonstrated significant improvements in the percentage of predicted forced expiratory volume in 1 second (FEV1), sweat chloride concentrations, and quality of life compared to placebo.[12,13] An additional phase 3 randomized trial in patients 12 years or older with either an F508del-gating or F508del-residual function genotype confirmed elexacaftor/tezacaftor/ivacaftor effectively increased FEV1 compared to active control with another CFTR modulator (either ivacaftor or tezacaftor/ivacaftor).[14] Across all 3 trials, the safety profile was favorable; however, these trials reported incidences of transaminase elevations. As a result, the prescribing information for elexacaftor/tezacaftor/ivacaftor includes dose adjustments based on elevations in liver function tests (LFTs). Specifically, when the alanine transaminase (ALT) or aspartate transaminase (AST) is more than 5 times the upper limit of normal (ULN), or when ALT or AST is more than 3 times ULN with bilirubin more than 2 times ULN, the prescribing information recommends that dosing be interrupted with laboratory tests closely followed until the abnormalities resolve.[11] Other modulators have also been associated with transaminase elevations, and there are published case reports regarding modulators and drug-induced liver injury (DILI).[8-11,15,16]

The risk of DILI is a concern for patients with CF due to the prevalence of CFLD. Theoretically, elexacaftor/tezacaftor/ivacaftor should benefit patients with underlying CFLD by improving the overall disease, but DILI from CFTR modulators could exacerbate and further complicate CFLD. The implications of stopping a CFTR modulator in this scenario are considerable, as discontinuing CF medications can worsen pulmonary outcomes, increase hospitalizations, and decrease quality of life.[17-20] There is a lack of high-quality evidence to help guide treatment decisions. Guidelines for the use of CFTR modulators did not address DILI and were published in 2018 before newer agents, including elexacaftor/tezacaftor/ivacaftor were approved.[6] Therefore, the only recommendations currently available are from the elexacaftor/tezacaftor/ivacaftor prescribing information.[11] Published evidence from clinical practice on how to manage patients with elevated transaminases is lacking.

Objectives

The purpose of this study was to determine the real-world incidence of transaminase elevations in adults with CF taking elexacaftor/tezacaftor/ivacaftor. We also sought to explore characteristics that might be associated with this adverse event.

Methods

This was a retrospective descriptive study conducted in an outpatient CF specialty clinic located at a 620-bed academic medical center. The clinic staff includes 2 physicians, and 1 physician assistant, as well as nurses, respiratory therapists, a social worker, a dietitian, and a research coordinator. Additionally, there is one clinic-based pharmacist and support from additional pharmacists and pharmacy technicians working in our institution's specialty pharmacy. The clinic serves approximately 90 adults with CF.

Each patient's medication list is reviewed by the pharmacist working in the CF clinic, as part of the pharmacist's clinical services, prior to initiation of elexacaftor/tezacaftor/ivacaftor. Potentially hepatotoxic antimicrobials or other medications are documented in the patient's medical record. The pharmacist maintains biannual in-person or virtual patient visits and reviews medication lists, discusses changes, reviews drug interactions, reviews administration of modulators and missed dose recommendations, and discusses monitoring plans. The CF pharmacist is also responsible for providing medication education and recommendations for follow-up monitoring. Standard practice at the institution's adult CF clinic is transaminase and bilirubin monitoring at baseline and every 3 months for the first year of therapy, then annually (as recommended in the elexacaftor/tezacaftor/ivacaftor prescribing information).[11] The frequency of monitoring may be adjusted on a case-by-case basis.

All patients prescribed elexacaftor/tezacaftor/ivacaftor were included in this study, with no exclusions. Data were extracted from the electronic health record starting from the date of elexacaftor/tezacaftor/ivacaftor initiation through January 31, 2022, or the date of discontinuation, whichever came first. Study data were collected and managed using REDCap electronic data capture tools hosted at our institution.[21] Demographic data included age, sex assigned at birth, race, insurance, alcohol use, cannabis use, and tobacco use. Diagnosis data included CFTR membrane protein mutation genotype, diagnosis of CFLD, and diagnosis of fatty liver disease. Lab data included ALT, AST, total bilirubin, and hepatitis B and C serologies. Medication data included days of elexacaftor/tezacaftor/ivacaftor therapy and the use of antibiotics or other medications known to elevate transaminases and moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors.[11,22,23] This study was approved as exempt research by our institution's Committee on Human Research (STUDY00001789).

We explored transaminase elevation outcomes in 2 separate analyses. First, we defined the incidence of transaminase elevations more than 3 times ULN, with the ULN defined as 50 IU/L for ALT and 46 IU/L for AST in accordance with our institution's definitions. Transaminase elevations were defined as an elevation in either AST or ALT. The second way we explored transaminase elevations was by identifying elevations 25% or more above baseline. We chose this outcome due to an anticipated low number of patients with elevations more than 3 times ULN.

Data were analyzed using descriptive and univariate statistics. We explored differences in characteristics between patients with elevations and those without elevations. We conducted separate analyses for elevations more than 3 times ULN and for elevations 25% or more above baseline. Analyzed characteristics included demographics (age, sex, race), substance use (alcohol, cannabis, tobacco), ALT, AST, bilirubin more than 2 mg/dL, disease-related characteristics (homozygous F508del), and medication factors (days of therapy, previous CFTR modulator use, concomitant use of potentially

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Table 1
Baseline characteristics of patients prescribed elexacaftor/tezacaftor/ivacaftor

Characteristic	N	(%)
Total patients	83	(100)
Age (y), median (IQR)	31	(23–42)
Female	43	(52)
Caucasian	78	(94)
Medicaid insurance	16	(19)
Current substance use		
Alcohol	53	(64)
Cannabis	18	(22)
Tobacco	6	(7)
Homozygous F508del	45	(54)
Diagnosis of cystic fibrosis liver disease	23	(28)
Diagnosis of fatty liver disease	15	(18)
Alanine transaminase, IU/L; median (IQR)	25	(19–34)
Aspartate transaminase, IU/L; median (IQR)	27	(21–32)
Use of medications known to elevate transaminases[a]		
Antibiotics	63	(76)
Other nonantibiotic medications	14	(17)
Moderate or Strong CYP3A4 inhibitors	3	(4)
Prior use of CFTR modulators		
ivacaftor	8	(10)
lumacaftor/ivacaftor	32	(39)
tezacaftor/ivacaftor	43	(52)

CFTR, cystic fibrosis transmembrane conductance regulator; IQR, interquartile range.
[a] The most common medications included macrolides, beta-lactams, fluoroquinolones, methotrexate, statins, and azole antifungals.

hepatotoxic medications and/or moderate-to-strong CYP3A4 inhibitors). We also explored days to detection of elevation, days to a resolution of transaminase elevation, and consultation of a hepatologist. Additionally, we reviewed clinical decision-making regarding holding or continuing elexacaftor/tezacaftor/ivacaftor, and noted modifications made from the standard dose (2 tablets of elexacaftor/tezacaftor/ivacaftor in the morning and 1 tablet of ivacaftor in the evening). Continuous data were analyzed with Wilcoxon rank sum tests, and Fisher exact test, or chi-square analyses were used for categorical data. Analyses were conducted using STATA 16.1 (Stata Corporation, College Station, TX), with a P less than 0.05 required for statistical significance. The analyses were exploratory and not adjusted for multiple comparisons. No patients had end-stage renal disease, and all hepatitis serologies were missing or negative, so these factors were not included in the analyses.

Results

Eighty-three adults were prescribed elexacaftor/tezacaftor/ivacaftor during our study time frame. Baseline demographic features are characterized in Table 1. The median age was 31 years, 52% were female, 94% were Caucasian, and 54% were homozygous for the F508del mutation. Twenty-eight percent of patients had a prior diagnosis of CFLD, and 18% had a prior diagnosis of fatty liver disease. The majority of patients received at least one potentially hepatotoxic drug, most commonly antibiotics (76%). Prior treatment with a CFTR modulator therapy was common, with 10% of patients treated with ivacaftor, 39% treated with lumacaftor/ivacaftor, and 52% treated with tezacaftor/ivacaftor.

Nine patients (11%) experienced a transaminase elevation more than 3 times ULN (Table 2). The maximum AST value was 645 IU/L, and the maximum ALT value was 1125 IU/L. Median (interquartile range) days to elevation was 108 (80-203), and 4 elevations resolved. Of the 4 resolutions, median (interquartile range) days to resolution was 197 (123-231). Hepatology was consulted for 6 patients. Bilirubin was elevated to at least 2 mg/dL in one patient. Therapy was held in 2 patients and modified in 2 patients. One modification was made due to adverse effects (not specifically for LFT elevations) with the dose decreased to one tablet in the morning of elexacaftor/tezacaftor/ivacaftor; initially, the evening tablet of ivacaftor was continued but this was subsequently stopped. The other patient's dose was modified to stop the evening dose of ivacaftor. No patients permanently discontinued therapy due to transaminase elevations more than 3 times ULN. There were no statistically significant differences in characteristics between patients with elevations more than 3 times ULN and no elevations.

Sixty-two patients (75%) experienced an elevation 25% or more above baseline. These 62 patients also included the 9 patients with elevations more than 3 times ULN. The maximum AST and ALT values 25% or more above baseline (but less than 3 times ULN) were 133 IU/L, and 129 IU/L, respectively. Median (interquartile range) days to elevation was 135

Table 2
Transaminase elevations among patients prescribed elexacaftor/tezacaftor/ivacaftor

Outcome	Elevation >3 times upper limit of normal		Elevation ≥25 % baseline	
	N	(%)	N	(%)
Total patients with elevations	9	(11)	62	(75)
Days to elevation, median (IQR)	108	(80–203)	135	(87–378)
Resolution of the elevation, # (%)	4	(44)	36	(58)
Days to resolution, median (IQR)	197	(123–231)	186	(107–341)
Hepatology consulted, # (%)	6	(67)	18	(29)
Bilirubin >2 mg/dL, # (%)	1	(11)	3	(5)
Therapeutic decision				
Therapy held, # (%)	2	(22)	2	(3)
Therapy modified, # (%)	2	(22)	4	(6)
Therapy discontinued, # (%)[a]	0	(0)	2	(3)

IQR, interquartile range.
[a] Both discontinuations were initiated by the patients due to other adverse effects (insomnia and a general lack of tolerability) and were not due to elevated transaminas

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(87-378), and 36 elevations resolved. Of the 36 resolutions, median (interquartile range) days to resolution was 186 (107-341). Hepatology was consulted for 18 patients. Bilirubin was elevated to at least 2 mg/dL in 3 patients. Of patients with elevations 25% or more above baseline, therapy was held in 2 patients, modified in 4 patients, and discontinued in 2 patients. Both discontinuations were initiated by the patients due to adverse effects and were not due to elevated transaminases. Of the 4 patients with modified doses, 2 of these patients had elevations more than 3 times ULN, and are described above. The 2 additional modifications were both related to adverse effects. One patient's dose was decreased to one tablet in the morning of elexacaftor/tezacaftor/ivacaftor and continuation of the evening dose of ivacaftor; the other patient's dose was decreased to 1 tablet in the morning of elexacaftor/tezacaftor/ivacaftor and the evening dose of ivacaftor was discontinued. There were few differences in risk factors between patients with elevations $\geq$25% above baseline and patients with no elevations. Median baseline ALT was lower (24 IU/L vs. 32 IU/L $P = 0.018$), median days of therapy was longer (733 days vs. 675 days $P = 0.047$), and there was a higher proportion of patients with a concomitant course of potentially hepatotoxic antimicrobials (82% vs. 57%, $P = 0.02$).

Discussion

Overall, we found a low incidence of transaminase elevations more than 3 times ULN (11%) in our patient population treated with elexacaftor/tezacaftor/ivacaftor; however, this was higher than previously documented in clinical trials (7.9%, 7.0%, and 3.2%).[12-14] The higher incidence seen in our study may be explained by differences in study design and duration. The present study likely reflects a more real-world incidence of transaminase elevations. Our study also has a longer study period (approximately 28 months) than previous clinical trials.[12-14] According to manufacturer recommendations, therapy should have been held for the majority of transaminase elevations seen in our study.[11] However, most patients in our study did not have their therapy modified or held, and no patients with elevations more than 3 times ULN had their therapy discontinued. These decision-making processes often involved a multidisciplinary and shared decision-making approach, as evidenced by the high proportion of patients with a hepatology consult. Reasons for not holding therapy were due to clinical suspicion of an alternative causative agent or to avoid the risk of clinical decline in CF control. This decline has been suggested by case reports that describe "ivacaftor withdrawal syndrome" precipitated by ivacaftor discontinuation or a reduction in ivacaftor exposure due to drug-drug interactions.[18,19,24]

The majority of patients (75%) experienced transaminase elevations 25% or more above baseline in this study. This is likely a reflection of the definition allowing for minor fluctuations being captured. The 25% threshold was chosen in an attempt to capture how elevations that are present (but do not meet the thresholds defined in the prescribing information) are managed. Patients with low baseline AST and ALT values were more likely to show a greater percentage elevation. In this population, therapy was still infrequently held or modified and was done so for reasons other than LFT elevations, such as adverse events.

Pharmacists have important roles in the multidisciplinary team approach to the management of CF. The CF Foundation recommends inclusion of a pharmacist on the care team, and prior literature has shown that pharmacists improve care of patients with CF by improving medication access and adherence.[25-27] Pharmacists provide important aspects of care to patients on elexacaftor/tezacaftor/ivacaftor, including medication reconciliation and review for drug-drug interactions, medication education, improved access to care by monitoring prior authorization requests or investigating other avenues to obtain treatment, answering questions about adverse effects, placing orders for follow up labs, and reviewing plans of care when labs are abnormal. CFTR modulators, including elexacaftor/tezacaftor/ivacaftor will continue to be an important aspect of CF treatment, and pharmacists working with patients with CF are well positioned to be a part of the clinical decision-making regarding appropriate continuation of therapy or therapy interruption in the setting of abnormal lab results.

This study has a number of strengths, including a real-world perspective with no exclusions. The study examined a wide variety of relevant, potential risk factors of interest to CF treatment team members, including pulmonologists, hepatologists, and pharmacists. Our findings that there was a higher proportion of patients in the transaminase elevation 25% or more above baseline group with concurrent potentially hepatotoxic antimicrobials may help direct future research and increase monitoring during these instances. Additionally, our finding that patients with transaminase elevations 25% or more above baseline were on elexacaftor/tezacaftor/ivacaftor for longer durations than those patients without elevations is hypothesis generating for future studies about the long-term risk-benefit profile of elexacaftor/tezacaftor/ivacaftor.

This study also has limitations. Retrospective chart review is limited by the documentation in the electronic health record. Notably, we found it difficult to quantify the use of alcohol, cannabis products, and tobacco. More research regarding the use of these products in patients with CF is needed to understand potential issues with CFTR modulators. We encountered missing data, such as laboratory data for patients who utilized laboratories that were out-of-network or never had hepatitis serologies drawn. Due to missing data, we were unable to calculate Child-Pugh scores for the majority of patients and therefore did not report this information. We were also missing adherence data on the majority of patients and therefore were unable to include adherence in our analysis. We could not definitively associate LFT elevations with elexacaftor/tezacaftor/ivacaftor, as patients concomitantly taking potentially hepatotoxic medications could have been the cause of the elevations. Our sample size also did not permit a multivariable modeling approach to understand risk factors for transaminase elevations.

Conclusion

Transaminase elevations were common but never directly resulted in the discontinuation of elexacaftor/tezacaftor/ivacaftor therapy in adults seen at our institution's CF clinic. Our clinic utilized a multidisciplinary team approach comprised of pulmonologists, a hepatologist, and a pharmacist for clinical decision-making processes. Despite our inability to detect independent risk factors for transaminase elevation during

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elexacaftor/tezacaftor/ivacaftor therapy, these data may impact the direction of future research aimed to elucidate the optimal approach to defining the risk-benefit profile of CFTR modulators use.

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