Gilbert’s Syndrome Leads to Elevated Bilirubin after Initiation of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis

Nidhi Patel1, Maria Ansar2, Anh Pham1, Kelly Thomsen3, Cameron McKinzie4, Deepika Polineni5, Charles Esther6, and Rebekah Brown3

1no affiliation  
2The University of North Carolina at Chapel Hill Department of Pediatrics  
3Vanderbilt University Medical Center  
4UNC Medical Center  
5Washington University in St Louis  
6The University of North Carolina at Chapel Hill School of Medicine  

June 27, 2023

Abstract

Nine people with cystic fibrosis (pwCF) were found to have isolated elevations in serum total bilirubin after starting elexacaftor/tezacaftor/ivacaftor (ETI) that were associated with Gilbert’s Syndrome. In longitudinal examination, total bilirubin levels increased substantially after initiation of ETI without elevations in liver transaminases in those with this syndrome. Because elevated bilirubin levels in Gilbert’s Syndrome are benign, ETI was able to be continued in these individuals. Genetic testing for this relatively common syndrome should be strongly considered for pwCF experiencing isolated hyperbilirubinemia after starting ETI, since appropriate diagnosis may help pwCF avoid unnecessary interruption in this therapy with significant health benefits in CF.

Gilbert’s Syndrome Leads to Elevated Bilirubin after Initiation of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis

Nidhi Patel
Maria Ansar, MD, PhD1
Anh Pham
Kelly Thomsen, MD2
Cameron J. McKinzie, PharmD, BCPPS, BCPS, CPP3
Deepika Polineni, MD, MPH4
Charles R. Esther, Jr, MD, PhD5
Rebekah F. Brown, MD6

1Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC
2Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN
3Department of Pharmacy, University of North Carolina Medical Center, Chapel Hill, NC
Abstract: Nine people with cystic fibrosis (pwCF) were found to have isolated elevations in serum total bilirubin after starting elexacaftor/tezacaftor/ivacaftor (ETI) that were associated with Gilbert’s Syndrome. In longitudinal examination, total bilirubin levels increased substantially after initiation of ETI without elevations in liver transaminases in those with this syndrome. Because elevated bilirubin levels in Gilbert’s Syndrome are benign, ETI was able to be continued in these individuals. Genetic testing for this relatively common syndrome should be strongly considered for pwCF experiencing isolated hyperbilirubinemia after starting ETI, since appropriate diagnosis may help pwCF avoid unnecessary interruption in this therapy with significant health benefits in CF.

Keywords: cystic fibrosis, gilbert’s syndrome, elevated direct bilirubin, CFTR modulator, elexacaftor/tezacaftor/ivacaftor

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Introduction

Cystic Fibrosis (CF) is a multi-system disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that codes for the CFTR anion channel protein. The CFTR modulator therapy elexacaftor/tezacaftor/ivacaftor (ETI; marketed as Trikafta or Kaftrio) substantially restores function of the CFTR protein in people with CF (pwCF) with at least one F508del mutation or another qualifying mutation. Studies have shown significantly decreased frequency of pulmonary exacerbations, improvements in pulmonary function tests, and a decrease in hospitalizations and outpatient intravenous antibiotics for pwCF treated with ETI. The components of ETI are metabolized in the liver, and hepatotoxicity with drug related elevations in liver transaminases or bilirubin occur in a subset of individuals and may be grounds for discontinuation or dose modification. Given the positive impact on clinical outcomes for pwCF related to ETI use, as well as risks of CFTR modulator interruption in patients with significant treatment responses, medication interruption or discontinuation is undesirable.

Here, we report seven pwCF who had elevations in serum total bilirubin, but normal aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase levels after starting ETI who had Gilbert’s Syndrome confirmed by genetic testing. This syndrome is a relatively common (estimated prevalence 3-7%) autosomal recessive disorder caused by mutations in the UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) gene promoter that is part of the mechanism for the synthesis of UDP glucuronosyltransferase (UGT). Reduced enzyme UGT decreases hepatic processing of bilirubin leading to elevated circulating unconjugated and total bilirubin, with normal transaminase levels. People with Gilbert’s Syndrome may experience jaundice and scleral icterus during times of stress, illness, and fasting. The elevated bilirubin levels in Gilbert’s Syndrome are generally believed to be benign for individuals when controlled for potential triggers.

Methods
Based on anecdotal reports of associations between Gilbert’s Syndrome and elevated bilirubin in individuals with CF treated with ETI, a CF Foundation sponsored survey was distributed to the CF provider community. The survey requested input on new diagnoses of Gilbert’s Syndrome and/or elevated bilirubin levels in individuals with cystic fibrosis after starting ETI. From those responses, detailed medical records were abstracted from seven pwCF from three institutions who all had diagnosis of Gilbert’s Syndrome confirmed by UGT1A1 genetic testing. Measurements of total bilirubin, direct bilirubin, AST, and ALT were obtained from their charts from the period 15 months prior to start of ETI to 36 months after starting therapy, though not all had values available throughout the range. For longitudinal measures, laboratory values were assessed in three-month intervals. If multiple values were present in the interval, those values were averaged. If no values were present in the interval, the value from the prior interval was assigned, or no value if prior values were not available. Laboratory values obtained post ETI during times in which ETI was discontinued were excluded.

Results

A survey on “CFTR Modulator Therapy and Gilbert’s Syndrome” yielded responses from 13 providers who reported on a total of 16 pwCF (Appendix A). Diagnostic genetic testing for Gilbert’s Syndrome was reported in 9 pwCF, with an additional 2 individuals reported to have Gilbert’s Syndrome but no genetic testing. Total bilirubin was reported in 14 of the 16 individuals and averaged 2.7±0.6 mg/dL (Figure 1, left). Average liver transaminases were in the normal range (aspartate transaminase [AST] 33.7±21.2 U/L, alanine transaminase [ALT] 34.5±24.9 U/L), though at least one value was elevated in 4 individuals.

Detailed data for a case series were abstracted from the medical records of seven pwCF followed at three different CF centers (University of Kansas, University of North Carolina at Chapel Hill, Vanderbilt University Medical Center), including six identified through the survey and a seventh added from outside of the survey. This study population was 14% male, with average age of 16 (SD +/- 8.38). 71% of the individuals had homozygous deletion of F508, and 100% of the individuals were Caucasian. Average of all available bilirubin values obtained after initiation of ETI was significantly higher (2.141 +/- 0.549) than the average of values obtained prior to starting ETI (1.247 +/- 0.578), though somewhat lower than the peak total bilirubin values reported from the survey (2.736 +/- 0.601) (Figure 1, right).

In longitudinal examination, average values over time demonstrated a significant increase in total bilirubin levels after initiation of ETI within the first three months, which then stabilized (Figure 2A). In 3 individuals, the elevated bilirubin values led to temporary suspension of ETI therapy, though therapy was successfully resumed in all pwCF once the diagnosis of Gilbert’s syndrome was established. AST and ALT levels extrapolated over time were not elevated post-ETI and actually showed a decrease in downward trend over time (Figure 2B-C).

Discussion

Our findings suggest that initiation of ETI increases bilirubin in pwCF who also have Gilbert’s Syndrome and may unmask the syndrome in affected individuals. Although elevations in serum bilirubin are considered an indication to discontinue ETI when they coincide with modest increases in transaminases, the increased bilirubin concentrations in Gilbert’s Syndrome are felt to be benign and not associated with hepatic dysfunction. Indeed, the minimal changes in AST and ALT levels after the initiation of ETI observed in our population do not suggest drug induced liver damage. Thus, isolated mild elevations in bilirubin with ETI therapy in the setting of Gilbert’s Syndrome need not be an indication to discontinue modulator therapy.

Based on these findings, genetic testing for Gilbert’s Syndrome should be strongly considered for pwCF experiencing isolated hyperbilirubinemia after starting ETI. Gilbert’s Syndrome is relatively common in the general population, and appropriate diagnosis may help pwCF avoid unnecessary interruption in this therapy with unprecedented health benefits in CF. Diagnosis of Gilbert’s Syndrome may also help avoid unnecessary diagnostic evaluations.

Figures
Hosted file


Figure 1. Single column fitting image.

Total bilirubin in Gilbert Syndrome and ETI treatment. Total bilirubin values as reported from the survey “CFTR Modulator Therapy and Gilbert’s Syndrome” (green, left), in which providers were requested to report the highest serum total bilirubin value recorded after initiation of ETI. Data represent reported values from 14 pwCF. Also shown are average serum total bilirubin values measured pre and post initiation of ETI in 7 pwCF from a case series (blue, right). Note that one individual did not have a pre-ETI bilirubin available for evaluation (recently changed CF Centers). Post-ETI total bilirubin was significantly higher than Pre-ETI. **=p<0.01 pre vs. post by paired Student’s T-test.

Hosted file


Figure 2. 2 column fitting image

Bilirubin and liver transaminases over time. A. Total serum bilirubin over time in 7 PwCF with genetically confirmed Gilbert’s Syndrome. Values were determined as described in the methods and are plotted as mean ± standard deviation. One individual did not have any values prior to 0 months and a second individual did not have any values available before 9 months post-ETI. B. Values over time for serum AST. C. Values over time for serum ALT.

Appendix A. “CFTR Modulator Therapy and Gilbert’s Syndrome” Survey Questions

1. Hospital Name
2. Physician Name
3. Modulator Therapy (Yes/No)
4. If Yes, Please indicate which Modulator Therapy (Ivacaftor, Lumacaftor/Ivacaftor, Tezacaftor/Ivacaftor, Elexacaftor/Tezacaftor/Ivacaftor)
5. Date of Diagnosis of Gilbert’s Syndrome (Month and Year)
6. Sex (Male/Female)
7. Peak Total Bilirubin
8. Peak Direct Bilirubin
9. AST level
10. ALT level
11. UGT1A1 Genetic Testing (Obtained/Not Obtained)
12. If Obtained, UGT1A1 Genetic Testing Results
13. Prior Work Up (Ultrasound, MRI elastography, Liver Biopsy, Other)

References


