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CASE REPORT | LIVER

The Role of Cystic Fibrosis Transmembrane Conductance Regulator Modulators After Liver Transplantation in Persons With Cystic Fibrosis

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ABSTRACT

Despite advances in treatment for cystic fibrosis (CF), liver disease remains a major contributor to morbidity and mortality for persons with CF. Therefore, liver transplantation may be considered in end-stage CF-related liver disease. We present a young patient with CF who underwent solo liver transplantation and has successfully restarted on elexacaftor/tezacaftor/ivacaftor without significant pulmonary or hepatic complications after transplant.

KEYWORDS: cystic fibrosis; liver transplant; ETI; elexacaftor/tezacaftor/ivacaftor; tacrolimus

INTRODUCTION

The advent of cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators has significantly improved pulmonary outcomes for persons with CF (PwCF). As a result, PwCF patients using CFTR modulators have improved life expectancy.[1] Therefore, gastrointestinal manifestations of CF, including CF-related liver disease (CFRLD), are emerging as important contributors to morbidity and mortality in PwCF.[2] No therapies have been found to reduce the risk of development or progression of CFRLD or portal hypertension among PwCF. However, evidence is emerging that CFTR modulators may decrease progression to end-stage liver disease.[2,3] The use of CFTR modulators in decompensated cirrhosis is challenging because of hepatic metabolism, but the lack of CFTR modulator treatment places patients at risk of worsening pulmonary function at the time of evaluation for liver transplantation. The consideration of single-organ liver transplantation has become exceedingly difficult because of a lack of consensus on using CFTR modulators after transplant, most significantly because of the possible CFTR modulator drug-drug interaction between CFTR modulators and calcineurin inhibitors because of uncertainty of outcomes. We present a 22-year-old woman with CF who experienced worsening pulmonary function after elexacaftor/tezacaftor/ivacaftor (ETI) was stopped because of decompensated cirrhosis who subsequently underwent only a liver transplant and was safely resumed on ETI thereafter.

CASE REPORT

A 22-year-old woman with CF (F508del/F508del genotype) complicated by exocrine pancreatic insufficiency, CF-related diabetes mellitus, and CFRLD experienced multiple CF exacerbations, during which time she had fluctuating liver function tests (aspartate aminotransferase 29–82 U/L, alanine transaminase 11–25 U/L, and total bilirubin ~0.8–1.3 mg/dL) before initiation of CFTR modulation. Further evaluation revealed hepatic steatosis on magnetic resonance imaging without evidence of portal hypertension, which was confirmed on endoscopic evaluation.

She commenced ETI at standard dosing and experienced improved pulmonary function and decreased frequency of exacerbations. Unfortunately, after starting ETI, her CFRLD progressed, warranting ETI dose reduction. Because of progressively elevated total

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bilirubin levels and first presentation of decompensated cirrhosis with ascites, ETI was stopped. Transjugular liver biopsy confirmed the diagnosis of cirrhosis with portal hypertension as evidenced by hepatic venous pressure gradient of 24 mm Hg.

After ETI discontinuation, she again experienced recurrent hospitalizations because of pulmonary exacerbations. Her forced expiratory volume (FEV1) decreased from 54% to 45% (Figure 1). In addition, her decompensated cirrhosis continued to progress, as evidenced by the development of hepatorenal syndrome requiring intermittent hemodialysis. Her Model for End-Stage Liver Disease (MELD) score increased to 40. Our multidisciplinary transplant committee reviewed her case and jointly agreed to proceed with liver transplantation alone, anticipating improved pulmonary function on future ETI reinstatement, given her previous response.

Orthotopic liver transplantation was performed without intraoperative complications. Induction immunosuppression included a rapid steroid taper, basiliximab, mycophenolate sodium 1,000 mg twice a day, and tacrolimus with a goal trough of 8–10. Explant pathology revealed cirrhosis, steatohepatitis, and cholestasis. After transplant, she maintained excellent graft function and experienced renal recovery, evident by discontinuation of hemodialysis. She did not experience pulmonary complications in the immediate postoperative period, despite progressive decline in FEV1 to 32%. To ensure stable graft function, the initiation of ETI was delayed for 4 months after transplant. During the initiation of ETI, liver function tests and tacrolimus troughs were checked biweekly and frequently required dose adjustments. During this time, she did experience elevated liver function tests concerning for acute cellular rejection. A graft biopsy was obtained and displayed nonspecific findings—portal eosinophilic-rich mixed inflammation, mild-moderate panacinar steatosis—suggesting a drug reaction. She was treated with oral steroids with improvement in liver function tests. Despite these challenges, she exhibited improvements in FEV1 from 32% to 79% and gained approximately 30 kg. One year after transplantation, she demonstrates improved liver and pulmonary function with continued ETI treatment.

DISCUSSION

Generally, CFRLD occurs in younger individuals with severe CFTR mutations, and its complications, particularly portal hypertension, significantly contribute to morbidity and mortality.[1] However, the incidence of CFRLD in adulthood seems to be increasing.[2] This could be due to the use of CFTR modulators delaying the onset of cirrhosis from childhood into adulthood. It should also be noted that the definition of CFRLD is not fully established, and there are variations in terminology that may impact the comprehensive understanding of its epidemiology.[2] Characterizing individuals with or without portal hypertension is crucial before starting ETI. Reduced dosing should be considered for moderate impairment (Child-Pugh class B), whereas treatment cessation is advised for severe impairment (Child-Pugh

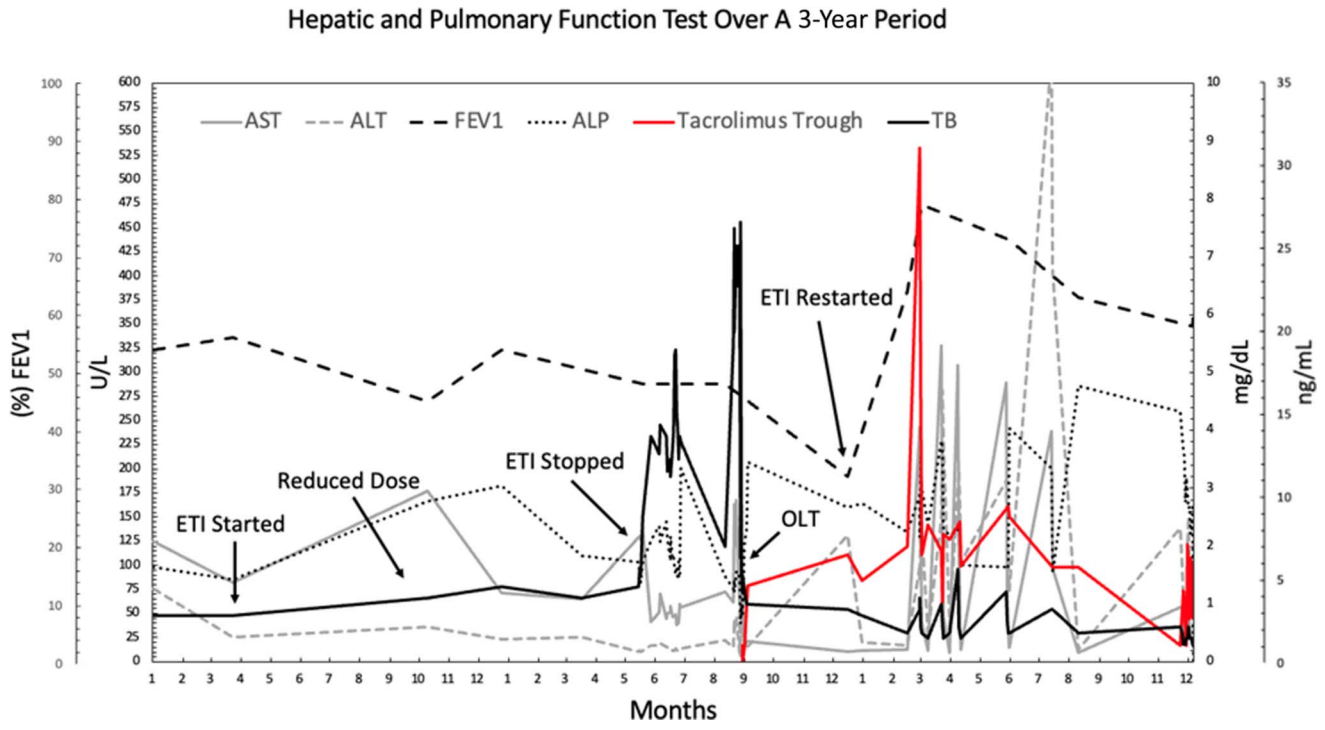

Figure 1. Pulmonary function as determined by FEV1 percentage of predicted and liver function as determined by liver function tests and tacrolimus trough level over a 3-year period in association with CFTR modulator therapy initiation, discontinuation, and resumption. ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CFTR, cystic fibrosis transmembrane conductance regulator; ETI, elexacaftor/tezacaftor/ivacaftor; FEV1, forced expiratory volume in 1 second; OLT, orthotopic liver transplant; TB, total bilirubin.

class C) or the development of portal hypertension.[4] Our patient initially presented with CF liver involvement progressing to CFRLD cirrhosis with portal hypertension, necessitating regular Hepatology and CF Clinic follow-up for guiding ETI dosing decisions during disease progression.

A multidisciplinary transplant team should oversee the management of end-stage liver disease among PwCF. The severity of lung disease at the time of hepatic decompensation should be weighed against the need for a liver transplant. The MELD Exception Study Group Committee has designated CF as a MELD exception disorder for which a candidate will receive an MELD score exception for CF if the candidate's diagnosis has been confirmed by genetic analysis and has an FEV1 below 40% of predicted within 30 days before submission of the initial exception request based on the transplant facility's median MELD at transplant.[5] However, in this case, the patient's MELD of 40 did not necessitate need to obtain exception scoring.

We advocate a solo liver transplant in PwCF with mild/moderate pulmonary disease with previous response to CFTR modulation as in the case presented. Dual lung and liver transplants should still be considered in patients who would also qualify for lung transplantation.

It is important to consider the challenges because of post-transplant medication regimens and the potential liver toxicity associated with ETI.[3,6,7] Standard post-transplant immunosuppressive regimens typically include calcineurin inhibitors, and the significant interaction with ETI is of particular significance: Ivacaftor, a cytochrome P450 3A enzyme substrate, can elevate tacrolimus levels and increase the risk of adverse effects such as acute kidney injury and increased risk of opportunistic infections.[6,7] In the presented case, fluctuations of tacrolimus trough levels were commonly observed, so we advocate for monitoring biweekly liver function tests and tacrolimus trough during the initiation of ETI until a consistent, therapeutic trough is achieved. This was our first attempt with this strategy. Our clinical decision making for this was based on limited case series and expert opinion. For our patient, we started standard dosing of ETI approximately 4 months after transplantation to ensure excellent graft function on stable dosing of immunosuppression. We had planned to adjust tacrolimus dose to maintain stable trough levels (target 8–10) and considered reducing ETI dose if tacrolimus levels could not be reliably achieved; however, ETI dose adjustment has not been required up to 12 months after transplant. No immunosuppression dosing changes were made before initiation of ETI; however, a dose reduction of around 40%–50% was required once ETI was reintroduced. A liver biopsy should be considered for a formal diagnosis if the patient develops elevated liver function testing after transplantation, such as in this patient, because this would help clarify a diagnosis of acute cellular rejection, drug-induced liver injury from ETI, or other etiologies. In this case, a quick response to high-dose steroids likely represented acute cellular rejection; however, drug-induced liver injury secondary to ETI could not be excluded.

In conclusion, we propose that PwCF who have primary liver disease and mild-to-moderate pulmonary disease can be managed with liver transplant alone, with resumption of ETI after transplant for management of pulmonary disease. This case adds to the growing body of literature describing the results of ETI treatment among patients with varying features of CFRLD. In particular, our case demonstrates that, despite some challenges and frequent lab monitoring, standard dosing ETI may be successfully used after a liver transplant.

DISCLOSURES

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