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Review

Safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with Cystic Fibrosis following liver transplantation: A systematic review

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Highlights

- •
  ETI is safe in most liver transplanted patients with CF.
- •

Close monitoring of liver function and tacrolimus level is warranted.

- An improvement in lung function after ETI is found also in liver transplanted patients.

Abstract

Background & Aims

Cystic Fibrosis (CF) liver disease progresses to liver failure requiring transplantation in about 3 % of patients, 0.7 % of CF patients are post liver transplant. The prognosis of CF has improved with the introduction of elexacaftor/tezacaftor/ivacaftor (ETI). Due to the paucity of data and concerns regarding interactions with immunosuppressive drug regimens, there is no general consensus on use of ETI post liver transplantation. The aim of this review is to report the safety and efficacy of ETI in CF patients who underwent liver transplantation.

Methods

A systematic review was conducted through MEDLINE/Pubmed and EMBASE databases. English-written articles reporting clinical data on liver transplanted CF patients treated with ETI were included. Article quality was evaluated using the Critical Appraisal Checklist for Case Reports.

Results

Twenty cases were retrieved from 6 reports. Temporary discontinuation and/or dose reduction due to elevated transaminases was required in 5 cases. ETI restarted on a reduced dose was tolerated in 3 out of 5 patients, 1 patient tolerated full dose. Tacrolimus dose change was required in 14 cases, in 1 case ETI was discontinued due to tacrolimus toxicity. Improvement in percentage predicted FEV1 was noted in 15/19 patients (median +17 %, range 8 %–38 %).

Conclusions

In the majority of liver transplanted patients ETI is well tolerated, although adverse events and liver function abnormalities may occur. Close monitoring of liver function and tacrolimus level is warranted. Significant improvement in lung function after ETI initiation is confirmed, highlighting the importance of accessing this medication for this group of patients.

Introduction

Cystic fibrosis (CF) is a multisystem disease caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and resulting in deficient or dysfunctional CFTR protein [1]. F508del is the most prevalent disease-causing variant in people with CF (pwCF), occurring in 80–85 % of cases [2,3]. The prognosis has largely been determined by the pulmonary complications of the disease.
Step-by step improvements in outcomes in CF have been accelerated by the introduction of highly effective modulator therapy (HEMT). [3]. These are small molecules that either correct protein misfolding and misprocessing (correctors) or improve channel gating to enhance apical anion transport (potentiators). The newest and most effective is the three-drug combination elexacaftor/tezacaftor/ivacaftor (ETI), composed of two correctors (elexacaftor and tezacaftor) and a potentiator (ivacaftor) [4,5].

The introduction of ETI has been associated with substantial improvements in respiratory-related quality of life, lung function and body mass index (BMI), and in a reduction of the rate of pulmonary exacerbations [4,5]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved ETI for pwCF aged 2 years and older with at least one copy of the F508del variant or another variant responsive to this treatment. There remains significant global inequality with regards to access to these medications [6].

Recently the CF Foundation (CFF) proposed a new terminology for CF hepatobiliary involvement: advanced CF liver disease (aCFLD) and CF hepatobiliary involvement (CFHBI) [7,8]. It is a well-known complication of CF, with a phenotypic expression extremely heterogeneous, ranging from cholelithiasis, hepatic steatosis, and liver fibrosis to cirrhosis, portal hypertension, and in a subset of

individuals, liver failure necessitating liver transplant or even liver-related death [7].

The CFHBI affects up to 32 % of pwCF by age 25 and is associated with pancreatic insufficiency, history of meconium ileus and class I, II, III CFTR variants (i.e. minimal function or gating variants) [7]. However not all pwCF with liver disease qualify for HEMTs such as ETI or ivacaftor [9].

The aCFLD, i.e. with cirrhosis or portal hypertension, occurs in early childhood, at median age 10–11 years and commonly associated with male sex [10]. The prevalence of aCFLD is approximately 10 % of pwCF, with 3 % requiring listing for liver transplantation [7], [8], [9], [10], [11], [12]. In the European CF population, 0.7 % of pwCF have received a liver transplant [13].

Due to the paucity of data and concerns regarding interactions with immunosuppressive drug regimens, the EMA does not recommend ETI in solid organ transplant recipients, including patients post liver transplantation [14]. No specific recommendations on the use of ETI after transplant are provided by FDA [15]. Recently, the CFF CFLD committee recommended, “CFTR modulator treatment in pwCF who have received a liver transplant, with close monitoring and collaboration with the transplant team/pharmacist, because the benefits to CF lung disease outweigh the liver related risk” [7]. To date, while ETI is being prescribed to a growing number of solid organ transplant recipients, including liver, there is no consensus around the efficacy and safety balance after liver transplantation.

Liver function test (LFT) derangement is a commonly reported adverse event (AE) [14], [15], [16], [17]: in a phase 3 trial of ETI in patients older than 12 years of age, more than 10 % of patients had AE of elevated transaminases greater than three times the upper limit of the normal (ULN) range or more, compared to 4 % of those receiving placebo [5]. According to EMA and FDA, management of deranged LFTs in pwCF on ETI includes suspension of the medication if alanine transaminase (ALT) or aspartate transaminase (AST) reach > 5 times the ULN, or ALT or AST reach >3 times the ULN with bilirubin >2 x ULN [14,15]. Close monitoring is indicated until the abnormalities resolve, or return to baseline, and following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered

[14,15]. In patients with moderate hepatic impairment, again if benefits outweigh the risks, ETI should be used with caution at a reduced dose [14,15]. After liver transplantation, the interpretation and management of acute changes in LFTs may be challenging [18]. As ivacaftor is an inhibitor of cytochrome P450 3A (CYP3A) it interacts with tacrolimus, the predominant immunosuppressive agent in use for organ transplant recipients. Tacrolimus is extensively metabolized by cytochrome CYP3A, the inhibition of CYP3A by ivacaftor presents a potential risk for elevated tacrolimus levels. Maintaining therapeutic concentrations of tacrolimus is crucial to prevent rejection or AEs, as it has a narrow therapeutic index [19]. The interaction with CYP3A also extends to other antimicrobial agents used in pwCF, including azoles and clarithromycin [19]. The use of ETI in pwCF post liver transplantation therefore requires additional monitoring of therapeutic drug levels.

ETI has a significant impact on pulmonary exacerbations, lung function, nutrition, inflammation, quality of life and survival [5,6]. In the context of liver transplant, treating the systemic disease including the lungs is likely to have a profound effect on outcome. Clinicians therefore need to assess the risks and benefits of ETI treatment post liver transplantation.

We sought to inform this assessment via a systemic review of publications on ETI treatment in pwCF post liver transplant.

We reviewed the available literature on the use of ETI in pwCF who underwent liver transplantation, via a descriptive analysis of published case reports and small case series.