Lung transplant list withdrawal in a liver transplant patient with cystic fibrosis thanks to elexacaftor-tezacaftor-ivacaftor

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To the Editor,

Elexacaftor-tezacaftor-ivacaftor (ETI) is a transmembrane conductance regulator modulator that has superior efficacy in patients affected by cystic fibrosis (CF) compared to previously approved modulators. This triple drug combination causes considerable increases in CFTR-channel function, and it is currently recommended for patients $\geq$ 2 years with at least one copy of F508del mutation or with other rarer mutations ETI-responsive based on in vitro data. ETI is associated with improved lung function, with a significant increase of the forced expiratory volume in the first second (FEV1) and reduced respiratory symptoms and lung exacerbations. Furthermore, this therapy provides several extrapulmonary effects, such as an improvement of body weight and body mass index (BMI), and some evidence suggests that it is also effective at delaying/reversing pancreatic insufficiency, reducing gastrointestinal symptoms, and improving glycemic control.

ETI is generally well tolerated without substantial adverse effects. However, due to possible increases in liver function tests and drug-to-drug interactions with several immunosuppressant medications, the triple modulator has not been approved for patients who have previously received a liver transplant. This contraindication represents a considerable limitation, as severe hepatic disease regards 4.5% to 10% of individuals affected by CF, and liver transplant represents a valid option in case of complications such as portal hypertension or cirrhosis [1].

We report on a 17-year-old girl affected by CF (homozygous for F508del mutation) with severe pulmonary and hepatic impairment. She presented chronic colonization by *methicillin-resistant Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* . She received a liver transplant at 11; however, her pulmonary function progressively deteriorated in the following 5 years. She underwent many hospitalizations for pulmonary exacerbations (10 episodes between 2020 and 2022), requiring intravenous multiple and prolonged antimicrobial therapy. In this period, her lung function showed fluctuating values of FEV1, between 40% and 50% of the predicted, with short-living recoveries after repeated intravenous antibiotic cycles. The combination of ivacaftor and tezacaftor has been tested for 12 months with no significant benefits. Due to the ongoing respiratory status, characterized by deteriorating functional tests and progressive radiological images worsening, chest-CT scans showing multiple giant apical bronchiectasis and a middle lobe syndrome (*figure 1*), lung transplantation had been considered. However, the patient could not get on the pulmonary transplant waiting list because of severe social and phycological problems leading her to poor treatment adherence. Regarding the hepatic function, the girl presented severe steatosis with normal levels of transaminases, compatible with a mild chronic liver rejection controlled by mycophenolate mofetil and tacrolimus.

In July 2022, she was admitted to ETI treatment at the recommended adult dose in an off-label regimen. Since starting this therapy, she has never needed hospitalizations for lung exacerbations or pulmonary complications, and her FEV1 has increased by 12-15% within two months. This significant recovery has persisted over time, with a mean steady FEV1 of 62% after a year of treatment. She also significantly improved her nutritional status, achieving an ideal BMI (from 16 to 22 kg/m^2). Remarkably, during ETI therapy, her liver function tests remained normal, and serum immunosuppressant concentrations remained stable without requiring dose adjustments.

In CF-related advanced pulmonary disease, defined by an FEV1 lower than 40% of the predicted, ETI treatment, if indicated, is associated with rapid clinical improvement, often leading to suspension or withdrawal of the patient from the lung transplantation list. In an observational study, ETI administration for one to three months in 245 patients with advanced lung disease was associated with a mean increase in predicted FEV1 by 15.1%, which is consistent with our case[2]. Furthermore, this improvement is long-lasting, as demonstrated by another study, where among 65 patients eligible for a lung transplant, the improvement in FEV1 after ETI initiation remained stable after a mean follow-up of one year, allowing most individuals to be removed and remain off the transplant list[3].

ETI treatment is currently contraindicated in case of moderate or severe hepatic impairment due to the possible risk of liver failure and, more frequently, an increase of transaminase and bilirubin. Moreover, ivacaftor weakly inhibits P-glycoprotein, an enzyme that metabolizes several drugs, including immunosuppressants such as cyclosporine, everolimus, sirolimus and tacrolimus, thus elevating their serum concentrations. Therefore, ETI is not indicated in liver transplant patients as it may cause further hepatotoxicity.

Our patient's respiratory impairment was so severe that lung transplantation was considered the only reasonable option. However, she was not eligible for this treatment for psycho-social reasons due to poor compliance with treatments and therapies. On the other hand, she did not meet the criteria to start the triple modulator because she had previously received a hepatic transplant. We tried administering the triple modulator to improve her poor prognosis based on previous reports exploring the ETI regimen's safety and tolerability in liver transplant patients with CF. Remarkably, two retrospective case series involving 12 liver transplant individuals with an immunosuppressive regimen of drug therapy metabolized by P-glycoprotein showed that the ETI regimen is safe and leads to clinical benefits in lung function, quality of life and BMI. In these patients, a transient elevation in transaminase and bilirubin resolved in most cases after ETI dose reduction and elevations in serum concentration of tacrolimus were managed with dose adjustments of the immunosuppressive regimen[4,5].

During the one year of follow-up, our young patient maintained regular hepatic markers, with stable serum concentration of the immunosuppressants, and no dose modulation was required. Considering the clinical outcomes, she has experienced a significant improvement in respiratory function (with a stable increase of FEV1 of more than 12%), BMI and quality of life, with a remarkable change in her life perspective.

Our case further proves that ETI can be well tolerated in patients with previous liver transplantation. It represents a lifesaving drug for patients without alternatives, dramatically improving their quality of life. This report adds to the evidence suggesting that the clinical benefits of ETI in liver transplant patients overcome risks, which may be limited with a close drug monitoring of immunosuppressants serum levels and functional liver tests.

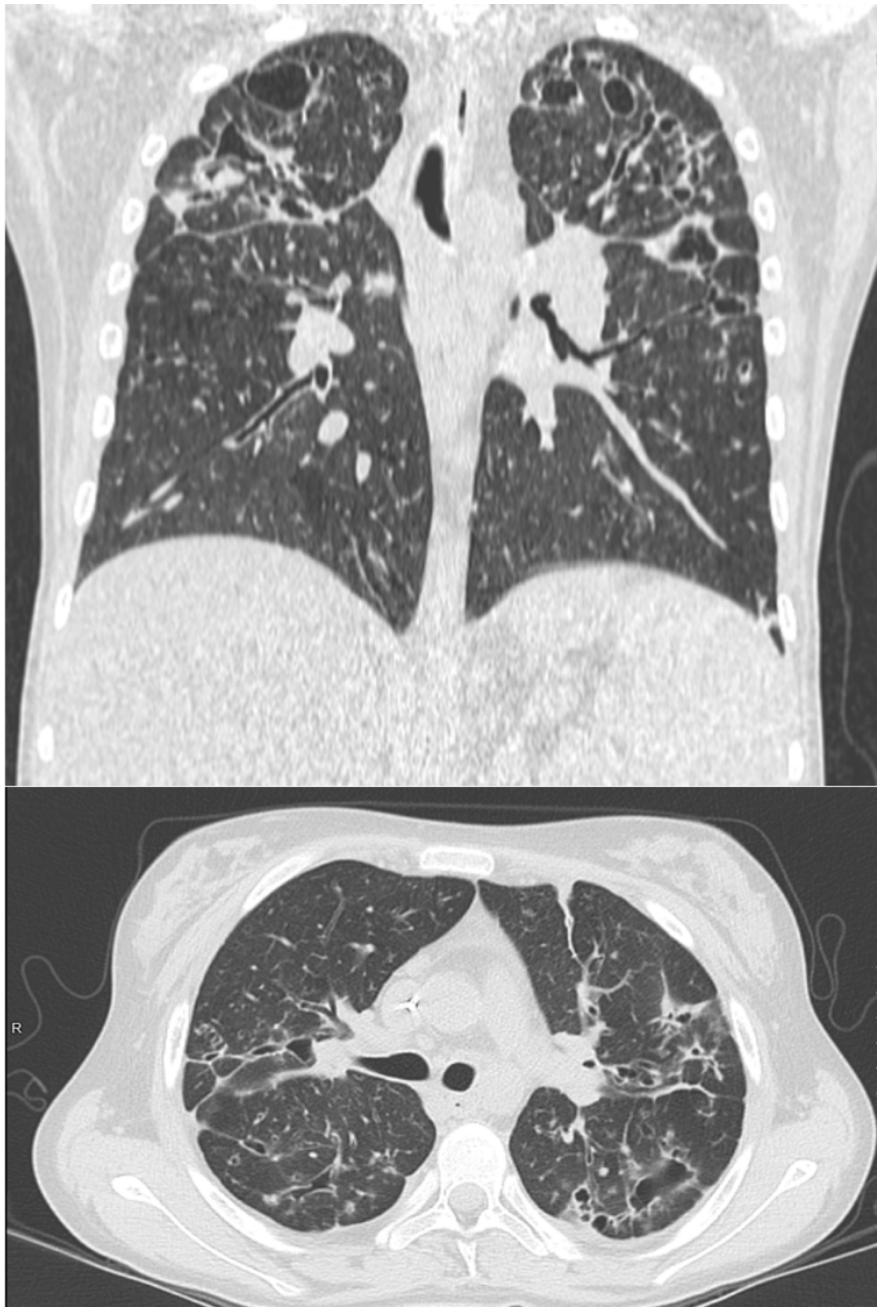

Figure 1: Chest CT-scans show multiple giant apical bronchiectasis and a middle lobe syndrome.

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List of abbreviations

ETI: elexacaftor-tezacaftor-ivacaftor

CF: cystic fibrosis

FEV1: forced expiratory volume in the first second

BMI: body mass index

MRSA: methicillin-resistant Staphylococcus aureus

Abstract

Not applicable.

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Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All experimental protocols were approved by the IRCCS Burlo Garofolo ethics committee.

Written consent was obtained from the parents of patients under 16 years old.

Consent for publication

Written consent was obtained from parents for participants under 18 years old. Written consent was obtained for the publication of potentially identifying images and clinical details.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declaration of competing interest

None.

Authors' contributions

Arianna Traunero: Conceptualization, Writing – original draft, Writing – review & editing. Anna Galletti: Conceptualization, Writing – original draft. Sergio Ghirardo: Conceptualization, Writing – review & editing.

Massimo Maschio: Conceptualization, Writing – review & editing. Egidio Barbi: Writing – review & editing.

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