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Personalised CFTR Modulator Treatment Initiation and Monitoring in CF-Related Liver Disease: When Less Is More

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ABSTRACT

Hepatotoxicity due to Elexacaftor/Tezacaftor/Ivacaftor (ETI) use has been well documented. There are no dose adjustments or increased-frequency monitoring algorithms recommended for people who experience elevated transaminases without cirrhosis, only suggested treatment interruption or withdrawal depending on the severity of the derangement. Here we describe a patient with non-cirrhotic hepatic steatosis who experienced persistently elevated liver function tests due to modulator therapy but demonstrated a remarkable response to a notably low dose of ETI.

1 | Introduction

Cystic fibrosis (CF) is a multiorgan disorder caused by CF transmembrane conductance regulator (CFTR) gene mutations [1]. CFTR modulator therapy has transformed the landscape of CF care. Oral Elexacaftor/Tezacaftor/Ivacaftor (ETI) is approved in Australia for patients with at least one copy of the F508del mutation, which affects approximately 85% of the global CF population [1]. Elevated serum liver function tests (LFTs) after ETI commencement are well described [1–4]. Here, we describe a patient with persistently elevated LFTs who benefited from a remarkably reduced ETI dosage.

2 | Case Report

A 27-year-old male with F508del and Ser549Arg CFTR mutations commenced single-agent ivacaftor in April 2020. His CF features included bronchiectasis, pancreatic insufficiency, chronic sinusitis and insulin-dependent diabetes mellitus. Baseline liver ultrasound reported non-cirrhotic hepatic steatosis. LFTs, full blood count and urea, electrolytes and creatinine were all within normal limits at the first dose. Baseline ppFEV$_1$ was 66%, and a January 2020 sweat chloride test was 107 mmol/L (> 60 mmol/L is considered abnormal and supports the diagnosis of CF). BMI was 25 kg/m^2 at commencement. Regular medications included azithromycin, Creon Forte and insulin. He denied any herbal or paracetamol (acetaminophen) use and rarely consumed alcohol. He had no significant pulmonary exacerbations warranting intravenous antibiotics in the past 10 years.

Four months into ivacaftor therapy, serial testing showed an elevated alanine aminotransferase (ALT) peaking at 208 U/L (normal value < 40 U/L) (Figure 1). The patient was asymptomatic, denied alcohol intake and was not taking unprescribed or herbal medicines. Ivacaftor was discontinued due to transaminitis, despite improved ppFEV$_1$ to 71%. Repeat liver ultrasound showed hepatic steatosis. Autoimmune and viral hepatitis screens were negative. ALT normalised to 48 U/L 4 weeks after ivacaftor cessation.

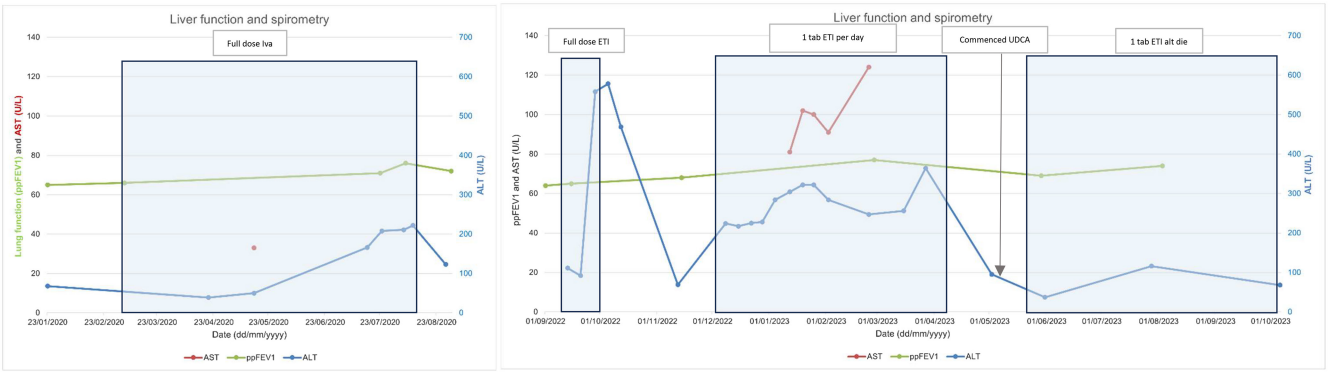

FIGURE 1 | Liver function and spirometry in response to varying doses of ETI over time. alt die: alternate daily; Iva: ivacaftor; UDCA: ursodeoxycholic acid.

ETI treatment was subsidised in Australia from 2022 for eligible mutations, and the patient expressed interest in triple therapy as his $ppFEV_1$ had returned to 64%. Hepatology services advised more frequent, tailored LFT monitoring while initiating therapy compared to the usual suggested three-monthly LFT monitoring. He commenced ETI at the standard dose in September 2022. Eight days into therapy, ALT was 558 U/L, but the patient remained asymptomatic. He did, however, report remarkable improvements in sinus congestion, anosmia and energy levels while taking ETI. The drug was discontinued for transaminitis, and LFTs were monitored until return to baseline in November 2022 (Figure 1).

After LFT normalisation, and at the patient's request, ETI was re-trialled in December 2022 at a reduced dose of only one tablet of ETI per day. Weekly ALT soon demonstrated a rise five times the upper limit of normal. He remained on one tablet of ETI per day with cautious monitoring. In March 2023, $ppFEV_1$ was 77%, and a sweat chloride test was 26 mmol/L.

ALT peaked at 365 U/L in March 2023, and treatment was discontinued. ALT returned to 95 U/L within 4 weeks (Figure 1). In consultation with Hepatology, the patient commenced oral ursodeoxycholic acid (UDCA) 500 mg twice daily. In May 2023, he resumed ETI at a further reduced dose—one tablet of ETI every 48 hours. ALT increased to 116 U/L in July 2023 and plateaued at 68 U/L in October 2023 (Figure 1). The repeat sweat chloride test conducted while on one ETI tablet 48-hours remained at 26 mmol/L. $ppFEV_1$ in November 2023 was 78%. The patient reported sustained improvement in sinus congestion, anosmia resolution, and improved energy levels despite the remarkably low dose of ETI.

Throughout ivacaftor and ETI treatment, the patient's bilirubin and gamma glutaryl transferase remained near normal. BMI peaked at 26 kg/m^2 one month after Ivacaftor commencement but has been maintained at 24 kg/m^2 years into ETI therapy. He has remained clinically stable for 18 months on just one ETI tablet 48 hourly and UDCA 500 mg twice daily.

3 | Discussion

Hepatotoxicity due to ETI use is well established [1–4]. The United States Food and Drug Administration Trikafta prescribing information [4] outlines limits and contraindications based on hepatic cirrhosis severity. There are no dose adjustments or increased-frequency monitoring algorithms for elevated transaminases *without* cirrhosis, only suggested treatment interruption or withdrawal.

This patient's significant ALT and AST peaks observed with standard doses of ivacaftor or ETI culminated in immediate treatment termination as guided by clinical prescribing information. This adverse reaction, even on challenging, should in theory, have rendered the patient contraindicated from treatment, as he would be considered intolerant of the standard dose of ETI recommended by the manufacturer. However, this case shows the potential positive outcomes of re-trialling CFTR modulators at patient-tailored doses for those who experienced adverse effects.

Clinical guidelines [4] suggest checking LFTs every 3 months for the first year, then annually thereafter. Our clinic has adopted a more conservative approach, with additional LFT reviews 1 month after ETI commencement for CFTR modulator-naïve patients or those with pre-existing hepatic derangement. In this case, a further-modified LFT monitoring regime was prescribed at ETI commencement: weekly LFTs for 4 weeks, then monthly for 3 months, then three-monthly for the remainder of the first year, then annually. This approach was validated when LFTs trended upwards a week after commencement, with ALT at 558 U/L 2 weeks into treatment. Waiting for a 3-month LFT review could have had devastating consequences.

In the absence of serum therapeutic drug monitoring assays to guide treatment individualisation, this case highlights the advantage of utilising readily available sweat chloride testing as an objective marker of individual response to ETI, especially at clinically subtherapeutic doses.

Pharmacokinetic and pharmacodynamic variability described here could highlight the possible role of pharmacogenomic testing to assess genetic polymorphism factors in drug metabolism, guiding individualised dosing.

Optimising liver health before starting CFTR modulators, or at the onset of liver-related side effects, is also highlighted here. Although UDCA's role in drug-induced liver injury remains

controversial [5], our patient benefited from addition of UDCA and reduced-dose ETI.

Author Contributions

Sona Vekaria: conceptualisation, formal analysis, investigation/data curation, writing original draft, review and editing. **Grace Kavanagh:** conceptualisation, writing original draft, review and editing. **Siobhain Mulrennan:** conceptualisation, review and editing, supervision.

Ethics Statement

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

Conflicts of Interest

Sona Vekaria and Grace Kavanagh declare no conflicts of interest. Siobhain Mulrennan reports speaker fees from Vertex and is PI for a number of Vertex clinical trials outside the submitted work.

Data Availability Statement

Data available on request due to privacy/ethical restrictions.

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