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A case of self-limited drug induced liver injury under treatment with elexacaftor/tezacaftor/ivacaftor: when it is worth taking the risk.

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Introduction

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a CFTR modulator therapy used in the treatment of cystic fibrosis (CF) in patients with at least one Phe508del allele [1,2]. The occurrence of biochemical liver abnormalities under this particular treatment is frequent but usually mild. In the registration studies, a minority of patients did show aminotransferase levels above three times the upper limit of normal (ULN) (prevalence of 2.5% in Phe508del heterozygous and 7% in Phe508del homozygous patients, respectively) but liver toxicity was never a reason for interruption of the interventional drug [1,2]. How treatment induces biochemical liver abnormalities is not known to date, but could potentially be attributed to the metabolization by the cytochrome p450 system producing toxic or immunogenic metabolites [3]. Here, we present a case of drug-induced liver injury (DILI) in a Phe508del homozygous patient treated with ELX/TEZ/IVA in a medical need program with a remarkable evolution in liver enzymes.

Case presentation

A 58-year old Phe508del homozygous female living with CF, complicated by pancreatic insufficiency, cystic fibrosis related diabetes mellitus and chronic rhino-sinusitis with nasal polyposis, was followed at our outpatient CF clinic. There was no history of liver cirrhosis, although the patient did suffer from a suspected severe drug-induced hepatitis following treatment with oseltamivir several years before, which spontaneously and completely recovered after four weeks of treatment interruption. Despite treatment with lumacaftor/ivacaftor since 2017, her forced expiratory volume in 1 second (FEV_1) had progressively declined from 40 %predicted in 2017 to 27 %predicted in July 2020. She was listed for lung transplantation, but was ultimately found to be eligible for participation in a medical need program with ELX/TEZ/IVA due to high symptom burden, frequent infectious exacerbations and FEV_1 below 30 %predicted.

As soon as one month after introduction of the treatment, an improvement in FEV_1 of 10%predicted from baseline was observed, together with a significant reduction in dyspnea and

sputum, with concomitant improvement of quality of life. Subjectively, treatment was well tolerated, however, an important elevation of liver enzymes compatible with a mixed cholestatic and hepatocellular pattern between 1 and 2 weeks after the start of therapy was noticed: alanine transaminase (ALT) and aspartate transaminase (AST) were both 15 times above the ULN, while alkaline phosphatase (AP) and gamma glutamyl transferase (gGT) were 5 times above the ULN. Bilirubin, albumin and coagulation tests were normal in the absence of any clinical signs of encephalopathy. A thorough anamnesis into the use of potentially hepatotoxic over-the-counter drugs and dietary supplements was negative apart from limited alcohol use, which she stopped completely when the first rise in liver enzymes appeared. Timing of the start of therapy and the onset of rising liver function tests was suggestive of DILI. Hence, treatment was interrupted after which a fast decline in liver enzymes was seen (Figure 1).

Because treatment with ELX/TEZ/IVA had substantially improved the patient's respiratory condition and quality of life, she requested to continue treatment despite the appearance of this significant side effect, potentially leading to a new rise in liver enzymes. After a shared-decision making process, in conjunction with close clinical and biochemical surveillance of liver function, ELX/TEZ/IVA treatment was resumed at a reduced dose (alternating 2 and 1 ELX/TEZ/IVA tablet in the morning without a tablet of IVA in the evening, as is proposed for patients with CHILD B liver cirrhosis [4]). Nevertheless, aminotransferases, AP and gGT increased again under this reduced dose. During the following weeks, the patient was alternately on and off treatment (at the reduced dose) depending on the results of liver tests as shown in Figure 1.

The hepatology department was consulted. Extensive blood work and magnetic resonance imaging of the liver excluded alternative causes of liver dysfunction (including infection, auto-immune hepatitis, portal thrombosis and liver cirrhosis). Because diagnosis of ELX/TEZ/IVA-induced liver injury was critical in this patient with a clear benefit of this CFTR modifier treatment, a liver biopsy was performed, showing minimal panlobular hepatitis in the presence of some eosinophils

and intrahepatocytic bilirubinostatis without fibrosis. These findings were compatible with the diagnosis of DILI. Despite continuing treatment after the biopsy, a gradual decrease in AST, ALT, gGT and AP under treatment with the reduced dose was observed (Figure1). Reverting to the standard dose of ELX/TEZ/IVA did not result in a significant rise in liver enzymes. Twenty weeks after initiation of treatment, the patient feels well and has a FEV_1 of 38 %predicted. She did not suffer any pulmonary exacerbations since she started treatment with ELX/TEZ/IVA and could be removed from the lung transplant list to date.

Discussion

We describe a case of a 58-year old Phe508del homozygous CF patient listed for lung transplantation because of a steep lung function decline (to a FEV_1 below 30 %predicted) in association with a high symptom burden and recurrent infectious exacerbations. She was treated with ELX/TEZ/IVA in a medical need program. Treatment was complicated by DILI, however a trend towards normalization of liver enzymes was noticed under ongoing treatment, suggesting the hepatocytes are adapting and presumably developing tolerance for the causal drug. Bearing in mind the significant clinical evolution in this critical patient, ongoing treatment under strict clinical and biochemical surveillance of liver function can be justified, provided the patient is thoroughly informed about the potential risks.

DILI can be classified as intrinsic (direct and dose dependent toxicity) versus idiosyncratic (with a longer latency period of days to weeks and without clear dose dependence). In both subtypes, the risk of development of DILI increases with age [5]. Liver injury in our patient appeared to be similar under a reduced dose compared to the full dose of ELX/TEZ/IVA, pointing to the presence of idiosyncratic DILI. The history of a potential prior episode of DILI following treatment with oseltamivir - which has been described in literature before [6] - may be indicative of a genetic susceptibility to DILI in this patient.

While interruption of the causative drug is the intervention of choice for DILI, favorable outcomes have been described when resuming treatment with essential non-replaceable drugs, for example with anti-tuberculosis drugs or immune therapy in cancer treatment [4]. Reintroducing a culprit drug can be successful - as described in this case - because of the adaptive capacity of hepatocytes and the immune system to chemical insults. However, the success of reintroducing a drug initially provoking DILI is unpredictable in an individual patient [5], who should be closely monitored upon reintroduction. According to the prescription of ELX/TEZ/IVA, treatment should be interrupted in the event of ALT or AST rise of more than 5 times the ULN, or ALT or AST above 3 times the ULN in conjunction with bilirubin levels above 2 times ULN. Even after liver enzymes have normalized, the risk of DILI re-emerging cannot be excluded, and should be balanced against potential treatment gains.

In conclusion, this case report outlines that even when ELX/TEZ/IVA provokes DILI in a certain patient, a favorable evolution can be obtained despite continuing treatment. We believe that in critical CF patients, benefits of continuing treatment in patients with DILI under this CFTR modulator therapy can outweigh the risks, provided that liver function is strictly monitored and patients are fully aware of the potential harms.

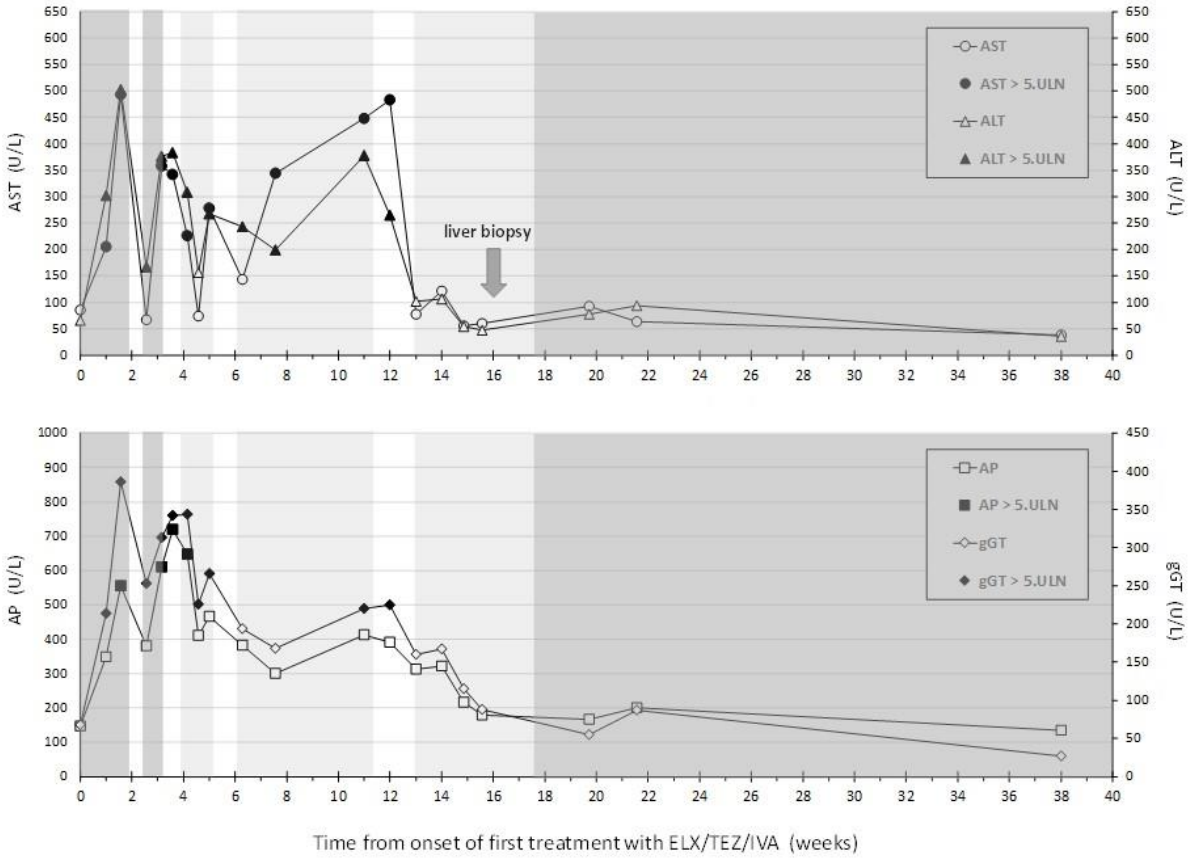

Figure 1: Time evolution of liver enzymes under treatment with elexacaftor/tezacaftor/ivacaftor. Dark grey area: on treatment (full dose). Light Grey area: on treatment (reduced dose). ALT: alanine transaminase, AST: aspartate transaminase, AP: alkaline phosphatase, gGT: gamma glutamyl transferase, ULN: upper limit of normal. Open circles AST: below or equal 5 times ULN (160 U/L); Closed circles AST: above 5 times ULN; Open triangle ALT: below or equal 5 times ULN (165 U/L): Closed triangle squares ALT: above 5 times ULN; Open square AP: below or equal 5 times ULN (520 U/L); Closed square AP: above 5 times ULN; Open diamond gGT: below or equal 5 times ULN (200 U/L); Closed diamond gGT: above 5 times ULN. Time of liver biopsy is also shown.

Conflict of interest

Stylemans Dimitri, Vincken Stefanie and Vanderhelst Eef have participated in multiple randomized controlled trials with different CFTR modulators from Vertex, Abbvie and Proteostatis as subinvestigator or investigator.

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