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**Carbamazepine intervention in a patient with efavirenz-induced liver injury**

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In 1-8% of patients efavirenz (EFV) is associated with grossly elevated serum aminotransferases (> 5 upper limit of normal) (1). We report on a patient with potential EFV-induced liver injury and persisting liver damage after discontinuation of EFV. Carbamazepine was introduced to increase EFV clearance through induction of CYP2B6 and CYP3A4 (2).

In June 2015, a 47-year-old HIV-positive (CD4+ cells: 460/mm3, HIV-1 viral load: 200,000 copies/mL) Caucasian male presented to the clinic because of recently diagnosed HIV. He was co-infected with CMV and EBV, and denied alcohol abuse and use of recreational drugs. Liver enzyme levels were within the normal range on commencement of therapy. In July 2015, combination antiretroviral therapy for acute HIV infection was initiated, consisting of emtricitabine/​tenofovir DF/​efavirenz (Atripla®; 200/245/600mg) once-daily with dolutegravir (DTG) 50mg twice-daily.

Two weeks after starting therapy, the patient complained about nausea, abdominal pain and difficulties in concentrating on tasks. One month later, the patient’s treatment regimen was simplified to dolutegravir/abacavir/lamivudine (Triumeq®; 50/600/300mg) once-daily as at least some of these adverse events were attributed to EFV and his preference for a once-daily dosing regimen. Meanwhile, his viral load had been reduced to 50 copies/ml.

Abdominal pain persisted three weeks after starting Triumeq®. Liver enzyme levels were consistent with liver damage (alanine transaminase (ALT) 344 U/L (normal <45 U/L) and aspartate transaminase (AST) 132 U/L (normal <35 U/L)(figure 1). The patient did not have rash or fever and his eosinophils were normal (0.13\*109/L). As no liver enzyme elevations were seen during initial treatment with Atripla® and dolutegravir, we assumed that abacavir/lamivudine caused the observed liver injury. Therefore, Triumeq® was discontinued and Atripla® was re-introduced (October 2015). ALT levels decreased in the following month. Subsequently, his liver enzyme levels again increased dramatically by the 24th of November 2015 (ALT: 1190 U/L, AST: 478 U/L) and total bilirubin (TBIL) was 0.76 mg/dL. The EFV blood concentration was 4.2 mg/L at November 25, slightly above the therapeutic range (1.0 – 4.0 mg/L) (3). The patient stopped treatment two days later and carbamazepine 400mg once-daily was started to increase EFV clearance. EFV blood concentration was 1.0 mg/L at December 2nd.

ALT did not decrease in the following month and serum bilirubin started to increase. A liver biopsy was performed and showed lobular infiltrates of lymphocytes and eosinophils indicating acute hepatitis injury. The findings are consistent with a drug-induced immunoallergic hepatitis with delayed onset.

Two months later, the patient’s liver enzymes returned to normal levels. Triumeq® was reinitiated without any liver toxicity observed since then. The patient was genotyped for CYP2B6 activity and was found to be an intermediate metabolizer (IM) with the genotype of CYP2B6\*1/\*6. In retrospect, EFV metabolites were determined in the November 25 sample, showing an 8-OH-EFV/EFV ratio and a 7-OH-EFV/EFV ratio of 0.80 and 0.12, respectively (normal: 0.68; 0.09).

To our knowledge, this is the first presented case in which carbamazepine has been used to increase the clearance of EFV after a serious adverse event (SAE). In this case EFV elimination half-life (t1/2) was around 60 hours in presence of carbamazepine, which is slightly longer compared to 40 – 55 hours after multiple doses in healthy volunteers (4). EFV t1/2 in IMs is poorly documented in literature; one study reported an average t1/2 of 78 hours (5). We assume carbamazepine had a minor effect on the clearance of EFV although we do not know what the EFV half-life would have been in this patient without carbamazepine. The relative modest effect of carbamazepine might be explained by less active enzymes due to the CYP2B6\*1/\*6 genotype which are less inducible.

High EFV blood concentration and the \*6 genotype of CYP2B6 are associated with a higher risk of liver injury in EFV users (6). This case strengthens this statement. The high EFV levels and intermediate metabolization of EFV might also explain the persisting high levels of liver transaminases in this patient. Usually, liver enzyme levels improve within a few days and patients are expected to fully recover within 2-8 weeks after cessation of therapy (7). ALT levels did not decrease for 21 days after discontinuation of EFV and full recovery was reached only after 3 months.

Although we are not sure the patient did benefit from carbamazepine, we recommend using carbamazepine to reduce toxicity of EFV in case of an SAE. More case reports and case series are needed to determine the clinical benefit of carbamazepine. This case also emphasizes the relevance of routine monitoring of liver enzymes in patients using EFV. EFV-DILI might occur several months after initiating EFV.

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