

Rare but Serious: Ibrutinib Induced Liver Failure

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The oral Bruton Tyrosine Kinase (BTK) inhibitor ibrutinib is increasingly prescribed for B-cell malignancies including chronic lymphocytic leukemia (CLL), mantle cell lymphoma and Waldenstrom Macroglobulinemia (WM). Recently, an extensive practical review on the side effects of ibrutinib and the management thereof was published.¹ However, ibrutinib-induced hepatotoxicity was not mentioned as an adverse event of interest. We would like to share our experience with ibrutinib-induced liver failure, including a summary of the emergent literature and data from national and global pharmacovigilance centers. We feel prescribers of ibrutinib should be aware of this rare but serious and potentially fatal side effect.

A 48-year-old female started ibrutinib monotherapy 420 mg once daily for refractory WM; she was otherwise healthy and did not use any other medication. Previous treatment consisted of dexamethasone/cyclophosphamide and ixazomib/dexamethasone (rituximab was withheld due to high IgM levels). Eleven weeks after starting ibrutinib therapy, she presented with jaundice and dark urine. Laboratory examination showed an almost 40-fold increase in transaminases (ALT 1808 U/L, AST 1288 U/L) and a hyperbilirubinemia of 123 µmol/L with

coagulopathy (INR 1.6 IU). Her Model for End-Stage Liver Disease (MELD) score was 22, which is considered high and prompted a pre-emptive consultation of a liver transplant center. An extensive work-up for viral hepatitis and auto-immune hepatitis was negative (consisting of IgG4, ceruloplasmin, ACE, ANA and mitochondrial antibodies, CMV, EBV, Hepatitis A (total and IgM), B(anti-HBs, anti HBC, HBs-Ag), C and E(IgM and IgG) serology and PCR's for CMV, EBV, hepatitis B, C, and E viruses). An ultrasound of the liver showed no signs of bile duct obstruction or liver injury. Ibrutinib was considered the most likely cause and was discontinued at the day of admission. Apart from a proton pump inhibitor (omeprazole), which was started 1 week earlier because of abdominal complaints, she did not have any other medication. In retrospect, the transaminases were already mildly elevated before the initiation of omeprazole. We did not perform a liver biopsy in this patient because liver tests improved very quickly after cessation of ibrutinib. In the first week after admission bilirubin levels rose to 307 µmol/L with an INR of 1.56 IU. The maximum MELD score was 23 (estimated 3 month mortality of 19.6%).² The liver enzymes as well as coagulation tests fully normalized within 5 weeks after discontinuation of ibrutinib (Fig. 1). She experienced a rapid IgM flare after stopping ibrutinib and started plasmapheresis as a bridge to her next line of WM treatment.

Two recently published case reports describe similar cases of ibrutinib induced severe hepatotoxicity, starting 2 weeks and 9 months after initiation of the drug.^{3,4} Ibrutinib was prescribed for relapsed Richter's transformation of CLL and relapsed WM respectively. Both patients had a liver biopsy compatible with drug-induced liver failure (hepatocellular cholestasis and signs of acute hepatitis). One patient developed full-blown acute liver failure with coagulopathy, encephalopathy and hypoglycemia. This patient, like ours, had a full recovery after discontinuation of ibrutinib. The other patient showed ongoing improvement of liver functions after stopping ibrutinib, but succumbed to relapsed Richter syndrome.

The Netherlands Pharmacovigilance Centre *Lareb*⁵ as well as the WHO global pharmacovigilance centre (Uppsala monitoring Centre (UMC))⁶ both report cases of liver and bile duct associated side effects of ibrutinib. In the Netherlands, 5 out of 47 ibrutinib-related reports (10.6%) concerned liver and bile duct associated side effects, including abnormal liver function tests (LFTs) (1 report), liver failure (1 report), liver necrosis (1 report) and liver injury/hepatotoxicity (2 reports).⁵ Of 25,525 ibrutinib-related reports made to the WHO, 348 reports (1.4%) were related to liver and bile duct associated side effects, of which 94 (0.4%)

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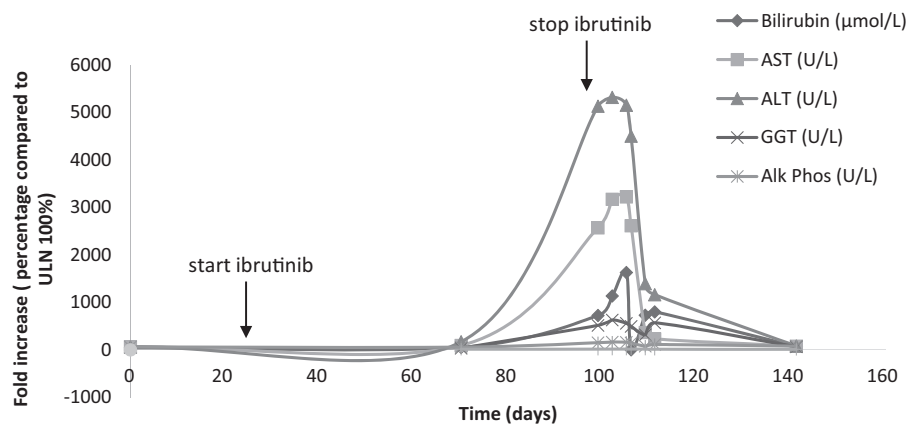


Figure 1. Liver function tests before and after stopping ibrutinib.

describe liver failure.⁶ The manufacturer of ibrutinib (Janssen) mentions very rare occurrences of severe liver toxicity in the post-marketing setting.⁷ They note a time of onset of 5 days to 3 months after initiation of ibrutinib. Interestingly, they mention most cases will resolve upon dose modification. In addition, they advise monitoring of liver function tests as well as discontinuation of treatment if \geq grade 3 liver function abnormalities develop.

The exact pathophysiology of ibrutinib-induced hepatotoxicity is unknown. All tyrosine kinase inhibitors (TKIs) are associated with hepatotoxicity (up to 35%, mostly limited to low grade elevations of transaminases) and rare occurrences of (sometimes fatal) liver failure, for which the exact incidence is unknown.⁷ Interaction of the tyrosine kinase signaling cascades with mediators of hepatocyte integrity have been suggested as the mechanism of TKI-induced hepatotoxicity.⁸ In addition, ibrutinib is largely metabolized by CYP3A4 and in lesser quantities by CYP2D6. Liver dysfunction caused by ibrutinib may thus increase the plasma levels of the drug, leading to a vicious circle of toxicity. Another consideration is the concurrent use of acetaminophen: many TKIs inhibit UDP-glucuronosyltransferase (UGT), which may increase the development of acetaminophen's hepatotoxic metabolite benzoquinoneimine (NAPQI). Although it is unknown whether ibrutinib inhibits UGT as well, it should be considered as a possible cause for the occurrence of hepatotoxicity. In our case, the patient denied taking any acetaminophen.

For the clinician, these data highlight the importance of monitoring liver functions in patients on ibrutinib, since there is a small but serious risk of drug-induced liver failure. There are no predictive risk factors available for these adverse events.

Ibrutinib-induced hepatotoxicity should be considered when abnormal liver function tests occur, even long after starting the drug. Mild cases (grade 1 or 2) could initially be handled by dose reduction and close monitoring. In severe cases (grade 3 or higher), the drug should be discontinued. We would recommend considering a liver biopsy if there is persisting uncertainty regarding the cause of the liver failure after serological testing and when there is no quick improvement after cessation of potentially hepatotoxic drugs including ibrutinib. It should be emphasized that viral hepatitis should be excluded, since ibrutinib has been associated with reactivation of hepatitis B.⁹

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