Chronic Hepatitis B Reactivation: Deadly, But Preventable

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Introduction

350 million people worldwide live with chronic hepatitis B virus (HBV) infection, though only ~10% are aware of their diagnosis. Of those untreated, 25% are at risk for premature death from hepatocellular carcinoma and end stage liver disease. Treatment reduces disease burden, but a functional cure is rare. Stopping treatment can provoke acute reactivation of chronic hepatitis B, defined as a rise in HBV DNA from baseline, and can result in severe hepatitis.

Case

A 51-year-old Vietnamese male with vertically transmitted chronic hepatitis B presents with symptoms of acute hepatitis for 2-3 weeks: jaundice, episodic fevers, diffuse abdominal discomfort, nausea, vomiting, and anorexia. He was previously treated with Tenofovir for a decade. 2 months prior: Tenofovir stopped based on an undetectable HBV viral load and negative HBsAg. 1 week prior to admission: New transaminitis. HBV viral load of 796 million IU/mL. Tenofovir restarted.

Physical Exam

Vitals: BP 151/91, HR 92, Temp 101.3, RR 18, 95% O2 RA
• Awake, alert, and comfortable
• Scolar icterus and jaundiced skin
• Abdominal and neurological exam unremarkable

Laboratory Tests and Imaging

• ALT 2,675, INR 1.6, total bilirubin 7.7
• CT: edematous liver suggesting hepatitis.
• ALT, INR, and total bilirubin trended upwards
• Scleral icterus and jaundiced skin

Our Patient’s HBV Serologies Confused for Functional Cure

First Hospitalization

• Tenofovir continued
• ALT, INR, and total bilirubin trended upwards without signs of fulminant hepatic failure
• Day 4: Lamivudine added to Tenofovir based on some studies improved survivability in acute reactivation
• Day 5: transaminits and INR began to improve
• Day 12: discharged despite increasing total bilirubin (takes days to normalize per transplant team)

Second Hospitalization (1 month later)

• Admitted with new ascites and melena
• Found to have liver cirrhosis by CT, portal hypertensive gastropathy. MELD score > 40, and increasing viral load compared to the previous week
• Developed fulminant hepatic failure
• Underwent liver transplant with drastic improvement of liver synthetic function

Course

Diagnosed with acute on chronic hepatitis B reactivation with severe hepatitis due to discontinuation of Tenofovir

Discussion

• Hepatitis B virus remains indefinitely within nucleus of infected hepatocytes:
  • viral DNA integrates itself into host DNA
  • viral DNA is turned into covalently closed circular DNA (cccDNA) which functions as stable mini-chromosomes
  • Host machinery transcribes viral DNA into mRNA, which is used by HBV reverse transcriptase to generate progeny virions.

• Tenofovir AF, the first line therapy for chronic HBV, is a nucleotide analogue which inhibits reverse transcriptase to prevent viral replication.

• Tenofovir reduces disease burden, but does not target the viral DNA integrated into the host genome. Thus the virus is not eradicated.

• Functional cure, where chronically infected patients can stop taking medication, is defined as the seroclearance of HBsAg. This occurs in only 1% of patients.

• In our case, a negative HBeAg was confused for HBsAg and interpreted as having achieved seroclearance.

• Discontinuation of Tenofovir in our patient led to enhanced viral replication which triggered the immune system to destroy infected hepatocytes, resulting in acute hepatitis, and ultimately need for liver transplant.

Take Away Points

• No cure for chronic hepatitis B currently
  • On Tenofovir, an undetectable viral load indicates medication adherence, not hepatitis B eradication

• Therapy is most often continued indefinitely.
  • Unlike Hepatitis C, it is rare (1%) to reach a functional cure of Hepatitis B (signified by the seroclearance of HBsAg)

• Black box warning: Discontinuation of Tenofovir can result in acute hepatitis B reactivation leading to severe hepatic injury and even fulminant hepatic failure

• Initiating immunosuppression or chemotherapy can cause iatrogenic hepatitis B reactivation in undiagnosed patients. Be vigilant of the undiagnosed chronic hepatitis B carriers, most commonly seen in patients immigrating from countries with high HBV prevalence or in patients with high risk behaviors

References

Yang, Y., Ho, H., Yang, H., Tseng, T., Hosaka, T., Trinh, H., & Zhang, J. (2019). Black box warning: Discontinuation of Tenofovir can result in severe hepatitis due to discontinuation of Tenofovir.