Should Hepatitis B be Biopsied?

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The primary objective of treatment for patients infected with hepatitis B virus (HBV) is to prevent progression of the disease, and its complications like liver cirrhosis and hepatocellular carcinoma (HCC).¹ Asian-Pacific consensus statement on the management of chronic hepatitis B recommends that chronic HBV-infected patients with alanine aminotransferase (ALT) equal to or greater than 2 times Upper Limit of Normal (ULN), and HBV DNA greater than 20,000 IU/ml if HBeAg positive and 2000 IU/ml if HBeAg-negative as well as patients with advanced fibrosis or cirrhosis with any ALT level should be considered for treatment.² There are certain predictors for the progressive liver damage in chronic HBV infection, which include persistently elevated level of HBV DNA and alanine aminotransferase (ALT), as well as the presence of pre-core and core mutations in patients with HBV genotype C and D infections.³ The older age, male gender, strong family history of HCC and presence of co-infection with hepatitis D (HDV), hepatitis C virus (HCV), or Human Immunodeficiency Virus (HIV) are also considered to be the potential risk factors for the progression of the disease.

As mentioned in the guidelines, treatment for hepatitis B is prescribed on the basis of serum HBV DNA and ALT level, and severity of liver disease on biopsy.⁴ However, there are certain caveats which need to be addressed. The normal serum ALT level alone in patients with active viral replication does not predict mild or normal histologic finding. One report found that up to 37% of patients with persistently normal ALT and HBV DNA levels > 2,000 IU/ml had significant fibrosis and inflammation on liver biopsy. On subgroup analysis, most of these patients had an ALT in the high range of normal and were older than 40 years of age.⁵ Another study investigated the correlation of normal ALT with the liver fibrosis stage in patients with persistently normal ALT. The distribution of fibrosis stages 0/1/2/3/4 were 35%/46%/19%/0%/0% respectively. In this study, 21% of HBeAg-negative patients with persistently normal ALT and HBV DNA < 20,000 IU/ml had histologically active liver disease (histologic activity index ≥ 3 and/or fibrosis stage ≥ 2).⁶ By contrast, two studies in patients with the immune tolerant phase of chronic HBV infection found that despite high HBV DNA levels, most patients had no or minimal fibrosis.⁷,⁸ Considered together, these data indicated that age and duration of infection were important in predicting severity of liver injury in patients with high HBV DNA but normal ALT levels. According to Goldstein et al. older age is in direct proportion to the increase risk of cirrhosis and HCC in patients with chronic hepatitis B.⁹

REVEAL study showed a strong association between baseline serum HBV DNA level and incidence of cirrhosis. HBV DNA level ≥ 10⁴ copies/ml independently and significantly predicted the risk of cirrhosis. Age, gender, HBeAg status, and ALT level also independently and significantly predicted for greater cirrhosis risk. Data indicated that high levels of serum HBV DNA may induce immune responses that can lead to liver injury and cirrhosis.¹⁰ HBV DNA < 20,000 IU/ml may not be a reliable marker for inactivity as it may follow a flare of ALT in patients with HBeAg-positive hepatitis B. Moreover, serum HBV DNA fluctuations are frequently seen in HBeAg-negative hepatitis B and there is a poor correlation of HBV DNA level with liver histology in HBeAg-negative hepatitis B. So values of < 20,000 IU/ml but greater than 2,000 are associated with a definite risk for long-term complication such as advanced fibrosis, cirrhosis and HCC.¹¹

Chronic HBV infection can be divided into different phases: immune tolerant phase, immune clearance phase, and inactive or residual phase. During the immune clearance phase, HBV DNA level is greater than 2,000/ml or 20,000 IU/ml depend upon the HBeAg negative or positive status of the patient.² Acute flares of hepatitis activity with elevated levels of serum ALT may occur during this phase. Higher ALT levels, therefore, usually reflect the more vigorous immune response against HBV and more extensive hepatocytes damage.⁸ On liver biopsy, nearly all of these patients have active hepatitis with variable degrees of fibrosis. Almost all experts would agree that these patients should be considered candidates for treatment. This phase is eventually followed by HBeAg seroconversion to its antibody (anti-HBe) and/or undetectable or low HBV-DNA < 2,000 IU/ml with normal ALT levels called inactive HBsAg carriers or low replicative phase. On liver biopsy, they have no evidence of inflammation and in most cases no fibrosis. As a result, there is no reason why

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these patients require treatment for HBV. Between these two extremes lies a gray zone of patients who do not fit into either of the two above-mentioned categories. Liver biopsy is most useful in these persons who do not meet clear cut guidelines for treatment. These are the patients who are greater than 40 years of age, with ALT greater than the upper limits of normal but less than 2 ULN, HBV DNA levels > 2000 but < 20,000, and other clinical features suggestive of chronic liver disease and concomitant diseases. In the presence of moderate to severe necroinflammation and/or at least moderate fibrosis on liver biopsy, treatment of hepatitis B is warranted.

One form of discordance is referred to as an immune tolerant phase. Patients in the immune tolerant phase are usually young, Hepatitis B e Antigen (HBeAg) seropositive with high viral loads > 20,000 IU/ml but normal serum alanine aminotransferase (ALT). A recent study has confirmed that patients in the immune-tolerant phase show minimal disease progression.2 However, HBeAg-positive subjects older than 40 years with persistent 'high normal' ALT may have significant hepatic necroinflammation or fibrosis.12-14 Even with the current potent antiviral agents, it is difficult to completely suppress the high levels of HBV DNA found in these patients and treatment may significantly increase the risk of developing resistance over time. These patients should be kept under regular follow-up with ALT measured every 3 - 6 months.2 Performing a liver biopsy in these patients is often helpful to ensure that there is no on-going inflammation and to confirm that the patient is indeed in an 'immune-tolerant state'.

The other type of discordance is the patient with low or undetectable HBV DNA but an elevated serum ALT. This pattern may be seen in patients co-infected with HCV or HDV as the coinfecting viruses inhibit HBV replication. Alternatively, non-viral causes for the elevation of serum ALT, like alcoholic, autoimmune, or metabolic liver disease with steatosis or steatohepatitis (NASH) may be present histologically. Thus, liver biopsy is often essential in such patients. Another optional role of liver biopsy may be assessing histological response to therapy defined as a decrease in the histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy or fibrosis reduction by at least 1 point by Metavir staging.15,16

A liver biopsy may also be helpful in many patients with mutations in the HBV genome having HBeAg negative but active disease.4 These patients harbor mutations in the precore and basal core promoter region. The goal of HBV therapy in these patients to suppress HBV DNA is typically a lifelong process. As a result, before committing a patient to lifelong treatment, it is often important to document that treatment needs to be initiated at this point in time and should not be deferred. This is particularly true in young persons, where the lifelong risk of resistance needs to be balanced against the need to treat HBV. As a result, a liver biopsy may be useful in these patients with HBeAg negative disease. Performing a liver biopsy and confirming active HBV infection through immunohistochemical staining of liver tissue and ruling out any concomitant liver disease has been often helpful in patients with atypical serologic HBV testing.

In conclusion, recognition of the underlying histology can guide therapeutic decisions when patients do not fit the clinical practice guidelines and treatment may be helpful. However, it is important to remember that a liver biopsy represents just approximately 1/50,000 sample of the entire liver, and that liver injury is typically irregularly distributed in the liver.17 The diagnostic accuracy of liver biopsy decreases because of sampling error and intra- and inter-observer variability in histological interpretation. Moreover, even if it is generally accepted to be a safe procedure, it is invasive and can be associated with rare but potentially serious complications.18 The use of non-invasive tests for assessing liver histology can significantly reduce, but not wholly replace, the need for liver biopsy in chronic hepatitis B.19,20 These tests should be seen as a complementary tool in the management of these patients.

REFERENCES


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