

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Management of the Immune-Tolerant Hepatitis B Patient

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**G&H** Can you define the four phases that compose the natural history of chronic hepatitis B infection?

**AM** For patients who contract hepatitis B perinatally, the first stage of chronic infection is the immune-tolerant phase. These patients are typically young people, in the teenage years through their early 30s, who have a high viral load, typically above 2,000,000 IU/mL. They are hepatitis B e antigen (HBeAg)-positive, have normal alanine aminotransferase (ALT) levels, and manifest minimal necroinflammation and fibrosis on liver biopsy.

The second phase that is described is the immune-active or immune-clearance phase. In these patients, the body's immune system attempts to fight off the virus by causing inflammation in the liver and injuring liver cells. During immunoactivity, viral levels are reduced, but, in the process of the immune mechanism, liver function is impaired and enzyme levels (ALT) are raised.

Third is the inactive carrier state, where viral levels are very low, below 2,000 IU/mL, and ALT returns to normal. In these patients, liver histology still reveals only mild damage.

Originally, these stages were considered the only three stages of chronic hepatitis B (CHB) infection. More recently, the stage of reactivation has been recognized. Patients lose HBeAg during the inactive phase but may develop an underlying spontaneous hepatitis B virus (HBV) mutation, which causes periods of further disease

activity and hepatic inflammation. In the reactivation phase, patients are HBeAg- but they have rising levels of HBV DNA, generally above 2,000 IU/mL, which can fluctuate as can liver function and ALT values.

It is important to note that none of these four phases of CHB are static in their characterization, particularly after HBeAg seroconversion. At any juncture, if a patient has a viral level of 1,500 IU/mL and normal ALT, for example, they cannot be confidently categorized as either belonging to inactive carrier state or HBeAg-negative CHB. Patients need to be followed longitudinally to confirm disease characteristics and disease phase. In particular, inactive and reactivated phase patients can be very difficult to distinguish. Both are HBeAg-negative and hepatitis B surface antigen (HBsAg)-positive. They can both have normal ALT and relatively similar viral loads. Without a series of measures to see if HBV DNA levels are static (inactive) or rising (reactivated), they appear the same.

**G&H** How often should viral and ALT levels be checked in order to assess disease phase?

**AM** When I see new patients for the first time and am not sure of their progression or disease phase, I monitor every 3 months for the first year. If they have persistently low DNA levels and normal ALT, I switch to every 6 months thereafter. This interval should provide sufficient monitoring to identify those who need treatment or more active management, including surveillance for occurrence of hepatocellular carcinoma (HCC)

**G&H** What are the clinical goals of CHB treatment with oral nucleos(t)ide analog therapy?

**AM** In treating CHB with standard first-line nucleos(t)ide agents, the ultimate goal is loss of surface antigen, which allows for the discontinuation of therapy. However,

although these drugs are very potent and successful suppressors of viral replication, surface antigen loss is much more difficult to achieve. Recent pivotal clinical trials of tenofovir in HBeAg-positive patients have yielded surface antigen loss rates of 3% in the first year of therapy and cumulative loss of 6% after year 2. Similar results have been seen with entecavir. Of note, these results were only seen in HBeAg-positive patients and apparently in patients with HBV genotypes A or D. However, most Asian patients with HBV have genotypes B or C. Among Koreans with HBV, more than 90% have genotype C. Similarly, Chinese patients generally have genotypes B or C.

Thus, loss of surface antigen is not a realistic short-term goal in most cases. Currently, debate centers around when and if therapy can be stopped in patients who are positive for HBeAg. However, it is generally accepted that one can stop treatment in those patients who achieve HBeAg seroconversion associated with normal ALT values and sustained complete viral suppression.

**G&H** Are there advantages to treating CHB patients earlier in the disease course (in the immune-tolerant phase) with the newest and most potent oral agents?

**AM** This is a somewhat controversial question with no definitive answer as of yet. Some clinicians ascribe to the philosophy that there is no safe level of virus or safe phase of disease and that all adult patients with HBV DNA levels over 2,000 IU/mL (10,000 copies/mL) should be considered for treatment. This is, in part, based on data from the landmark observational REVEAL study, which was conducted in Taiwan and first published in 2006. These investigators recruited about 4,000 treatment-naïve CHB patients in 1991 and 1992 and followed them for a median of about 11 years. All patients were asymptomatic at baseline but tested positive for HBsAg. Based on the initial measure of viral load at study entry, subjects were divided into five groups. The first had undetectable levels of DNA (<300 copies/mL or <60 IU/mL). The second had low levels (60–200 IU/mL). The intermediate group had between 200 and 2,000 IU/mL, followed by a group with the HBV DNA levels of 2,000–200,000 IU/mL. The group with high levels of HBV DNA had greater than 200,000 IU/mL. The investigators found, after a long-term follow-up of disease course, that patients with the highest viral levels at baseline had the highest chance of developing cirrhosis or HCC. Such findings led some clinicians to consider the advisability of treating all patients with HBV DNA levels of above 20,000 IU/mL (100,000 copies/mL) in order to minimize viral levels and improve long-term

outcomes. In a follow-up study, the same investigators looked at pre- and end-of-study viral levels and concluded that sustained high levels of virus imparted even greater risk of disease complication, further supporting this argument.

An important caveat to this conclusion is that the REVEAL study originally recruited patients between the ages of 30 and 65 years. Among those patients who eventually developed cirrhosis, the median age at study enrollment was around 49 years. Thus, these patients have at least one significant characteristic difference from the typical immune-tolerant patients that we see in clinical practice, who are generally in their early 30s or younger.

**G&H** Given the high potency and low development of resistance that has been seen with the newest nucleos(t)ide agents, why would early treatment of patients with high viral load be of concern?

**AM** If we have an ideal medication with minimal side effects and no significant resistance rates seen through 15–20 years of therapy, then recommending treatment for all patients with high viral load would seem to be reasonable. However, these data are simply not available. The longest experience that we have is with lamivudine, which has a 70% resistance rate at 5 years of therapy. The low or complete lack of resistance in treatment-naïve patients that has been seen with both tenofovir and entecavir is encouraging, but these agents have not been utilized for prolonged therapy yet, with 5-year and 2-year data available so far for entecavir and tenofovir, respectively. It is important to establish safety and a lack of resistance in that, although these nucleos(t)ide therapies suppress viral replication very effectively, they do not accelerate the seroconversion rate of HBeAg. Each available oral agent, regardless of its antiviral potency, achieves an HBeAg seroconversion rate around 20% at 1 year of therapy. Furthermore, among patients with persistently normal ALT, the HBeAg seroconversion rates may be similar to those seen with placebo.

Thus, the chance of achieving HBeAg seroconversion is indeed small in immune-tolerant patients with normal ALT, although we can certainly lower the viral level. They may need to remain on medication for many years to achieve HBeAg seroconversion. Without safety data for that span of therapy and with the fact that some patients will seroconvert spontaneously without treatment, many experts argue that we should wait to treat immune-tolerant patients. They advocate that we should consider antiviral treatment in those patients at risk of developing cirrhosis or HCC within the ensuing 10–20 years.

## G&H How do you determine risk for eventual HCC among patients in the immune-tolerant stage?

**AM** The REVEAL study from Taiwan strongly implies that the higher the baseline viral load, the higher the chance of developing HCC in the future. However, decisions must frequently be made based on individual cases. Family history is an important risk factor that can affect the decision of when to treat. I have an Asian patient whose older brother developed HCC at age 27. The patient has CHB and a high viral load, and, based on his brother's illness, he was put on medication. If a patient has a strong family history of HCC risk, it is reasonable to start them on treatment early.

Further, ALT is not always a definitive measure. Patients can have normal liver enzymes but have stage 2–3 fibrosis or even cirrhosis on biopsy. The very definition of normal ALT can also pose a challenge, based on the standards of different laboratories, both AASLD guidelines, and the updated US algorithm on HBV by Keeffe and co-authors, which recommends revising the upper limit of normal ALT for men and women to 30 and 19 U/L, respectively. Obese patients can have raised enzymes due to the presence of fatty liver disease, independent of the course of their CHB. Finally, the age of the patient makes a difference. In patients up to 35 years old, persistently normal ALT values in general may indicate immune-tolerance. In a patient who is 40–45 years old, normal ALT may be more suspect.

## G&H What other data exist to demonstrate the efficacy of therapy in preventing disease complications?

**AM** Benefit from treatment has been demonstrated in patients with existing liver damage. Liaw and colleagues, in the *New England Journal of Medicine*, showed that patients with stage 3 or 4 fibrosis, when treated for 3 years with lamivudine versus placebo, had decreased incidence of liver complications or developing HCC. However, these patients, by definition, were not immune-tolerant, based on their level of fibrosis.

Conversely, Hui and associates followed 57 patients who were young, had high viral levels, normal liver enzymes, and biopsy-proven minimal liver damage. These

patients met the true definition of immune-tolerance. The investigators followed them for 5 years without treatment. After 5 years, nearly 85% of the patients had maintained minimal liver damage. Of the total cohort, only 9 patients developed raised enzymes, necessitating antiviral therapy.

## G&H What further evidence is needed to more fully illuminate this question?

**AM** With the introduction of nucleos(t)ide therapies, the number of transplants from CHB-related liver failure has decreased. However, the number of liver transplants from the development of HCC in CHB has not gone down. Some clinicians argue that we are treating too late to avoid HCC. If we treat earlier, for example, in patients in their teens and early 20s, we might theoretically prevent more liver cancer. However, other researchers wonder if even this is too late, and if we need to begin treatment in children or even toddlers. Until we know the answers to all of these questions, we may never change the way we treat.

Finally, the question of de novo combination therapy must be addressed. Currently, there are no data showing that combination therapy is better than monotherapy in previously untreated CHB patients. There is a trial currently ongoing, comparing entecavir monotherapy with a combination of entecavir and tenofovir in treatment-naïve patients. However, this is only a short-term study. Because the resistance rates to both drugs are already extremely low or none at 2 years, this study may not show any difference. Currently, de novo combination is only recommended in extreme cases of advanced liver disease or decompensated cirrhosis, not in immune-tolerant patients.

## Suggested Reading

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