Antiviral Therapy for Patients with Immune Active Hepatitis B: What, When and is Forever?

Hepatitis B is the most common chronic viral infection in the world and leads to significant complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma. Treatment of hepatitis B in patients with immune active disease is recommended in order to decrease the risk of these complications. Antiviral therapies currently available are highly effective in achieving viral suppression and recently updated guidelines from the American Association for the Study of Liver Diseases provide specific criteria for initiating antiviral therapy treatment in patients with chronic hepatitis B. However, once started, the issues of if and when providers can consider discontinuation of antiviral therapy continue to evolve. Increasingly, there is emphasis on treating until HBsAg loss occurs, but this means many patients will be on life-long therapy. A finite duration of therapy is attractive to patients and providers but one must consider the potential risks when stopping treatment. New data continue to inform this question and are reflected in this review.

INTRODUCTION

An estimated 240 million persons are affected by chronic hepatitis B infection, making HBV the most common chronic viral infection worldwide. Forty percent of chronic hepatitis B (CHB) patients will progress to liver complications of decompensated cirrhosis and hepatocellular carcinoma (HCC), leading to 1 million deaths/year. Given this tremendous disease burden, the WHO and CDC have made hepatitis B part of the viral hepatitis “elimination by 2030” initiative.

In the United States, approximately 2.2 million persons have chronic HBV, and this may be an underestimate since prevalence studies may underestimate immigrant and other high-risk populations. Over the past 35 years, it has become evident that up to 75% of persons with chronic HBV in the United States are foreign-born, and therefore despite implementation of universal vaccination in the United States, chronic hepatitis B is an ongoing public health problem in our country.

With current therapies, hepatitis B cannot be cured, as hepatitis B virus exists as cccDNA in the hepatocyte and this serves as a reservoir, unaffected by the nucleoside analogues used to treat CHB. However,

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Indications for Treatment in Chronic Hepatitis B

The dynamic nature of chronic hepatitis B requires careful monitoring of patients with CHB throughout their lives. Patients who are not candidates for treatment on initial evaluation may become treatment candidates in future. Phases of infection (see Figure 1) include the HBeAg positive immune tolerant phase where there is no significant necroinflammatory activity and ALT is normal despite marked HBV DNA elevation, and the immune clearance phase characterized by active HBeAg positive hepatitis B defined by HBV DNA > 20,000 IU/mL and ALT elevated at ≥2 times the upper limit of normal (ULN). Once HBeAg is cleared, the immune control phase is characterized by inactive CHB with suppressed HBV DNA and normal ALT, although CHB reactivation can occur, and is defined by elevated HBV DNA and ALT despite HBeAg negative status. The presence of precore and basal core promoter mutations often characterizes this phase and can lead to marked elevations of HBV DNA with abnormal ALT values. In a small number of patients clearance of HBsAg occurs, although this is not common.  

Treatment of CHB during HBeAg positive and

Figure 1. Natural history of CHB Infection

The dynamic nature of chronic hepatitis B infection is reflected in this figure. Patients in the HBeAg positive and HBeAg negative immune active phases (indicated by red boxes), characterized by elevated HBV DNA and ALT levels, are recommended for treatment, as these patients are at the highest risk of liver-related complications if left untreated. Patients in the immune tolerant phase and inactive CHB phases are not recommended to be treated.  

Adapted from Lok ASK, Ann Intern Med 2007

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HBeAg negative immune active phases, characterized by elevated HBV DNA and ALT levels, is recommended as these phases of infection place patients at the highest risk of liver-related complications (see Figure 2). The viral load threshold advised by AASLD guidelines is HBV DNA levels of ≥ 2000 IU/mL if HBeAg negative and HBV DNA ≥ 20,000 IU/mL if HBeAg is positive, along with elevated ALT ≥2 times ULN. For patients with HBV DNA near but not quite at the treatment thresholds or ALT levels at 1-2 ULN, a liver biopsy may be useful in determining whether there is sufficient necroinflammation and/or fibrosis to warrant initiation of therapy.

Treatment Options for Immune Active Hepatitis B

Providers can choose between peg-interferon alfa-2a, entecavir (ETV), tenofovir dipovoxil fumarate (TDF), and the recently approved tenofovir alafenamide (TAF) (Table 1). Antiviral agents such as lamivudine and adefovir, which have been previously recommended, are no longer indicated given significantly higher risks of resistance. Although peg-interferon has no risk of resistance and achieves the highest rates of HBsAg loss with finite duration of treatment of 12 months, its use is limited by the higher frequency of side effects and more limited applicability (its use is contraindicated in those with cirrhosis, significant psychiatric disease or cardiopulmonary disease, for example). The oral antiviral agents, ETV, TDF and TAF all have high potency and very low rates of resistance in treatment naïve patients. For nucleoside analogue experienced patients, TAF and TDF are preferred drugs (Table 1).

As mentioned, the oral antiviral drugs are generally very well tolerated. However, prolonged use of TDF has been associated with kidney and bone toxicity (specifically Fanconi’s syndrome), and therefore monitoring of renal function (and phosphate level and urine studies) as well as bone scans need to be performed annually. The recently approved drug, TAF, which has been found to be non-inferior to TDF in efficacy, minimizes these toxicities, and therefore offers a better safety profile long-term. Entecavir is not associated with significant side affects other than rare reports of lactic acidosis in patients with decompensated cirrhosis. Thus, TAF and ETV are offer similarly high efficacy and excellent safety without the need for monitoring for toxicities.

<table>
<thead>
<tr>
<th>Elevated ALT &gt;2X ULN</th>
<th>ALT &lt;2X ULN</th>
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</thead>
<tbody>
<tr>
<td><strong>HBeAg Positive</strong></td>
<td><strong>HBeAg Positive</strong></td>
</tr>
<tr>
<td>HBV DNA &gt;20,000 IU/mL</td>
<td>HBV DNA &gt;20,000 IU/mL</td>
</tr>
<tr>
<td><strong>HBeAg Negative</strong></td>
<td><strong>HBeAg Negative</strong></td>
</tr>
<tr>
<td>HBV DNA &gt;2,000 IU/mL</td>
<td>HBV DNA &gt;2,000 IU/mL</td>
</tr>
</tbody>
</table>

**Figure 2. Algorithm for Making Treatment Decision**

This treatment algorithm for patients with chronic hepatitis B reflects different management based on ALT > 2x ULN versus ALT < 2x ULN in patients with HBeAg positive and HBeAg negative disease, utilizing guideline-driven cutoffs for HBV DNA that inform initiation of treatment. Patients who have ALT > 2x ULN and are HBeAg positive should be started on treatment if HBV DNA > 20,000 IU/mL, and patients who are HBeAg negative should be started on treatment if HBV DNA > 2,000 IU/mL. Patients who do not meet these criteria may benefit from fibroscan or liver biopsy for further assessment of disease stage.
Antiviral Treatment Discontinuation
Considerations for discontinuation of nucleos(t)ide analogue therapy differ for patients with immune active HBeAg positive versus HBeAg negative CHB. For patients with HBeAg positive immune active disease treated with ETV or TDF, about 20% of patients will undergo HBeAg seroconversion to HBeAb after 1 year of therapy and this percentage increases to ~35% after 5 years of treatment. Given that HBeAg seroconversion is a key event in CHB natural history which signals an improved level of immune control and decreased risk of cirrhosis, HCC and liver-related death, the AASLD guideline recommends that persons with HBeAg-positive disease who achieve seroconversion to anti-HBe, may discontinue treatment after a period of treatment consolidation for at least 12 months. This recommendation does not apply to patients with cirrhosis, given ongoing high risk of clinical decompensation with discontinuation of antiviral therapy.

Although antiviral therapy may be discontinued, the durability of response is often not sustained, and treatment may have to be re-initiated. In patients who stop treatment with HBeAg seroconversion, studies have demonstrated virological relapse defined by HBV DNA>2000 IU/mL in up to 80% of patients. Furthermore, seroreversion back to HBeAg positive status occurs in up to 44% of patients. Thus, it is important to identify which patients are more likely to sustain virologic control. The factors most consistently associated with a durable response off treatment are younger age (<40 years) and longer duration of treatment consolidation after seroconversion (>12-15 months). Thus, adults under the age of 40 years with 18 months of consolidation therapy may be the best candidates for treatment discontinuation. Due to the risk of relapse and HBV flare, recommendations are to continue close monitoring of HBV DNA and ALT for at least a year after treatment withdrawal.

The AASLD guideline recommends that HBeAg negative immune active patients receive indefinite antiviral therapy, but adds that treatment discontinuation can be considered after HBsAg loss has occurred. The rationale for indefinite therapy stems from studies of treatment withdrawal that show that HBV DNA becomes elevated again in more than 90% of patients. Clinical relapse occurs in up to 53% of patients, with the rate dependent upon how relapse is defined. Hepatitis flares and even hepatic decompensation occurred, with those with cirrhosis at highest risk.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Antiviral Potency</th>
<th>Side Effects</th>
<th>Risk of Resistance</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alfa-2a</td>
<td>++</td>
<td>Fatigue, cytopenias, depression, exacerbate autoimmune disease</td>
<td>None</td>
<td>Not recommended in cirrhosis, significant cardiopulmonary disease, uncontrolled seizures, psychiatric disease, or pregnancy</td>
</tr>
<tr>
<td>Entecavir (ETV)</td>
<td>+++</td>
<td>Lactic acidosis (Decompensated cirrhotics)</td>
<td>Very Low</td>
<td>Not recommended If prior nucleoside analogue treatment</td>
</tr>
<tr>
<td>Tenofovir dipovoxil fumarate (TDF)</td>
<td>+++</td>
<td>Renal and bone toxicity</td>
<td>Very Low</td>
<td>Dose adjustment if CrCl &lt;50 ml/min</td>
</tr>
<tr>
<td>Tenofovir Alafenamide (TAF)</td>
<td>+++</td>
<td>Minimal renal and bone toxicity</td>
<td>Very Low</td>
<td>Dose adjustment if CrCl &lt;15 ml/min</td>
</tr>
</tbody>
</table>
Predictors of relapse have been investigated, and similarly to HBeAg positive patients, a prolonged period of HBV DNA undetectability and low HBsAg titer are most consistently associated with less hepatitis flares and clinical relapses. A recent study showed that sustained suppression of HBV DNA for over 3 years compared to 1 year was associated with lower rates of disease relapse.\textsuperscript{13} Even after treatment consolidation, once treatment is discontinued, patients should be monitored closely for recurrent viremia, flares, and clinical decompensation. HBeAg-negative patients with cirrhosis are not recommended for withdrawal of antiviral therapy due to concerns of HBV flare leading to liver decompensation.

Thus in order to determine whether to discontinue antiviral therapy, the patient and provider preferences need to be weighed against clinical considerations such as the risk of resistance and liver outcomes. In a survey of patient preferences, more than 80\% of patients preferred a finite duration of therapy, when asked if they were willing to have lifelong treatment, more than 40\% of patients agreed.\textsuperscript{13} Thus, patient preferences in discussion with their provider may help to inform the duration of treatment.

CONCLUSIONS

With currently available treatment options, CHB is controlled and not cured. Thus, a long-term treatment plan is needed in those with active disease. Tenofovir (TDF and TAF), ETV, and peg-IFN are the preferred treatment agents, as they have been shown to decrease progression of disease and disease-related complications. The endpoints of treatment are evolving, and although HBsAg loss is desirable, it is infrequently obtained with current therapies. Thus, discontinuation of therapy requires careful weighing of the risks and benefits of health outcomes, as well as patient/provider preference, with close monitoring after treatment discontinuation. Ongoing and future studies will help to define those patients with immune active disease who are best suited for discontinuation of antiviral treatment prior to achievement of HBsAg loss. Encouragingly, many new drug classes are being evaluated for CHB, and the hope is that future drug combinations will more frequently achieve HBsAg seroconversion (functional cure) with a finite treatment course.

References

14. Degertekin B, Lok AS. When to start and stop hepatitis B treatment: can one set of criteria apply to all patients regardless of age at infection? Ann Intern Med. 2007;147(1):62-4