Update on Chronic Hepatitis B (CHB) Treatment

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Abstract

The availability of newer antiviral agents, as well as comprehensive treatment recommendations, has equipped clinicians with sufficient options to formulate hepatitis B virus (HBV) treatment regimens and individualize therapeutic strategies. This article reviews the most recent guideline recommendations on goals, treatment indications, and endpoints, and resistance to anti-HBV treatment. In advocating an individualized approach to HBV treatment, currently available agents are further introduced separately.

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Introduction

Accumulating evidence indicates that anti-HBV treatment can reduce and/or prevent progression of HBV-related liver disease, especially in patients with sustained response. Newer antiviral agents with improved efficacy and safety have changed the paradigm of HBV treatment by reducing progression to cirrhosis and development of hepatocellular carcinoma (HCC).[1] These therapeutic advances are particularly pertinent to Asian-Pacific Islander patients, who comprise the majority of chronic HBV infections in the U.S. While these patients stand to benefit tremendously from emerging treatments, clinicians should be aware of therapeutic considerations specific to Asian patients in order to optimize therapeutic outcomes.

Current treatment Recommendations

Goals of HBV therapy. With sustained viral suppression considered critical to the reduction and/or prevention of complications from chronic hepatitis B (CHB), the primary goal of therapy is to reduce and maintain serum HBV DNA at the lowest possible levels (i.e., durable HBV DNA suppression).[2-5] Attaining this goal will, in turn, lead to other therapeutic milestones, including histological improvement and ALT normalization.[5]

Treatment indications. Two systemic recommendations for the management of HBV infection, and a NIH consensus statement are available in the U.S.[2,5,6] As summarized in Tables 1, the American Association for the Study of Liver Disease (AASLD) guidelines were updated in 2007 and the Keeffe et al algorithm was updated in 2008.[2,5] HBV viral load and ALT levels are the two major factors used in determining the need to treat. Treatment indications also vary, depending on HBeAg status. In treating Asian patients, clinicians must be aware that their ALT levels tend to be normal, serum HBV DNA may be high and HBeAg conversion is lengthier.

According to the AASLD guidelines and Keeffe's algorithm, a viral load of 20,000 IU/mL (i.e., 100,000 copies/ml) or higher is used as a viral load threshold for treatment initiation in HBeAg (+) individuals.[2,5] ALT levels help guide the decision further. Although both the AASLD guidelines and Keeffe's algorithm recommend treating HBeAg (+) patients with elevated ALT levels, they differ somewhat on the degree of ALT elevation that warrants treatment (Table 1). Both guidelines generally allow for a treatment delay of 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs. Patients with normal ALT levels (especially those older than 40 years of age) may undergo a liver biopsy and only be treated if active disease is histologically confirmed.[2,5]

For HBeAg (-) patients, the AASLD guidelines differ from Keeffe's algorithm on treatment indications. Because HBeAg (-) patients tend to have lower levels of serum HBV DNA than HBeAg (+) patients (yet still have disease), Keeffe et al. recommend treating those with serum HBV DNA levels of 2,000 IU/mL (i.e., 10,000 copies/ml) or higher and any degree of ALT elevation.[5] The AASLD guidelines, however, denote a higher viral load threshold (20,000 IU m/L, or 100,000 copies/ml), with ALT levels of greater than two times the upper limit of normal (ULN; **Table 1**).

Patterns of treatment response: Because HBV treatment may result in different outcomes, it is important to understand the patterns of therapeutic responses. A virologic response (VR) is defined as a decrease in serum DNA to

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undetectable levels by polymerase chain reaction (PCR) assays and loss of HBeAg in patients who were initially HBeAg (+). A biochemical response (BR) is characterized by normalization of once elevated ALT levels. An optimal treatment outcome involves a sustained off-therapy response, which can be determined 6 and 12 months after discontinuation of therapy.[2] Definitions of other HBV treatment responses are well described in the literature.[2,5]

Treatment strategy: In choosing which agent to use as first-line therapy, consideration should be given to the safety and efficacy of the treatment, risks of drug resistance, and costs. A comparison of FDA-approved agents for HBV treatment is summarized in Table 2. When treatment is indicated for patients with HBeAg (+) CHB, entacavir and tenofovir are preferred for those with high HBV DNA levels and/or mildly elevated ALT levels because response to interferon (IFN) therapy is low and lamivudine is associated with a high rate of resistance.[5] Asian patients tend to exhibit lower responses to IFN and lamivudine, since many of these individuals have normal ALT levels at presentation. Moreover, IFN rarely results in permanent clearance of HBV in Asian patients, as evidenced by a study showing that 91% of Chinese patients had detectable HBV DNA following IFN treatment, even after HBeAg seroconversion.[7]

In patients with HBeAg (-) CHB, Peg-IFN-alfa, entecavir, or tenofovir are preferred in view of the need for long term treatment.[2] Patients who fail IFN-alfa therapy may be retreated with NAs. Recent studies indicated 55% of HBeAg (-) patients remained negative HBV DNA 5 years after discontinuing adefovir treatment.[7] Baseline levels and kinetics of HBsAg may also be valuable in predicting response to HBV treatment CHB.[8,9] These results indicate the possibility to discontinue HBV treatment in some HBeAg (-) patients. Research evaluating more effective, combined regimens is ongoing but will not be discussed in this article in the interest of focusing more on the general principles of HBV therapy.

Antiviral Resistance. A major concern with long-term NA treatment is the selection of antiviral-resistant HBV mutations, which may be associated with loss of initial virologic response (i.e. HBV DNA rebound) followed by increasing ALT levels. In some cases, antiviral resistance can be associated with severe exacerbations of liver disease. The terms and definitions related to antiviral resistance are well summarized in the literature.[2,5,11,17] Generally, genotypic resistance is defined as in vitro detection of a mutation that confers NA resistance, while phenotypic resistance is *in vitro* confirmation that the detected mutation decreases susceptibility to a particular NA. Judicious use of NAs (e.g., regular monitoring and choosing potent agents with low rates of genotypic resistance) is the most effective prophylaxis against development of antiviral resistant HBV.[2] Several regimens of "switching" or "adding on" therapy have been reported and ongoing studies are evaluating more effective strategies.[2,5,11] Since management of individuals who develop antiviral resistance could be complicated, it is this author's opinion that these patients should be referred to experienced gastroenterologists/hepatologists.

Individual Agents for HBV Treatment

This section provides a more detailed discussion of the individual agents that have been approved by the US FDA for HBV treatment (Table 2).

Conventional IFN-alfa: IFN-alfa-2b has been used for over two decades in both HBeAg (+) and HBeAg (-) CHB, but its efficacy is limited and its clinical application use has been replaced by peginterferon.

Peg-IFN alfa-2a: Because of its convenience (weekly vs. daily or thrice weekly dosing) and higher response rate, Peg-IFN alfa-2a has replaced use of conventional IFN.[2,12-15] In one Asian study, a 24-week course of weekly peg-IFN yielded a higher HBeAg seroconversion rate than did conventional IFN, even in patients with a low likelihood of response to IFN.[12] A higher response rate to peg-IFN has been reported in patients with HBV genotype A infection.[16] Although peg-IFN treatment requires subcutaneous injection and is associated with a variety of adverse effects, it is not associated with antiviral resistance and is given for a fixed treatment course, which may be beneficial for those who will not, or cannot, undergo a prolonged course of HBV treatment with NAs.

Lamivudine: The first NA to become available for CHB, long term therapy with lamivudine has been associated with HBV DNA suppression, ALT normalization, and improvement in liver histology in both HBeAg (+) and HBeAg (-) patients.[4,13] HBeAg seroconversion after one year of lamivudine therapy is reported to be approximately 17%.[2,4] Unfortunately, lamivudine is associated with a high rate of antiviral resistance, affecting 70% to 80% of patients after 4 to 5 years of treatment.[16] Studies suggest that patients with HBV genotypes A experience a higher rate of resistance to lamivudine than those with genotypes D. No difference in the risk of lamivudine resistance is found between patients with HBV genotypes B and C. Since newer therapies with lower risks of resistance are currently available, lamivudine is no longer a first line drug for HBV treatment.[2,5] A switch to alternative treatment should be considered in patients who have received lamivudine for more than 2 years.[2]

Adefovir dipivoxil: Adefovir is associated with a modest decrease in HBV DNA levels and an improvement in ALT levels in approximately one-third of HbeAg (+) CHB patients. Higher pretreatment HBV DNA levels, adefovir resistance, and the agent's modest antiviral activity may be predispositions to non-response.[13] Although the rate of antiviral resistance is lower in adefovir than in lamivudine, it could be as high as 29% after 5 years of treatment. With more available potent HBV drugs, adefovir is no longer a preferred drug for HBV treatment.

Entecavir: This agent has been shown to be more potent than lamivudine and adefovir and to have high rates of HBV DNA

suppression.[2,13] Rates of HBeAg clearance at one year were similar to lamivudine, but higher than reported for adefovir. Studies have reported that long-term treatment with entecavir is associated with continued suppression of HBV replication and histological improvement. Antiviral resistance to entecavir is reportedly low, approximately 1.2% after 6 year of therapy.[18]

Telbivudine: A potent NA, telbivudine has been shown to be more effective in suppressing HBV replication than lamivudine. In one large trial, telbivudine produced a 60% rate of HBV DNA loss, compared with a 40% rate associated with lamivudine.[12] Telbivudine may have lower rates of resistance compared with lamivudine. At 1 and 2 years, the resistance rates to telbivudine were 5% and 25%, respectively in HBeAg (+) patients, higher than other therapies. telbivudine exhibits cross-resistance with lamivudine.[5,19] Because undetectable HBV DNA at 24 weeks of treatment is associated with a significantly lower rate of telbivudine-resistance, it is important to monitor treatment response in patients given telbivudine, or any other NAs for that matter.

Tenofovir disoproxil fumarate and emtricitabine: A nucleotide analog, tenofovir is more potent than adefovir and is effective against lamivudine-resistant HBV strains.[2,20,21] The two-year data of tenofovir indicated it remains a high percentage of HBV suppression, and showed no evidence of development of tenofovir related HBV resistance. In addition, those who switched from adefovir to tenofovir also achieved a high rate of HBV suppression.[21] Emtricitabine is structurally similar to lamivudine and is, therefore, similar to lamivudine in efficacy and pattern of resistance. A combination product containing tenofovir and emtricitabine is approved for HIV infection and is being tested for HBV treatment.

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Table 1. HBV Treatment Criteria: HBeAg (+) or (-) Patients without Cirrhosis[2,5]

HBeAg (+) CHB	**AASLD (2007)**	**Keeffe EB, et al, 2008**
Viral load	>20,000 IU/mL (or >10^5 copies/mL)	≥20,000 IU/mL (or ≥10^5 copies/mL)
ALT	>2 x ULN	Elevated
HBeAg (-) CHB		
Viral load	>20,000 IU/mL (or >10^5 copies/mL)	≥2,000IU/mL (or ≥10^4 copies/mL)
ALT	>2 x ULN	Elevated

IU=International units; ULN=Upper limit of normal

Table 2. A List of US FDA approved drugs for HBV treatment

Generic Name	Trade Name	Approved	Structure	Features
Interferon alfa-2b	**INTRON A (IFN)**	**1992**	**Cytokine**	**• Daily/TIW injections • Significant SEs**
Lamivudine	**EPIVIR-HBV (LAM)**	**1998**	**Nucleoside**	**• Potent • High resistance**
Adefovir	**HEPSERA (ADV)**	**2002**	**Nucleotide**	**• Less potent • Moderate resistance**
Entecavir	**BARACLUDE (ETV)**	**2005**	**Nucleoside**	**• Potent • Low resistance**
Peginterferon alfa-2a	**PEGASYS (PEG-IFN)**	**2005**	**Cytokine**	**• Weekly injections • Significant SEs**
Telbivudine	**Tyzeka (LdT)**	**2006**	**Nucleoside**	**• Potent • Moderate resistance**
Tenofovir	**Viread (TDF)**	**2008**	**Nucleotide**	**• Potent • Low resistance**

TIW: three times a week; SEs: side effects