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Hepatitis B treatment: Current best practices, avoiding resistance

■ ABSTRACT

All patients who are positive for hepatitis B virus (HBV) DNA should be considered for antiviral treatment. Potency in suppressing HBV DNA is the main factor in the choice of first-line therapy; entecavir and tenofovir constitute the most potent nucleoside and nucleotide analogues to date with the lowest rates of resistance. Viral negativity may reduce the development of liver failure and the need for transplant, although these benefits need to be demonstrated prospectively. Loss of hepatitis B surface antigen, or seroconversion, may represent a new treatment paradigm. The development of resistance to therapy can result in virologic breakthrough and serious clinical consequences. Use of the most potent agents as first-line therapy lowers the risk of resistance; but if resistance develops, adding an additional agent, rather than switching to another therapy, is advised.

■ KEY POINTS

Consider treatment for chronic HBV infection for all patients who are positive for HBV DNA, as viral load levels as low as 300 copies/mL confer a risk for hepatocellular carcinoma.

The goal of therapy is an undetectable level of HBV DNA; initiate therapy with the most potent agent to limit the possibility of resistance.

Preventing resistance to therapy is crucial for successful treatment of chronic HBV infection.

Guidelines for the management of hepatitis B virus (HBV) infection can be daunting to clinicians. Further, although established practice guidelines can provide direction, treatment of chronic HBV infection is characterized by uncertainties that can hinder optimal patient care. Reservations about when to initiate and terminate therapy, cost issues, and the development of resistance to therapy are among the factors that impede adequate treatment. This article

offers a straightforward roadmap for the management of chronic HBV infection, based on interpretation of recently released guidelines,¹⁻³ and strategies for preventing and managing resistance to antiviral therapy.

■ DECIDING TO TREAT

Key factors: Viral load and ALT

Two important factors influencing the decision to treat are viral load (HBV DNA) and alanine aminotransferase (ALT) level; although these are relatively straightforward measures, other factors can cause clinicians to avoid or delay treatment.

A simple guideline is to discuss treatment with any patient who is positive for HBV DNA. The most recent guidelines for the treatment of HBV infection, published by the European Association for the Study of the Liver (EASL), recommend an HBV DNA level of 2,000 copies/mL as a threshold for initiating therapy; this recommendation applies to patients who are either positive or negative for hepatitis B e antigen (HBeAg).³

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study investigators used ultrasensitive polymerase chain reaction (PCR) to quantify HBV DNA levels and conducted a time-dependent multiple Cox regression analysis of HBV DNA level and the risk of hepatocellular carcinoma (HCC).^{4,5} The length of time at a given DNA level was weighted in determining the adjusted hazard ratio. With an HBV DNA level less than 300 copies/mL defined as the reference group, risk of HCC increased commensurate with increasing HBV DNA level; even at levels ranging from 300 to 10,000 copies/mL, longer duration of HBV DNA positivity increased risk. This group also found HBV DNA level to be an independent risk factor for cirrhosis.

Patients who are HBV DNA negative are at much lower risk of cirrhosis and HCC than HBV DNA-positive patients; HBV DNA-negative patients being treated with antiviral drugs are much less likely to develop resistance to treatment, provided that first-line medications such as tenofovir or entecavir are used.

The definition of a “healthy” ALT level is controversial. In my opinion, an abnormal ALT is greater than 19 IU/mL

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for women and greater than 25 IU/mL for men; in either setting, treatment should be instituted if the patient is HBV DNA positive. This position is supported by a recently published algorithm,⁶ a recent National Institutes of Health conference on management of HBV,⁷ and other sources.⁸⁻¹²

Barriers to optimal treatment

Patient reluctance to undergo invasive tests, concerns about resistance, confusion about when to initiate therapy, cost, and other issues can impede timely and effective treatment of HBV infection.

Invasive studies. Liver histology is a key driver for initiating treatment, but many patients resist undergoing a liver biopsy. Ultrasonography has enabled noninvasive determination of spleen size, portal vein size, and liver tissue and surface heterogeneity; noninvasive assessments such as measurement of aspartate aminotransferase, varices, serum markers of fibrosis, and platelet count may provide clues to advanced liver fibrosis. Eventually, ultrasonographic elastography to measure liver stiffness and magnetic resonance scans may be common in clinical practice for noninvasive evaluation of liver damage. Ultimately, however, liver biopsy remains a valuable tool to motivate patients with chronic HBV infection to initiate and continue antiviral therapy.

Rationales for avoiding or delaying treatment. Concern about the development of resistance to treatment, as with antiviral therapy directed against human immunodeficiency virus (HIV), is one reason not to treat. The absence of clear guidelines regarding the appropriate time to terminate therapy has also led to avoidance or delay of treatment. The lack of risk calculators similar to the Framingham risk score, which estimates the risk of coronary heart disease, has limited the treatment of chronic HBV infection.

Cost. Cost must be examined in relation to the cost of resistance developing and the cost of treating complications. Lamivudine, considered a third-line treatment for chronic HBV infection, is an inexpensive drug. However, up to 70% of patients will develop resistance to lamivudine over 5 years^{3,6}; most will require combination therapy, with its attendant costs, and may eventually require transplants or experience poor clinical outcomes. Although the initial costs of potent first-line therapies (tenofovir, entecavir, and pegylated interferon) are high, cost modeling shows that they are less expensive over the long term when the overall cost of care is considered.^{13,14}

GOALS OF THERAPY: VIRAL LOAD SUPPRESSION, SEROCONVERSION

Profound suppression of viral load reduces the risk of resistance and is the ultimate goal of therapy for HBV infection. We can infer from recent data¹⁵ that achieving HBV DNA negativity has led to improved outcomes in patients with chronic HBV infection; ie, with the increased use

Case: Viral breakthrough after switching therapy

A 31-year-old man born in San Diego of Asian parents presented in September 2000 with pain in the right upper quadrant, diarrhea, yellow eyes, and dark urine. He was refused a life insurance policy 2 years previously because of a liver problem, but did not know the details. His mother and brothers are positive for hepatitis B virus (HBV). At first presentation, his alanine aminotransferase (ALT) level was 3,285 U/L, his bilirubin was 21 mg/dL, and his HBV DNA was not especially high: 10^3 copies/mL. He was hepatitis B surface antigen positive. He was diagnosed with probable acute exacerbation of chronic HBV infection.

The patient was followed without treatment, and his bilirubin and transaminase levels soon returned to normal. By February 2001, his transaminase levels were again elevated (ALT, 395 U/L) and his viral load was 10^6 copies/mL. Treatment with lamivudine was initiated in 2002, and his ALT promptly normalized and has remained normal to the present time. His viral load became undetectable and remained undetectable until 2004, when it increased to 10^7 copies/mL; at that point the decision was made to switch therapy from lamivudine to adefovir, after which his HBV DNA again became undetectable and he seroconverted from HBe antigen (HBeAg) positive to HBeAg negative. His HBV DNA was monitored regularly and remained undetectable until October 2008, when it was 10^2 copies/mL, representing a second virologic breakthrough.

Should we add therapy, switch to yet another agent, or continue the course?

of antiviral drugs in the United States over the past 2 decades, the number of liver transplants for end-stage liver disease has fallen dramatically,¹⁵ suggesting that profound suppression of viral loads has translated into fewer cases of liver failure and less need for transplants.

Over the same period, the number of patients diagnosed annually with HCC has increased by 146%.¹⁵ One interpretation of these data is that patients with chronic HBV infection are living longer, allowing time for HCC to develop. In addition, aggressive surveillance guidelines may account for the increased number of HCC cases since 1990. If detected early, HCC is curable by liver transplant at a rate exceeding 80%.¹⁶⁻¹⁸

In discussing treatment duration with patients, I present the ultimate goal of therapy as loss of HB surface antigen (HBsAg), or seroconversion to anti-HBs. At our clinic, we monitor HBsAg at least annually when patients are on long-term therapy.

The cost-effectiveness of treating all patients until they are HBsAg negative needs to be assessed. Incremental cost-effectiveness ratios per quality-adjusted life-year are key to identifying the best course of action.

TABLE 1
Rates of viral resistance to drugs for treating HBV

Drug	Resistance at year of therapy (% patients)				
	1	2	3	4	5
Lamivudine ¹⁹⁻²²	23	46	55	71	80
Entecavir (naïve) ^{23,24}	0.1	0.4	1.1	1.1	1.2
Entecavir (lamivudine-resistant) ^{23,24}	6	15	35	43	—
Telbivudine ^{1,24-26}					
HBeAg-negative	2.7	8.6	—	—	—
HBeAg-positive	4.4	21.61	—	—	—
Adefovir (naïve)					
HBeAg-negative ^{27,28}	0	3	11	18	29
HBeAg-positive ²⁹	—	—	—	—	42
Adefovir (lamivudine-resistant) ³⁰	0-18	—	—	—	—
Tenofovir ³¹	0	0	—	—	—

TREATMENT OPTIONS

The nucleoside analogues lamivudine, entecavir, and telbivudine, and the nucleotide analogues adefovir and tenofovir, are indicated for the treatment of HBV infection. These agents differ in their capacity to suppress HBV DNA, are associated with differing rates of resistance (Table 1),^{1,19-31} and therefore have different roles in the management of chronic HBV infection (see “Case: Viral breakthrough after switching therapy,” page S15). Pegylated interferon has also demonstrated utility in certain patients with chronic HBV infection.

Nucleoside analogues

Lamivudine. The incidence of lamivudine resistance increases with increased treatment duration, reaching a peak of 80% after 5 years of treatment¹⁹⁻²²; use of this agent eventually requires combination therapy. For this reason, lamivudine is considered a third-line drug and is not recommended as a first-line therapy.

Entecavir. Entecavir induces profound suppression of HBV DNA (to undetectable levels by weeks 24 to 36) in patients who are HBeAg positive or negative, regardless of baseline HBV DNA levels; resistance rates are very low in treatment-naïve patients,²³ and entecavir is therefore considered first-line therapy. More than 90% of HBeAg-positive or -negative patients who are adherent to entecavir are HBV DNA negative at 5 years.²⁴ Loss of HBsAg is 5% in entecavir-treated patients at follow-up of approximately 80 weeks, which is roughly double the rate of HBsAg loss with lamivudine.³²

Telbivudine. Telbivudine has a secondary role in treatment of HBV infection. In a study by Lai et al,^{25,26} the cumulative incidence of telbivudine resistance and virologic breakthrough in HBeAg-positive patients rose from nearly 5% after 1 year to 22% after 2 years of treatment. Although the incidence was lower in HBeAg-negative patients, rates of genotypic resistance with virologic breakthrough rose to 9% in this population.

Since these results report genotypic resistance and virologic breakthrough, the rates of genotypic resistance in these patients may actually be higher than reported. Indeed, genotypic resistance was detected in 6.8% of the entire study population after 1 year of treatment. In this study, it must be remembered that patients with HBV DNA levels that were detectable by PCR (≥ 300 copies/mL) but were less than 1,000 copies/mL were not assessed for resistance.

Because of high rates of resistance associated with telbivudine, its role in the treatment of chronic HBV is secondary. I may use it in pregnant patients because most other nucleoside analogues are category C drugs and telbivudine is a category B agent (see “Management of hepatitis B in pregnancy: Weighing the options,” page S25). There are risks of myositis and neuropathy with telbivudine; although these risks are low, I mention them to patients when discussing a treatment plan.

Nucleotide analogues

Adefovir. Adefovir is considered second-line or add-on therapy when resistance to lamivudine develops because of its low potency in suppressing viral load. At 48 weeks, only 12% of HBeAg-positive patients are HBV DNA negative when treated with adefovir monotherapy.^{33,34}

In a phase 3 clinical trial, genotypic resistance to adefovir was detected in 29% of HBeAg-negative patients treated for up to 5 years.²⁷ The probability of resistance with virologic breakthrough was 3%, 8%, 14%, and 20% after 2, 3, 4, and 5 years of treatment, respectively.

In patients infected with lamivudine-resistant HBV, the probability of adefovir resistance is reduced by adding adefovir to ongoing lamivudine therapy, according to data from a large retrospective comparative study.³⁵ In patients treated with adefovir monotherapy, the probability of virologic breakthrough (defined as $> 1 \log_{10}$ rebound in HBV DNA compared with on-treatment nadir) reached 30% over 36 months. In patients treated with add-on adefovir, the probability of virologic breakthrough was reduced to 6%. Similarly, the probability of adefovir resistance over 36 months of treatment was greater in the adefovir monotherapy group (16%) than in the add-on adefovir group (0%).

Although adefovir resistance is observed infrequently when adefovir is added to lamivudine, the effectiveness of adding adefovir is still limited by its low potency.

Tenofovir. More than 90% of HBeAg-negative

Algorithm to prevent and manage resistance

Preferred treatment options

Tenofovir Entecavir

Response and resistance monitoring

Measure HBV DNA with sensitive assays;
monitor virologic changes every 3 to 6 months;
monitor for breakthrough and adherence

Outcome

No resistance identified with viral negativity Resistance identified Inadequate virologic response

Therapeutic plan

Continue with planned medication Switch to second medication Add second medication

Combination therapy

FIGURE 1. The algorithm used at California Pacific Medical Center for preventing and managing resistance incorporates the use of sensitive assays to measure viral load (HBV DNA), frequent monitoring to detect possible virologic breakthroughs, and a therapeutic plan that includes options to switch or add on to current therapy. Combination therapy is appropriate only for patients in whom therapy has failed to suppress viral load, who are drug resistant, who are posttransplant, and who are coinfecting with human immunodeficiency virus.

patients and nearly 80% of HBeAg-positive patients treated with tenofovir have persistent virologic responses and HBV DNA levels less than 400 copies/mL by 72 weeks, with minimal side effects.^{33,34} Marcellin et al reported no development of resistance to tenofovir after 48 weeks of treatment.³¹ Although the nucleotide analogues have been associated with renal toxicity,³⁶ the risk of renal toxicity associated with tenofovir is 1% or less per year; it can be reduced even further by calculating renal function through the use of the Cockcroft-Gault equation or the Modification of Diet in Renal Disease equation prior to therapy and adjusting the dosage accordingly.³⁷

With profound HBV DNA suppression, HBsAg loss occurs in about 5% of tenofovir-treated patients at 64 weeks.³³

Treatment with tenofovir in treatment-experienced patients leads to potent suppression of HBV DNA independent of HBV genotype, HBV mutations (YMDD mutations) that signal lamivudine resistance, or HBeAg status at baseline.³⁸ Patients with genotypic resistance to adefovir at baseline had a lower probability of achieving HBV DNA suppression during treatment with tenofovir.

Pegylated interferon

Pegylated interferon has proven useful in subsets of HBV DNA-positive patients. These include patients with genotype A or B who are young, those with high ALT levels (≥ 2 or 3 times the upper limit of normal) and low viral load ($< 10^7$ copies/mL), and patients without significant comorbidities.⁶ Pegylated interferon is also an option for

patients who require a defined treatment period (eg, a woman wishing to become pregnant in 1 to 2 years). The patients who would benefit from pegylated interferon as first-line therapy must be better defined, and early markers of virologic response need to be identified.

PREVENTING AND MANAGING RESISTANCE

Antiviral drug resistance has a negative impact on the treatment of patients with chronic HBV infection. The development of resistance can result in virologic breakthrough (a confirmed $1 \log_{10}$ increase in plasma HBV DNA levels)¹; increased ALT levels^{1,39}; and the progression of liver disease,⁴⁰ including hepatic decompensation, development of HCC, and need for liver transplant. In addition, resistance mutations may re-emerge, with covalently closed circular DNA representing a genetic archive for development of resistance; this can significantly limit future treatment options.⁴¹ Early detection and regular monitoring are critical to prevention and management of resistance.

Detection

Detecting virologic breakthrough as early as possible increases the likelihood of achieving virologic response. In a study by Rapti and colleagues,⁴² patients with lamivudine-resistant chronic HBV were treated with a combination of lamivudine and adefovir. The 3-year cumulative probability of virologic response ($< 10^3$ copies/mL) was 99% with the addition of adefovir when baseline viral load levels were less than $5 \log_{10}$ copies/mL, but only 71% when baseline viral loads were greater than $6 \log_{10}$ copies/mL.

Case revisited

The patient is an example of an individual who first had resistance to lamivudine and then to adefovir. A lamivudine-resistant strain of HBV that includes the resistance mutation rtA181T has been described, and also confers resistance to adefovir. In this particular patient, I would switch to tenofovir and add entecavir to manage him over the long term, and defend my action to the insurance company if it denied payment for this treatment approach. Tenofovir alone, based on in vitro data and recent data presented by van Bömmel et al,³⁸ can be predicted to have a substantial chance of failure; this patient is therefore a candidate for combination therapy.

Monitoring

Patient response must be defined correctly. In adherent patients who show an early favorable response to therapy, I advise HBV DNA testing every 3 to 6 months. For those whose response flattens and whose viral load remains high, switching therapy or adding on should be considered. We continue therapy and monitor regularly after HBV DNA reaches an undetectable level. If the response is suboptimal, the treatment regimen is adapted by adding a new agent or switching to an alternative therapy (see “Case revisited”).

For patients who are being treated with tenofovir or entecavir, I typically extend the interval of measuring DNA levels to every 6 months because rates of resistance with these agents are low. If response is suboptimal but resistance is absent, I consider switching to the opposite drug. In those patients with a resistance mutation, I add the other agent.

Managing resistance

At California Pacific Medical Center, our strategy for limiting the possibility of resistance is to use entecavir or tenofovir as first-line therapy (Figure 1). Combination therapy with these two agents is preferred for any patient with resistance mutations. We do not use lamivudine or adefovir because of their low potency and the availability of tenofovir and entecavir.

Combination therapy has a role in individuals in whom medication has failed to suppress viral load, in the setting of drug resistance, after liver transplant, and in individuals coinfecting with HIV (see “Strategies for managing coinfection with hepatitis B virus and HIV,” page S30). If patients demonstrate resistance to their current therapy, we examine viral factors, adherence to therapy, and medication availability (eg, cost and insurance coverage). Switching to entecavir in adefovir-resistant patients produces profound suppression of HBV DNA. Patients in whom entecavir or lamivudine have failed may respond to tenofovir, depending on the resistance mutations.

A POTENTIAL FUTURE OPTION

Clevudine is a nucleoside analogue in phase 3 clinical studies in the United States. Its potential role in therapy is not yet clear. To be determined is whether it will induce a long-term, off-treatment viral response, in which case treatment may be able to be terminated earlier, and whether it will show clinically important cross-resistance with other nucleoside analogues. The availability of more sensitive assays to demonstrate the emergence of early viral resistance would enable earlier changes in treatment for more successful outcomes.

SUMMARY

Preventing resistance is crucial to the success of antiviral drug therapy for treatment of chronic HBV; a persistently high viral load increases the risk of cirrhosis and HCC, and resistance is associated with increased HBV DNA levels. The best chance for long-term success depends on initiating therapy before cirrhosis develops, when viral load is still low; profound suppression of viral load using the most potent agents as first-line therapy; and long-term monitoring of HBV DNA. The development of resistance can result in virologic breakthrough and liver complications. Entecavir and tenofovir represent the most effective first-line options to suppress HBV DNA. Because cross-resistance can occur, adding another agent is preferred to switching agents if resistance to initial therapy develops.

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