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Chronic Hepatitis B: Integrating Long-Term Treatment Data and Strategies to Improve Outcomes in Clinical Practice

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Abstract

A number of agents can reduce viral replication in patients with chronic hepatitis B, but most patients do not undergo a curative response to these drugs and therefore require long-term therapy. Thus, recent studies have investigated the long-term safety, efficacy, and resistance profiles of several antiviral nucleotide/nucleoside agents: lamivudine, telbivudine, adefovir dipivoxil, entecavir, and tenofovir. The most recent data have revealed that lamivudine and telbivudine produce high rates of resistance when treatment is continued for 2–5 years; as a result, these agents are no longer preferred for first-line monotherapy. Entecavir and tenofovir, on the other hand, appear to have favorable safety and efficacy profiles when used as monotherapy, with very low rates of resistance over 5 years. In order to help clinicians incorporate these data into clinical practice, this monograph will review recently published data on hepatitis B antiviral medications, as well as explore when to consider cessation of therapy. The treatment of special patient populations and the need to screen patients for hepatocellular carcinoma will also be discussed.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists, hepatologists, nurses, and other healthcare professionals involved in the treatment of patients with hepatitis B virus (HBV) infection.

Statement of Need/Program Overview: Increasing knowledge gained from recent studies of antiviral drugs has contributed greatly to progress in the management of chronic hepatitis B (CHB). However, most CHB patients do not undergo a curative response to available medications and require long-term therapy. Therapeutic management approaches should be individualized for patients to optimize outcomes, but staying up to date can be challenging for healthcare professionals who care for patients with HBV. This program is designed to meet those needs with the latest data, information, and practical recommendations from renowned experts.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Summarize the differences and relationships between surface antigen status, e antigen seroconversion, and DNA measurements in the monitoring of HBV activity.
2. Compare the long-term data for the available agents in the treatment of patients with CHB.
3. Identify the best strategies for the management and prevention of drug resistance in the treatment of CHB.
4. Describe effective, individualized, long-term treatment strategies for patients with CHB.

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Introduction

Defined as continuous serum positivity for hepatitis B surface antigen (HBsAg) lasting for more than 6 months, chronic hepatitis B (CHB) affects approximately 350 million people worldwide and 1.2–2 million people in the United States.[1-3] CHB is associated with significant morbidity, including liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[4] Mortality is also increased for patients with CHB, with 25–40% of patients dying from complications of liver disease.[5]

Although a number of therapeutic agents are approved for CHB and can effectively suppress the virus, most patients do not achieve a curative response to these agents and will require long-term therapy. Optimizing patient outcomes and avoiding liver-related complications therefore requires an understanding of the long-term safety, efficacy, and resistance profiles of hepatitis B virus (HBV) drugs, as well as application of this knowledge in clinical practice. There are currently 7 agents that are used for the treatment of CHB; they include 2 immunomodulatory drugs, interferon (IFN)-α and pegylated interferon (peginterferon), plus 5 antiviral nucleotide/nucleoside agents: lamivudine, telbivudine, adefovir dipivoxil, entecavir, and tenofovir difumarate.

IFN-α, the first agent approved for CHB in the United States, has antiviral, antiproliferative, and immunomodulatory effects. Although IFN-α has been shown to be effective for suppressing HBV replication and inducing remission of liver disease, its efficacy is limited to treatment-naïve, hepatitis B e antigen (HBeAg)-positive patients who have high pretreatment alanine aminotransferase (ALT) levels and lower levels of serum HBV DNA.[6,7] Peginterferon was subsequently developed to provide a more advantageous weekly dosing schedule than IFN-α. Clinical trial data suggest that the efficacy of peginterferon is slightly better than IFN-α; like IFN-α, however, peginterferon is only useful in small subsets of patients with HBeAg-positive and HBeAg-negative disease.[6,8]

Lamivudine monotherapy is effective for suppressing HBV replication and improving liver disease, with HBeAg seroconversion rates of up to 50% after 5 years of treatment in HBeAg-positive patients and response rates of up to 70% after 1 year of treatment in HBeAg-negative patients.[9,10] However, lamivudine monotherapy is associated with high rates of viral resistance and relapse; for this reason, lamivudine is not recommended as first-line monotherapy for CHB.[6,11] Similarly, telbivudine is not used as first-line monotherapy due to its high rates of resistance mutations, despite the fact that telbivudine is even more potent than lamivudine for suppressing HBV replication.[12,13] Similarly, although adefovir has a lower resistance rate than lamivudine and telbivudine, its lower potency and higher resistance rate compared to newer agents have reduced its use as a first-line agent.

Given these limitations, the first-line monotherapy choices recommended for CHB are entecavir and tenofovir.[6] Over the last few years, the hepatitis research community has pushed for long-term clinical studies to assess the efficacy, safety, and resistance profiles of these antiviral medications. Long-term data are particularly important for patients with HBeAg-negative disease, as these patients will likely be on therapy for many years. The most recent data, including presentations from the 2010 meeting of the American Association for the Study of Liver Diseases (AASLD), will be discussed in the first section of this monograph.

With the emphasis on long-term therapy, clinicians have recognized a need for better treatment guidance and endpoints that can help clinicians determine when to start and stop therapy in HBV patients. The ultimate goal of treatment is to prevent cirrhosis, hepatic failure, and HCC; however, clinicians cannot easily determine whether such goals have been achieved. Thus, the usual endpoint of treatment for patients with HBeAg-positive disease is seroconversion, with loss of HBeAg-negative disease and development of anti–hepatitis B e (HBe) antibodies. For HBeAg-negative disease, the endpoint of therapy is less clear. Limited data suggest that the presence or level of HBsAg may prove useful for guiding decisions about when to stop therapy, but this issue remains a subject of ongoing debate. Data on treatment endpoints and guidelines for therapy will be reviewed in the second section of this monograph.

Taken together, the wealth of clinical trial data that have become available in the past 2 years now enables clinicians to provide more individualized treatment plans for patients with CHB. The final section of the monograph will discuss how to leverage the current data to optimize treatment for patients with treatment-naïve and resistant disease, as well as those with special concerns, such as HIV co-infection.

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Long-Term Data on Current Treatments for Chronic Hepatitis B

Robert S. Brown, Jr., MD, MPH

Sustained virologic suppression is a primary goal of therapy for CHB. Currently available treatment agents include the immunomodulatory drugs IFN-α and peginterferon, as well as several antiviral nucleotide/nucleoside agents: lamivudine, telbivudine, adefovir, entecavir, and tenofovir. Over the last 2 years, the field of CHB treatment has seen an expansion of long-term data on several of these agents, both when used as monotherapy and when used in combination.

Long-Term Data from Monotherapy Trials

Lamivudine monotherapy produces virologic response rates of approximately 40–50% after 2 years of treatment.[1] Although this efficacy formerly supported the use of lamivudine monotherapy, this drug is no longer a preferred first-line agent, since antiviral resistance rates are above 70% after 5 years of treatment.[2,3] Telbivudine is associated with a higher virologic response rate than lamivudine, in the range of 60–70%, but telbivudine too is not a preferred monotherapy agent due to its relatively high rates of resistance.[2,3]

One alternative to lamivudine and telbivudine, adefovir, was evaluated in a recent study. In early 2010, Lee and colleagues published a study in which long-term adefovir salvage monotherapy was administered to 320 Korean patients with lamivudine-resistant CHB.[4] Of these patients, 81.3% were HBeAg-positive and all had genotype C HBV infection. Patients received 10 mg adefovir once daily. At Year 5, the overall cumulative virologic response rate was relatively modest (48.8%), although the virologic response rate was significantly higher in HBeAg-negative patients than HBeAg-positive patients (62.0% vs 45.9%; P=.010). Unfortunately, resistance and viral breakthrough were common in this cohort (65.6% and 61.8%, respectively).

Based on these studies and other data supporting their higher efficacy and lower resistance rates, the nucleoside entecavir and the nucleotide tenofovir are now the preferred first-line monotherapy agents for treatment of CHB.[2] An exciting development in the last year has been the release of data from several long-term studies of these 2 agents. For example, Chang and colleagues published encouraging data from an extension study showing that entecavir could achieve sustained viral suppression with minimal resistance during long-term treatment of HBeAg-positive patients.[5] In the original placebo-controlled study, ETV-022, entecavir (at a dose of 0.5 mg once daily) was found to be more effective than lamivudine for virologic suppression in HBeAg-positive CHB patients, as shown by a greater decrease in HBV DNA levels between baseline and Week 48 (6.9 $\log_{10}$ copies/mL vs 5.4 $\log_{10}$ copies/mL; P<.001).[6] Following this study, 183 entecavir-treated patients from ETV-022 entered ETV-901; the treatment gap between studies was no more than 35 days. Patients in ETV-901 received entecavir at a dose of 1.0 mg daily for 4 years. At Year 5 of treatment, 94% of patients (n=94) had HBV DNA levels below 300 copies/mL, and 80% (78/98) had normal ALT levels. HBeAg seroconversion was achieved in 23% of patients (33/141) who had not seroconverted at the end of ETV-022, and 1.4% of patients (2/145) lost HBsAg during the ETV-901 study. Throughout the 5 years of treatment, entecavir resistance was seen in only 1 patient. The safety profile of entecavir in this study was consistent with previous reports.

Several studies presented at the 2010 AASLD meeting also supported the long-term use of tenofovir in both HBeAg-positive and HBeAg-negative CHB patients. In Study 102, Marcellin and colleagues presented Year 4 results from an ongoing, 8-year study of tenofovir in patients with HBeAg-negative disease; in this double-blind study, 375 patients were randomized 2:1 to tenofovir 300 mg or adefovir 10 mg.[7] All patients who underwent liver biopsy at Week 48 were switched to open-label tenofovir for up to an additional 7 years of treatment. Patients whose HBV DNA level was at or above 400 copies/mL on or after Week 72 were offered the option to convert to combination therapy, in which emtricitabine was added to the treatment regimen.

The authors of this study reported that tenofovir treatment yielded very good virologic response rates; in the intent-to-treat (ITT) analysis at Week 192, 86% of patients had HBV DNA levels below 400 copies/mL (85% in the tenofovir-tenofovir subgroup and 87% in the adefovir-tenofovir subgroup). No patients developed resistance to tenofovir, and the safety profile of tenofovir was favorable through Year 4, with no drug-related adverse events leading to discontinuation. Cumulatively, 4 cases (1%) of HCC were reported during open-label treatment. Also, a

0.5 mg/dL–increase in creatinine level was observed in 2 patients: 1 case was associated with advanced HCC, and the other patient improved with every-other-day dosing.

Similar data were reported by Heathcote and colleagues for patients with HBeAg-positive CHB.[8] This phase III study (Study 103) used the same protocol as Study 102 and randomized a total of 266 patients. In the ITT analysis, 77% of patients had HBV DNA levels below 400 copies/mL at Year 4 (74% in the tenofovir-tenofovir subgroup and 84% in the adefovir-tenofovir subgroup), with complete viral suppression in over 95% of patients on therapy. Cumulatively, 10% of patients achieved loss of HBsAg, and 7.5% of patients seroconverted to anti-HBs. No resistance mutations were found in this study. As in Study 102, tenofovir was well tolerated; 1 patient experienced a 0.5 mg/dL–increase in serum creatinine level during Year 4 but remained on study, and no other issues were noted.

Long-Term Data on Combination Therapy

Combination therapy—with either 2 nucleotides, 2 nucleosides, or a nucleotide plus a nucleoside—has been the subject of much debate and interest in the CHB community. However, clinicians currently have little or no clinical trial data that could help to answer their many questions: Should patients who have had extensive pretreatment with lamivudine or adefovir be treated with combination therapy, or are those patients adequately treated with entecavir or tenofovir monotherapy? If combination therapy is indicated, what agents should be used? Finally, how should we treat patients who have a suboptimal response to tenofovir or entecavir? Regarding this last question, most clinicians have advocated combination therapy utilizing both agents, but data in this group of patients are extremely limited. From the data, it appears clear that when combination therapy is used, a nucleotide should be combined with a nucleoside (rather than combining 2 drugs from the same class) to minimize toxicity and persistence or emergence of resistant viral strains.

One study that sheds some light on the question of combination therapy was presented at the 2010 AASLD meeting. In a study by Berg and colleagues, tenofovir monotherapy was compared to fixed-dose combination therapy of emtricitabine plus tenofovir in CHB patients who had an incomplete virologic response following at least 6 months of treatment with adefovir.[9] In both blinded treatment arms, patients were permitted to switch to open-label combination therapy after 24 weeks if persistent viremia (HBV DNA level >400 copies/mL) was confirmed. A total of 105 patients were randomized 1:1 to receive either monotherapy or combination therapy; of these patients, 13 had resistance mutations to lamivudine at baseline, and 10 had resistance mutations to adefovir at baseline.

At Week 156, 88% of the patients randomized to monotherapy and 85% of the patients randomized to combination therapy had HBV DNA levels below 400 copies/mL (P=.757). ALT normalization occurred in 71% of the monotherapy group and 77% of the combination therapy group (P=.521). Of note, all 13 patients with baseline lamivudine resistance mutations and 9 of the 10 patients with baseline adefovir mutations achieved undetectable HBV DNA levels by Week 156. Both monotherapy and combination therapy were well tolerated, and no changes in renal laboratory parameters were observed.

Many questions about CHB remain unanswered, and more data on viral resistance following longer treatment periods are needed, but the currently available data seem to indicate that monotherapy with entecavir or tenofovir is beneficial for patients who are nucleoside-naïve or lack established resistance. Available long-term trials have demonstrated very durable responses to these agents without any late increase in the rate of antiviral resistance. For patients who have been exposed to lamivudine or adefovir, the available data suggest that 3 years of monotherapy with tenofovir is as effective as combination therapy with tenofovir and emtricitabine.

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Understanding Measurements of Hepatitis B Virus Activity

Nezam H. Afdhal, MD

In order to predict long-term outcomes in patients with CHB, we must be able to categorize these patients in clinically meaningful ways, select treatments that are appropriate for each group, and monitor the effects of these treatments. Ultimately, our goal is to predict and prevent the long-term sequelae associated with CHB.

Treatment Criteria

By definition, all patients with CHB have been HBsAg-positive for at least 6 months; within this population, however, patients can be divided into 3 broad clinical profiles. The first subgroup includes CHB patients with active disease; these patients are HBeAg-positive or -negative with serum HBV DNA levels above 2,000 IU/mL (10^4 copies/mL), persistent or intermittent elevation in ALT levels, and a liver biopsy showing chronic hepatitis with moderate or severe necroinflammation. The second subgroup is comprised of immunotolerant patients; these individuals tend to be young patients who are HBeAg-positive and infected with wild-type HBV. Typically, these patients have HBV DNA levels above 20,000 IU/mL (10^5 copies/mL), normal or minimally elevated ALT levels, and no significant inflammation on liver biopsy. The third subgroup of CHB patients includes those formerly called "chronic carriers," but it is more accurate to describe them as patients with nonreplicating virus. These patients are usually HBeAg-negative and anti–HBe-positive with normal or minimally elevated HBV DNA levels (<2,000 IU/mL [104 copies/mL]) and persistently normal ALT levels. A liver biopsy in these patients will confirm the lack of significant inflammation. While these categories are a useful schema for organizing CHB patients, clinicians should keep in mind that these profiles are not fixed and that patients can move between disease states. As a result, CHB patients require continuous monitoring.

Categorizing patients into 1 of these 3 groups is a necessary prerequisite to therapy, as treatment decisions are usually based on which clinical profile a patient fits at the time of evaluation. Clinical guidelines from the AASLD state that patients with active disease should receive treatment, while those with nonreplicating virus do not require treatment and can be adequately managed with ongoing monitoring. The guidelines recommend that immunotolerant patients also be monitored, at least initially, and that treatment be withheld until ALT levels become elevated or moderate or severe necroinflammation or significant fibrosis is seen on liver biopsy.[1]

This last recommendation has been the subject of some debate, in part due to the results of 2 major studies that have linked persistent viremia with an elevated risk of HCC, even among HBeAg-negative patients whose ALT levels are within normal limits. The Haimen City study followed 2,763 HBsAg-positive patients 25–64 years of age over the course of 11 years to assess the relationship between viral load and risk of HCC.[2] The relative risk of mortality associated with a high viral load (HBV DNA level $\geq 10^5$ copies/mL) was found to be 11.2 (95% confidence interval 3.6–35.0); however, a low viral load (HBV DNA level $<10^5$ copies/mL) had no significant association with mortality. In this study, nearly 20% of patients with a high viral load died of HCC.

A second study, the REVEAL-HBV study, was a multicenter, observational cohort study of 3,653 Taiwanese patients 30–65 years of age with HBsAg-positive disease.[3] This study found that the cumulative incidence rate of HCC increased with increasing viral load; patients with undetectable levels of HBV DNA had a rate of 1.3%, while patients with very high HBV DNA levels ($>10^6$ copies/mL) had a rate of 14.9%. This gradient of risk remained significant even after adjustments were made for sex, age, cigarette smoking, alcohol consumption, HBeAg status, and serum ALT levels.

These data suggest that there may be some rationale for earlier initiation of treatment in immunotolerant patients. Coupled with the development of new, potent oral antiviral agents that show low levels of resistance even with long-term use, such concerns have prompted some prominent hepatologists to discuss the benefits of treating the immunotolerant population.

Measurement of HBV Activity

Like patients with chronic hypertension or chronic diabetes, patients with CHB have a condition that places them at risk for adverse clinical outcomes. Indeed, approximately 40%

of patients with CHB will develop significant liver-related morbidity and mortality due to disease sequelae such as cirrhosis, liver failure, and/or HCC.[4] Thus, clinicians' first goal is to prevent these complications. Unfortunately, clinicians cannot easily determine whether this goal has been achieved, as it can take many years to demonstrate that a treatment is effective for the prevention of long-term sequelae.

HBV DNA Levels

In the absence of data on long-term complications, the next best strategy is to use surrogate measures of HBV activity that will hopefully provide indirect information on long-term outcomes. One surrogate measure that is often used in the management of HBV is viral suppression, defined as an HBV DNA level below the limit of detection. For most of the currently available polymerase chain reaction (PCR)-based assays, the threshold for detection is less than 50 IU/mL.[5]

Certainly, measurement of HBV DNA levels is critical in the assessment of antiviral treatment efficacy, although the cutoff values used to define treatment indications and response continue to be a subject of discussion. Complete viral clearance is an unrealistic treatment endpoint, as some HBV DNA persists even in individuals who achieve serologic recovery following acute HBV infection.[6] In addition, patients with CHB can have HBV DNA levels that fluctuate over time, sometimes going from undetectable to very high (>2,000,000 IU/mL).[7] For these reasons, the AASLD guidelines state that serial monitoring of HBV DNA levels is necessary to predict clinical progression and determine the need for treatment.[1]

Seroconversion

Immunologic changes can also be used to monitor HBV activity and response to therapy. A major goal of therapy in HBeAg-positive patients is seroconversion to HBeAg-negative, anti-HBe disease, as clearance of HBeAg reduces the risk of hepatic decompensation and improves survival.[8] In patients who have confirmed HBeAg seroconversion, treatment is often discontinued after 6 months of consolidation therapy. The most recent AASLD clinical guidelines suggest that the durability of response after cessation of treatment is 70–90%. However, exacerbations of HBV do occur among patients who have achieved seroconversion, so close monitoring is still recommended.

A second immunologic change that can be used to monitor disease progression and response to therapy is seroconversion from HBsAg-positive disease to HBsAg-negative, anti-HBs–positive disease. Patients who achieve HBsAg loss and seroconversion have a very positive prognosis, with increased length of survival, lower rates of hepatic decompensation, reduced frequency of HCC, and regression of liver fibrosis.[9] Surface antigen loss is rare, however, occurring in approximately 1–2% of patients each year.[10] Patients who receive IFN-α therapy have a rate of HBsAg loss of approximately 3–12%, and long-term studies of entecavir and tenofovir have shown HBsAg loss rates of approximately 5% and 10%, respectively.[8,11-13] Because HBsAg loss has been quite rare, it has not historically been considered as an endpoint of treatment. However, recent data are prompting more discussion about the clinical implications of HBsAg level and seroconversion.[14]

Providing data to fuel this discussion, Jung and colleagues followed 28 HBeAg-positive, treatment-naïve patients who received entecavir for 1 year and found that patients who showed a response in HBsAg level (a decrease of >1 $\log_{10}$ IU/mL from baseline) were significantly more likely to achieve HBeAg seroconversion.[15] The cumulative incidence of HBeAg seroconversion after 1 year of entecavir treatment was 80% in patients with an HBsAg response versus 30% in those without an HBsAg response (P=.034).

Similar data were presented by Cardoso and colleagues at the 2010 AASLD meeting.[16] This retrospective analysis included 228 patients with HBV infection, 10% of whom were HBeAg-positive. Of these patients, 51% had active CHB, 39% were inactive carriers, and 16% had hepatic cirrhosis. During the study period, 4% of patients developed HCC. Approximately half of the patients in the study received antiviral therapy, and 14% had previously received IFN-α. The investigators found that HBsAg levels above 250 IU/mL were associated with a higher prevalence of chronic hepatitis (57% vs 28%; P<.05) and use of antiviral therapy (56% vs 28%; P<.05) compared to HBsAg levels below 100 IU/mL. Lower levels of HBsAg also predicted eventual seroconversion. Thus, HBsAg status—in addition to viral load and HBeAg status—could represent an important tool for anticipating a patient's clinical course and optimizing therapy.

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Optimizing Long-Term Treatment Strategies in Chronic Hepatitis B

Bruce R. Bacon, MD

If patients with CHB are clearly candidates for treatment, then optimizing long-term treatment strategies is fairly straightforward. As discussed in the previous sections of this monograph, we have 2 excellent first-line therapies, tenofovir and entecavir, both of which offer very good efficacy with very low levels of resistance. Indeed, monotherapy with either of these agents is safe and effective in the vast majority of patients. For patients with HBeAg-positive disease, the goal of treatment is HBeAg loss and seroconversion; for patients with HBeAg-negative disease, treatment will likely need to be continued indefinitely.

One issue that should be considered in these patients is noncompliance. While available drugs are effective *when used as prescribed*, noncompliance can not only cause patients to fail these highly effective therapies, but it can also lead to the development of resistance mutations. Therefore, careful patient education and close monitoring is critical. I recommend monitoring HBV DNA and liver enzyme levels every 3 months to ensure continued improvement and encourage compliance. If a patient responds poorly to tenofovir or entecavir, the use of combination therapy with tenofovir plus emtricitabine can show clinical benefit.

Treatment of Special Populations

While treatment of most CHB patients is straightforward, treatment of special populations can be more complex. Specifically, careful consideration is required when treating HBV/HIV co-infected patients, HBV carriers who are receiving immunosuppressive or cytotoxic chemotherapy, and HBV-infected pregnant women. In addition, any discussion of CHB should review the need for HCC screening in this population.

HBV/HIV Co-infected Patients

HBV infection tends to be more aggressive in HIV-positive patients, with higher levels of viremia, more frequent exacerbations, and faster progression to cirrhosis.[1] A study by Thio and colleagues found that liver-related mortality was almost 19 times higher in co-infected men than those infected with HBV only and more than 7 times higher in co-infected men than those infected with HIV only.[2]

For co-infected patients who do not yet require HIV therapy, HBV treatment should avoid monotherapeutic use of agents that have activity against HIV (that is, tenofovir, entecavir, emtricitabine, or lamivudine), so as not to compromise future HIV care. Patients with HBeAg-positive disease can be treated with peginterferon if their CD4 T-cell count is above 500 cells/μL.[3] Adefovir has negligible activity against HIV when used at the dose approved for HBV treatment (10 mg), so adefovir can be considered for patients with HBeAg-negative disease or those with HBeAg-positive disease and low CD4 T-cell counts.[4] If highly active antiretroviral therapy is planned for patients with HBV/HIV co-infection, then clinicians should select a combination therapy that is effective against both viruses, such as tenofovir combined with lamivudine or emtricitabine.[5]

HBV Carriers Receiving Immunosuppressive or Cytotoxic Chemotherapy

Approximately 20–50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy experience reactivation of HBV replication, resulting in an increase in HBV DNA and ALT levels.[6,7] Reactivation of HBV has also been reported in HBsAg-positive individuals after intra-arterial chemoembolization for HCC and in rheumatoid arthritis or inflammatory bowel disease patients who are treated with immunosuppressive biologic therapies such as anti–tumor necrosis factor (TNF) agents.[8-10] Therefore, all HBsAg-positive patients should be counseled on the risks of HBV reactivation, and those receiving cancer chemotherapy or biologic therapy with rituximab should receive prophylactic antiviral therapy from the onset of immunosuppressive therapy until 6 months following its discontinuation. Patients receiving other types of immunosuppressive therapy should be carefully monitored, and prophylactic antiviral therapy can be considered.[3]

To quantify the morbidity and mortality associated with HBV reactivation, Mendelsohn and colleagues at Memorial Sloan-Kettering Cancer Center conducted a retrospective study of patients with HBV reactivation. These data, which were presented at the 2010 meeting of the American Society of Clinical Oncology, showed that 241 patients at their institution had HBV DNA levels above 1,000 copies/mL between 2003 and 2009.[11] Of these patients, 22 had no risk factors for acute HBV exacerbation and were therefore considered to be cases of HBV reactivation. Patients had a median age of 53 years, were of different ethnicities, had varied cancer types, and were treated by a variety of chemotherapeutic agents (in 1 case, only high-dose steroids were received). In this cohort, 4 patients died from liver failure and 19 patients required hospitalization, with a median length of stay of 5 days (range, 2–33 days). Four patients had clinically significant delays in cancer treatment due to HBV reactivation, 3 patients were transferred for liver transplantation evaluation, and 1 patient underwent transplantation.

Because of these results, Memorial Sloan-Kettering Cancer Center now screens patients for HBV before initiating immunosuppressive therapy, and subsequent use of antiviral prophylaxis is considered. Prevalence results from the first year of this screening program were reported at the 2010 AASLD meeting.[12] Of 5,061 new patients who received immunosuppressive therapy, 3,028 patients (59.8%) were screened for HBV. The prevalence of HBsAg positivity was 0.8%, and hepatitis B core antibody (anti–HBc-total) positivity was found in 7.3% of patients. PCR results were positive in 2.7% of HBsAg-negative/anti-HBc-total–positive patients. While these data are valuable, prospective studies are needed to identify which individuals should receive treatment and to determine the optimal timing, duration, and type of antiviral prophylaxis. The goal of this effort is to completely prevent HBV reactivation.

HBV-Infected Pregnant Women

Another subpopulation of HBV patients who require special attention is pregnant women. Because of the risk of vertical transmission, infants born to pregnant women who are HBsAg-positive should receive hepatitis B immune globulin (HBIG) and hepatitis B vaccine immediately after delivery.[13] Although the combination of HBIG and hepatitis B vaccination has been shown to prevent perinatal transmission in 95% of cases, the efficacy of this regimen is lower among maternal carriers with HBV DNA levels above 8 $\log_{10}$ IU/mL.[14] Therefore, some clinicians have considered using antiviral therapy during pregnancy to reduce the rates of vertical transmission among maternal carriers with high viral loads.

Pan and colleagues reported data on this topic at the 2010 AASLD meeting.[15] Their open-label, controlled study enrolled 88 pregnant women (12–32 weeks gestation) who had HBeAg-positive disease, a high viral load (HBV DNA level >6 $\log_{10}$ copies/mL), and an ALT level above the upper limit of normal (ULN) but less than 10 times ULN. Telbivudine at a dose of 600 mg daily was given to 53 women who desired treatment; the remaining 35 women did not want treatment and were enrolled in the control arm. At postpartum week 4, the women either discontinued telbivudine therapy or transitioned to a commercially available CHB therapy. Infants received HBIG (200 IU) within 24 hours after birth plus HBV vaccine (20 ug) at 0, 1, and 6 months of age.

Undetectable HBV DNA levels were achieved in 53% of the telbivudine-treated women prior to delivery and in 62% of this group by postpartum week 4; none of the women in the control arm achieved HBV DNA undetectability at either time point. At birth, 4% and 23% of the newborns in the telbivudine-treated and control arms were HBsAg-positive, respectively ($P<.001$). No congenital deformities were reported at postpartum week 4, and the study found no differences between the 2 arms in terms of postpartum hemorrhage, gestational age, infants' height/weight, or Apgar scores. Based on these data, antiviral therapy can be considered for HBV-infected women with very high viral loads during the second and third trimesters of pregnancy.

Screening for Hepatocellular Carcinoma

Finally, a key component of any long-term treatment plan for CHB patients is determining whether or not these individuals should be part of a surveillance program for HCC. The AASLD recently updated their guidelines on this subject, and HCC screening is now recommended for multiple high-risk groups, including Asian male HBV carriers over 40 years of age, Asian female HBV carriers over 50 years of

Table 1. Guidelines for HCC Surveillance

Surveillance recommended
- Asian male hepatitis B carriers over 40 years of age
- Asian female hepatitis B carriers over 50 years of age
- Hepatitis B carriers with a family history of HCC
- African/North American blacks with hepatitis B
- Cirrhotic hepatitis B carriers
- Patients with hepatitis C cirrhosis
- Patients with stage 4 primary biliary cirrhosis
- Patients with genetic hemochromatosis and cirrhosis
- Patients with alpha 1-antitrypsin deficiency and cirrhosis
- Patients with cirrhosis from other causes

Surveillance benefit uncertain
- Hepatitis B carriers younger than 40 years of age (males) or 50 years of age (females)
- Patients with hepatitis C and stage 3 fibrosis
- Patients with noncirrhotic NAFLD

HCC=hepatocellular carcinoma; NAFLD=nonalcoholic fatty liver disease.
Adapted from Bruix J, Sherman M.[16]

age, HBV carriers with a family history of HCC, African or North American blacks who are infected with HBV, and cirrhotic HBV carriers (Table 1). The recommended method of surveillance is ultrasonography every 6 months.[16]

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Question-and-Answer Forum

When is combination therapy appropriate for patients with CHB?

Dr. Nezam H. Afdhal The main question we have to ask ourselves is: What is the goal of treatment when we are using oral agents? I would say our goal is viral suppression, and the data show that we can achieve very good viral suppression in the vast majority of patients with tenofovir or entecavir monotherapy. At the moment, therefore, combination therapy is usually reserved for patients who show a suboptimal response to tenofovir or entecavir.

Dr. Bruce R. Bacon I agree with that statement. In my practice, I only use combination therapy for patients who show a suboptimal response to tenofovir. If a patient on tenofovir fails to achieve undetectable HBV DNA levels, then I will switch to combination therapy with tenofovir and emtricitabine.

Dr. Robert S. Brown, Jr. One caveat I would mention is that most of the data for combination therapy with tenofovir and entecavir come from very controlled settings. In the real world, where compliance is often suboptimal, I think there is still a question of whether we gain an advantage by using the "belt and suspenders" approach that combination therapy represents. As more and more physicians begin using these agents in the clinic, I think we will begin to gain a clearer understanding of whether combination therapy can help to prevent long-term resistance in difficult-to-treat patient populations.

Which HBV carriers receiving immunosuppressive therapy should receive prophylactic antiviral therapy?

RB First of all, I do not think that patients who are currently receiving immunosuppressive treatment are being counseled appropriately about the risk of HBV flares. Physicians who prescribe these therapies need to be educated about the risk of flare in HBV carriers, both those with resolved infection and those with active disease. At-risk patients include those receiving chemotherapy, particularly rituximab, as well as those receiving anti-TNF therapy for inflammatory bowel disease or rheumatoid arthritis.

NA Which patients should receive prophylactic antiviral therapy remains an open question. Should there be some criteria based on HBsAg status or HBV DNA level? What about prophylaxis of patients who are anti-HBc-total–positive? This latter group includes a large number of patients, and they could represent the bulk of patients receiving prophylaxis if it were to be used routinely. I think patients who are HBsAg-positive and have detectable HBV DNA levels certainly need prophylaxis if they are receiving an immunosuppressive regimen, even a relatively mild one.

BB For patients who are only anti-HBc-total–positive or who are HBsAg-positive but have undetectable HBV DNA levels, my approach would be to use prophylaxis only with intensive immunosuppressant therapy. For patients on more mild therapy, close monitoring will enable us to address any reactivation before it becomes a problem.

What role does alpha-fetoprotein monitoring play in HCC surveillance?

BB The updated AASLD guidelines state that HCC surveillance should be based on ultrasound imaging, not alpha-fetoprotein (AFP) testing, although I think the point the AASLD was making was that AFP should not be used as a *substitute* for imaging. I agree with that concept, although I still use AFP testing in combination with interval hepatic imaging in my practice. I think a rising AFP level is certainly a cause for concern in any patient, and this finding would lead to a change in my screening strategy.

NA I cannot imagine that the majority of expert hepatologists have abandoned AFP monitoring in favor of only ultrasound, because AFP testing is easy and relatively inexpensive. I do think we need better screening tests—tests that are both sensitive and specific—or perhaps we need better predictors that can identify a subgroup that is at higher risk.

BB With the development of more potent antiviral drugs, I think HCC is going to become a major cause of demise for patients with CHB. We must spread the word that all patients with CHB are at risk for HCC, regardless of histology, viral load, or treatment. Patients differ greatly in terms of their relative risk for HCC, and we need to monitor them in different ways, but all patients need lifelong HCC screening and surveillance.

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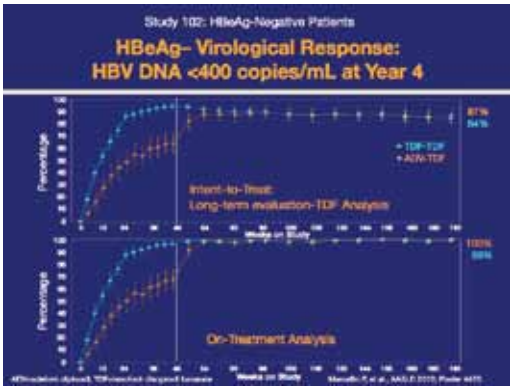

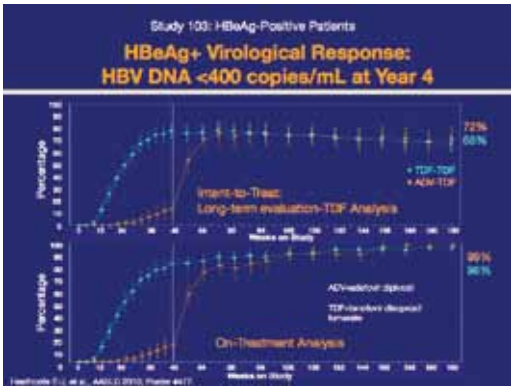

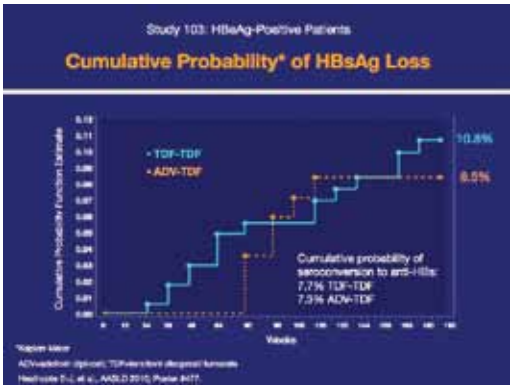

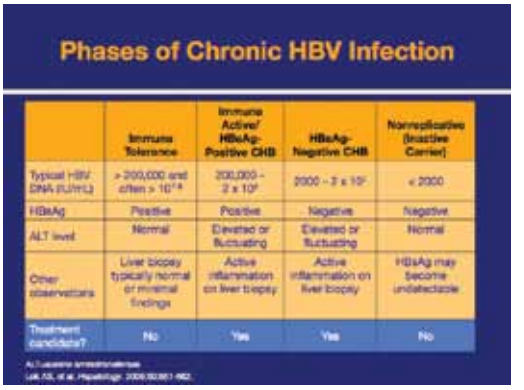

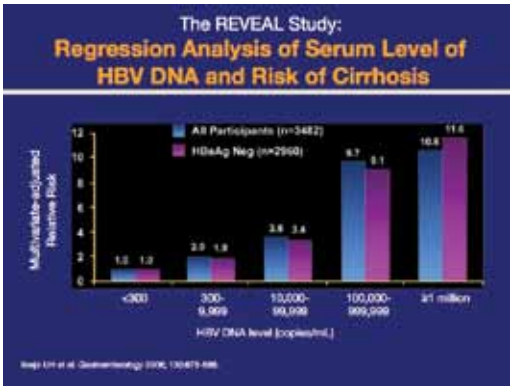

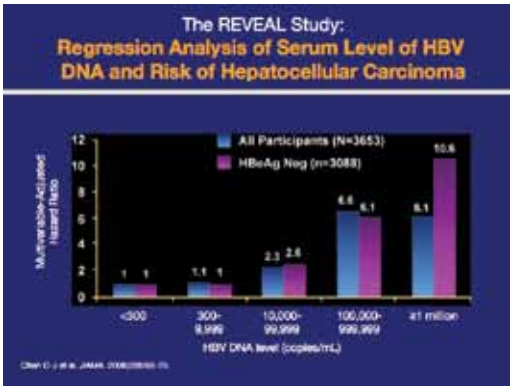

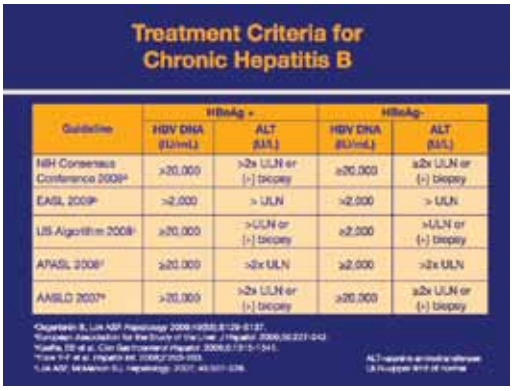

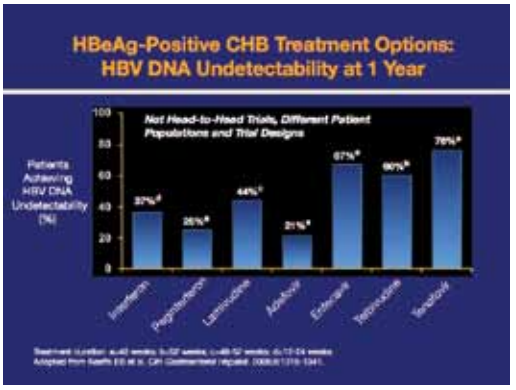

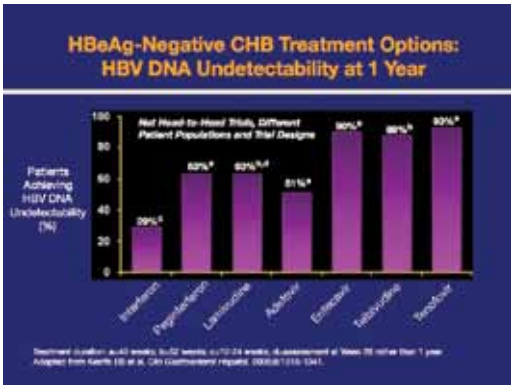

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