

REVIEW

Report of an International Workshop: Roadmap for Management of Patients Receiving Oral Therapy for Chronic Hepatitis B

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An international group of experienced hepatologists and virologists conducted a single-day workshop to review the management of patients with chronic hepatitis B receiving treatment with oral nucleosides or nucleotides. Guidelines regarding on-treatment management and available published data on the importance of serum hepatitis B virus (HBV) DNA as a marker of outcomes were reviewed. On-treatment monitoring strategies to define early virologic responses that might be predictive of better outcomes and a reduced risk of viral resistance were proposed for further study. This treatment plan, labeled the *roadmap concept*, recommends monitoring of serum HBV DNA levels to identify outcomes of therapy. Primary treatment failure was defined as a reduction of serum HBV DNA levels by less than 1 log₁₀ IU/mL from baseline at week 12. Measurement of the HBV DNA level at week 24 was considered essential to characterize virologic responses as complete, partial, or inadequate. Complete virologic response was defined as negative HBV DNA by a sensitive assay (<60 IU/mL or <300 copies/mL); partial virologic response was defined as HBV DNA levels less than 2000 IU/mL (4 log₁₀ copies/mL), and inadequate virologic response was defined as HBV DNA levels of 2000 IU/mL or greater (4 log₁₀ copies/mL). Strategies are proposed for managing patients in each of these categories, depending in part on the rapidity with which HBV DNA suppression is achieved and the emergence of genotypic mutations that reduce the effectiveness of a specific drug. Future studies of the use of the roadmap concept in improving outcomes of chronic hepatitis B are warranted.

Despite the availability of highly effective and safe vaccines for a quarter of a century, hepatitis B virus (HBV) infection remains the most common worldwide cause of death from liver disease. It accounts for an estimated 500,000–900,000 deaths per year owing to cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Natural history studies of chronically infected individuals have linked the risk of progression to cirrhosis and HCC to continuing HBV replication.^{1–3} A number of therapies for chronic hepatitis B have been developed and are directed at reducing or interrupting replication of

the virus and thereby reducing liver and serum levels of HBV DNA and/or enhancing host immune control of infection. Reducing serum HBV DNA levels to undetectable levels or possibly to levels less than 20,000 IU/mL (5 log₁₀ copies/mL) is associated with improved outcomes.⁴ However, with increasing assay sensitivity and additional experience, it is clear that disease progression may occur in patients with serum HBV DNA levels as low as 2000 IU/mL (4 log₁₀ copies/mL).^{5,6}

Thus, the degree of viral suppression achieved during treatment appears to be the most important determinant of therapeutic outcomes.⁴ The overall goal of therapy in chronic hepatitis B is to reduce progression to cirrhosis, hepatic decompensation with liver failure, development of HCC, and need for liver transplantation. However, achievement of these treatment goals has been hampered by the limited efficacy of current therapy and by the development of viral resistance during therapy with oral agents. Patients may be infected with drug-resistant variants, or resistance may arise as a result of exposure to drug therapy. The currently available oral drugs may be classified as having either high or low resistance to the virus as reflected in the term *genetic barrier*. The general definition of genetic barrier is the threshold probability that the virus will mutate and escape from the selective action of the drug, thereby making the virus resistant to that specific drug. In this terminology, drugs with a high genetic barrier have a low risk for the emergence of viral resistance, whereas those with a low genetic barrier have a higher risk of viral resistance. The development of resistance, when associated with viral rebound, has been linked with an increase of serum alanine aminotransferase (ALT) levels, hepatitis flares, and an increased risk of hepatic decompensation and death from liver failure.^{6–8} Because HBV exists as quasispecies that include both the wild-type and mutant viruses that may confer drug resistance, persistent HBV replication in the presence of an

Abbreviations used in this paper: ALT, alanine aminotransferase; anti-HBe, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

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1542-3565/07/\$32.00
doi:10.1016/j.cgh.2007.05.004

antiviral drug may lead to resistance and to virologic breakthrough, defined as an increase in serum HBV DNA level of 1 log₁₀ or more greater than the nadir. In turn, this increase in viral load may be followed by increased ALT levels and disease progression.⁹ Thus, the emergence of drug resistance depends on the rate of viral replication, the frequency of viral mutations, the mutability of the antiviral target site, and other viral and host factors.¹⁰

Limitations of Current Guidelines on Management of Chronic Hepatitis B

Major nongovernmental organizations devoted to the study of liver disease as well as other expert groups have developed and refined guidelines designed to aid in the management of patients with chronic hepatitis B.¹¹⁻¹⁴ These guidelines address the criteria for patient selection, the objectives and timing of therapy, and the advantages and disadvantages of the available therapies. Available guidelines are either evidence-based or supplemented by expert opinion, and show the presence of a relationship between certain baseline parameters and therapeutic outcomes. However, the guidelines provide very little information on the use of on-treatment responses (other than management of resistance) to predict outcomes. Important questions regarding management during therapy remain largely unanswered: how and when should patients be monitored, what tests are most useful, and how may such information be used in decision making to optimize treatment outcomes?

A panel of international hepatologists and virologists with extensive experience in the management of patients with chronic hepatitis B met on September 2, 2006, in London, England, to review available data on the value of monitoring patients during treatment. The panel proposed a roadmap (ie, a schedule for monitoring) and defined clinically meaningful on-treatment responses with the goal of enhancing patient management. The panel also recommended future research studies designed to assess the value of these proposals.

What is the Relationship Between Serum HBV DNA and Outcomes?

Natural History Studies

The association of chronic HBV infection, as determined by the prolonged presence of hepatitis B surface antigen (HBsAg), with cirrhosis and HCC has been recognized for decades since the landmark studies of Beasley et al¹⁵ in Taiwan. Among HBsAg-positive people, risk factors for HCC included male sex, older age, hepatitis B e antigen (HBeAg)-positivity, increased ALT levels, presence of cirrhosis, cigarette smoking, and alcohol consumption. The linkage of HBV replication and ongoing liver disease with HCC was described in some early studies of HBV-infected individuals, but was dependent on relatively insensitive assays.^{16,17} Among HBsAg-positive individuals, there is a relationship between the detection of HBeAg and the development of HCC.¹⁸ Hence, a relationship between serum HBV DNA levels and progressive liver disease had been suspected, but large natural history studies of untreated patients were not available until recently.^{1-3,19}

A large prospective cohort study of HBsAg-positive individuals negative for antibody to hepatitis C virus, between 30 and 65 years of age, participating in a 7-Taiwanese-township cancer screening

Table 1. Multivariate Adjusted Relative Risk of Cirrhosis and HCC by Serum HBV DNA on Entry Into a Prospective Cohort Study of HBV-Infected Patients in Taiwan

Baseline HBV DNA (copies/mL)	Relative risk of cirrhosis (n = 3582)	Relative risk of HCC (n = 3653)
<300	1.0	1.0
300–9.9 × 10 ³	1.4 (0.9–2.2)	1.1 (0.5–2.3)
1.0–9.9 × 10 ⁴	2.5 (1.6–3.8)	2.3 (1.1–4.9)
1.0–9.9 × 10 ⁵	5.6 (3.7–8.5)	6.6 (3.3–13.1)
≥1.0 × 10 ⁶	6.5 (4.1–10.2)	6.1 (2.9–12.7)

NOTE. 95% confidence interval shown in parentheses.

Adapted from Chen et al¹ and Iloeje et al.²

program, was undertaken to assess the natural history of chronic HBV infection.^{1,2} The study began in 1991–1992 and ended in 2004, and enrolled approximately 3600 HBsAg-positive individuals. More than 90% of the cohort had serum ALT levels less than 45 U/L, 85% were HBeAg negative, and 98% had no sonographic evidence of cirrhosis. At study entry, HBV DNA, HBeAg, ALT, and alpha-fetoprotein levels also were measured. Changes in serum HBV DNA levels on follow-up evaluation were analyzed and correlated with outcomes. Incident cases of HCC were identified by follow-up health examinations with linkage to a national cancer registry. Criteria for the diagnosis of HCC included histology, lesions seen on 2 different imaging techniques, or on one imaging technique with an alpha-fetoprotein level greater than 400 ng/mL. Among the 3600 participants, 385 developed cirrhosis and 164 developed HCC. The cumulative incidence of cirrhosis and HCC increased progressively based on HBV DNA levels at study entry. The multivariable-adjusted relative risk of HCC appeared to reach a peak with levels greater than 5 log₁₀ copies/mL (Table 1). However, HBV DNA levels of 4 log₁₀ copies/mL or greater also were associated with a significant risk for both cirrhosis and HCC, and patients with increasing levels of HBV DNA levels over time or with persistently increased levels during follow-up evaluation had the highest risk of HCC. In contrast, lowering of HBV DNA levels from the highest levels was linked with a reduction in risk of HCC only when the HBV DNA level decreased to less than 4 log₁₀ copies/mL. The authors of these studies recommend monitoring HBV DNA levels in the management of chronic HBV infection.^{1,2}

In a concurrent prospective cohort study undertaken in Haimen City, China, with a similar 11-year follow-up period, nearly 2800 HBsAg-positive subjects were included in an analysis of liver disease-related mortality and morbidity.³ The viral load at entry was categorized as less than 1.5 × 10³ copies/mL, less than 10⁵ copies/mL, and 10⁵ copies/mL or greater. As in the Taiwan study, mortality rates for chronic liver disease and HCC were highest in the group with the highest viral load at entry, and a linear trend in the risk of liver disease mortality and HBV viral load from lowest to highest was suggested with a threshold effect for a viral load of 10⁴ copies/mL or greater. About 20% of those in the highest viral load group died from chronic liver disease or HCC. Among the surviving participants, there was a positive association of entry viral level and disease severity 11 years later, with nearly 30% of those with a high viral load having severe liver disease or HCC. In 2 small studies of Asian patients with chronic hepatitis B, a minor proportion of pa-

tients with HBV DNA levels less than 10^4 copies/mL also developed evidence of disease progression,^{5,6} suggesting that 10^4 copies/mL may be an imperfect threshold.

Thus, a serum HBV DNA level of 10^4 copies/mL or greater is a strong risk factor for disease progression and HCC, independent of HBeAg status and serum ALT level. Although these observations were made in individuals likely to have acquired HBV infection early in life, there is little a priori reason to believe that the natural history of adult infection persisting over several decades is importantly different.

Impact of Treatment-Induced Viral Suppression on Outcomes

Patients with chronic hepatitis B treated with parenteral interferon or oral antiviral drugs provide compelling evidence that reduction of HBV DNA levels improves clinical outcomes.^{4,20–25} In lamivudine-resistant decompensated cirrhotic patients, treatment with adefovir improved Child–Turcotte–Pugh scores.²⁶ Long-term treatment with lamivudine in patients with either advanced hepatic fibrosis or cirrhosis delays clinical progression, with a lower frequency of hepatic decompensation, a reduced rate of HCC, fewer episodes of spontaneous bacterial peritonitis and bleeding esophagogastric varices, and fewer liver disease-related deaths.²⁷ A similar but less dramatic benefit in asymptomatic, noncirrhotic chronic hepatitis B patients has been described.²⁸

Current Guidelines for On-Treatment Management

A number of guidelines have been published and generally are followed in practice. The updated 2007 American Association for the Study of Liver Diseases practice guideline¹² provides limited discussion of on-treatment management. For HBeAg-positive chronic hepatitis B patients treated with lamivudine, it is suggested that HBV DNA levels should be measured every 3–6 months and HBeAg and antibody to HBeAg (anti-HBe) levels should be measured after 1 year and then every 3–6 months. No specific HBV DNA level is cited as a criterion for changing therapy for this group of patients or for those with HBeAg-negative disease. Similarly, the use of HBV DNA responses in patients on treatment with adefovir, entecavir, or telbivudine is not mentioned in the guideline. The guideline recommends that patients who have less than a 2- \log_{10} IU/mL decrease from baseline of HBV DNA after at least 6 months of treatment should be switched to an alternative Food and Drug Administration-approved therapy.

Other guidelines, including the 2002 European Association for the Study of the Liver consensus conference on hepatitis B,¹² the 2005 Asia Pacific Association for the Study of Liver Diseases consensus statement on the management of chronic hepatitis B,¹³ and the updated 2006 treatment algorithm specifically focused on management of chronic hepatitis B in the United States,¹¹ all address the importance of monitoring patients on antiviral treatment. However, none describe in detail how measurement of HBV DNA levels should be used. Similarly, published recommendations for monitoring for the development of resistance¹⁰ describe primary treatment failure based on changes in HBV DNA levels measured at week 12.

On-Treatment Management: Evidence Supporting the Key Role of HBV DNA Monitoring

The conventional on-treatment measurements most often recommended in current guidelines are ALT, HBeAg and anti-HBe, and HBV DNA levels.

Normalization of Serum ALT Levels

The normalization of serum ALT levels in patients with increased levels before initiating therapy usually is considered predictive of improvement in necroinflammatory disease. Monitoring ALT levels also is useful in documenting treatment-associated flares or viral breakthrough as a result of noncompliance or viral resistance. In patients with normal levels at baseline, including patients with cirrhosis, ALT levels may not be helpful in assessing the response to therapy. Lowering of the upper limit of normal (to 30 U/L in men, and to 19 U/L in women) has been proposed²⁹ to help guide therapy, but this recommendation is not accepted universally.¹¹

HBeAg Serostatus

Loss of HBeAg and, perhaps more importantly, HBeAg seroconversion to anti-HBe during treatment generally has been accepted as indicative of a therapeutic response. Some suggest that sequential monitoring of quantitative HBeAg levels during treatment with interferon or lamivudine may be helpful in predicting outcomes.^{30,31} However, quantitation of HBeAg has not been used widely, is not approved in the United States by the Food and Drug Administration, is expensive, and available data about the predictive value of HBeAg serostatus remain limited. Serum HBV DNA levels of greater than 10^4 copies/mL typically are associated with a lack of HBeAg seroconversion (loss of HBeAg and appearance of anti-HBe), whereas about one third of those with lower levels of serum HBV DNA will seroconvert,³² suggesting a close relationship of the degree of HBV DNA suppression to the likelihood of seroconversion. In HBeAg-negative patients at the outset of treatment, serum HBV DNA and ALT monitoring are the only useful markers of response to therapy.

Serum HBV DNA Levels

Suppression of serum HBV DNA while on treatment appears to be the best predictor of improved long-term outcomes. The evidence supporting this approach to monitoring and predicting response to treatment is available from a number of sources summarized later.

Clearance of HBV DNA by the less-sensitive hybridization methodology and closely linked HBeAg seroconversion on interferon therapy was associated with an improved survival, reduced need for liver transplantation, and fewer severe complications as a result of cirrhosis.⁴

In a review of 26 prospective clinical trials involving more than 3400 patients, there were statistically significant correlations between changes in the serum HBV DNA level on-treatment and histologic, biochemical, and serologic responses.³³ These data suggest that treatment-associated suppression of HBV replication can be used to assess the efficacy of therapy.

Discontinuation of adefovir therapy in HBeAg-negative patients was associated with an increase in HBV DNA levels, lower frequency of ALT normalization, and reversal of improvement

in inflammatory activity and reduction in fibrosis scores on biopsy examination.³⁴

Among patients receiving lamivudine therapy for more than 1 year and developing the YMDD mutation, about two-thirds had increases in serum HBV DNA and ALT levels and reduced histologic benefit in necroinflammatory activity.⁷

Clinical progression in patients with advanced disease was reduced in patients treated with lamivudine with lowering of serum HBV DNA levels, but this beneficial effect was attenuated in those who developed lamivudine resistance.²⁷ HBV DNA breakthrough with reappearance of detectable HBV DNA by a branched-chain hybridization assay occurred in more than 60% of those with the YMDD mutant but in only 5% of those without the mutation.

In HBeAg-positive patients without advanced disease receiving long-term lamivudine therapy, reductions of HBV DNA levels were greatest in those without YMDD mutations and the risk of developing cirrhosis and HCC was decreased compared with those with the mutations or in a control group.²⁸

In HBeAg-negative Greek patients treated with long-term nucleos(t)ides, those who achieved viral remission, defined as serum HBV DNA levels less than 10^3 copies/mL at any point while on treatment, had significantly fewer complications and better event-free survival than patients unresponsive to lamivudine or those who experienced virologic breakthroughs.²⁵

All of the previous data support the concept that suppression of serum HBV DNA to very low or undetectable levels should be the critical goal in the on-treatment management of chronic hepatitis B. Moreover, it seems likely that maintenance of viral suppression is a requisite for long-term clinical benefit.

Time-Course of HBV DNA Suppression During Treatment

The emergence of viral resistance and viral breakthrough while receiving oral antiviral therapy is related in large part to the level of ongoing viral replication. This is a reflection of the antiviral potency as well as the drug's genetic barrier to resistance, which is the ability of the drug to retain efficacy in the face of mutations in the virus. Thus, it seems reasonable that the longer viral replication continues unabated in the presence of the antiviral drug, the greater the risk of breakthrough and attenuation of the benefits of therapy. The key issue that is the focus of this proposed roadmap concept is the time point that one can predict the outcomes of therapy by the serum HBV DNA level.

The following is a summary of data providing insights on the optimal timing for monitoring serum HBV DNA levels during treatment with different agents.

Peginterferon Alfa-2a

Rates of HBV DNA reductions to less than 20,000 copies/mL or normalization of serum ALT levels at 24 weeks after ending therapy were significantly higher in those with HBV DNA levels less than 400 copies/mL at week 12.³⁵ The positive predictive value to achieve a week 72 response for patients with an HBV DNA level less than 2.5 log₁₀ copies/mL at week 12 was 64%, but the negative predictive value was just 70%. Thus, HBV DNA levels at weeks 12, 18, or 24 were not sufficiently predictive to develop a stopping rule similar to that developed in the treatment of chronic hepatitis C.³⁶

Peginterferon Alfa-2b With or Without Lamivudine

A 1 log₁₀ copies/mL decrease in serum HBV DNA levels at week 32 predicted loss of HBeAg in genotype A patients only.³⁷

Lamivudine

In contrast to the limited use of the on-treatment measurement of serum HBV DNA levels in predicting outcomes, emerging data suggest that early and profound reductions in HBV DNA levels during therapy with nucleos(t)ides predict the likelihood of viral resistance and outcomes. In a study of 159 Asian HBeAg-positive patients treated with lamivudine and followed up for a median period of almost 30 months, those with HBV DNA levels greater than 10^3 copies/mL at week 24 had a 63% chance of developing the YMDD mutant vs 21% of those with HBV DNA levels less than 10^3 copies/mL.³⁸ In a smaller study of largely non-Asian patients, those with HBV DNA levels above the limit of detection by polymerase chain reaction (10^2 copies/mL) continuously during lamivudine therapy had an increased risk of developing resistance.³⁹ Loss of HBeAg occurred only in patients whose serum HBV DNA was undetectable at week 24.

Telbivudine Versus Lamivudine

In a phase 2b trial involving 104 patients treated with telbivudine, lamivudine, or the combination of both drugs, the degree of viral suppression at week 24 was associated strongly with clinical and virologic efficacy outcomes at week 52 of treatment.⁴⁰ All patients with undetectable HBV DNA levels (<200 copies/mL) at week 24 remained below that level at week 52. In the phase 3 GLOBE trial, 921 HBeAg-positive patients were randomized to treatment for 2 years with telbivudine vs lamivudine. In multivariate analysis, a lower HBV DNA level at week 24 was the best predictor of clinical and virologic efficacy responses at 52 weeks, irrespective of HBeAg serostatus.⁴¹ Among patients who were HBV DNA negative by polymerase chain reaction at week 24, 90% were HBV DNA negative (<300 copies/mL) at week 52, and less than 1% developed resistance.⁴² Furthermore, week 24 HBV DNA levels also were highly predictive of efficacy outcomes after 2 years of treatment.⁴³

Telbivudine or Adefovir

In a study of HBeAg-positive patients treated with either telbivudine or adefovir for 52 weeks, significantly more patients treated with telbivudine achieved HBV DNA negativity (<300 copies/mL) at week 24 (38.6%) than those treated with adefovir (12.4%), and the degree of HBV DNA reduction observed at week 24 of treatment was predictive of efficacy outcomes at week 52.⁴⁴ In addition, patients with the highest HBV DNA levels at week 52 were likely to have high viral loads at week 24 of treatment.

Adefovir

Adefovir, the only nucleotide analog that is approved by the Food and Drug Administration for the treatment of hepatitis B, appears to induce a slower rate of HBV DNA decrease as compared with lamivudine and telbivudine. Changes in HBV DNA levels at weeks 4 and 12 did not predict resistance to adefovir at week 144 in HBeAg-negative patients.⁴⁵ However,

HBV DNA levels at week 48 were predictive of the development of resistance on multivariate analysis. In patients with HBV DNA levels less than 3 log₁₀ copies/mL at week 48, only 4% developed resistance at week 144, vs 26% of those with levels of 3–6 log₁₀ copies/mL and 67% of those with greater than 6 log₁₀ copies/mL. As a consequence, proposals for use of earlier (eg, 24 week on-treatment virologic levels [see later]) may not hold for adefovir. The emergence of genotypic resistance to adefovir is reported to be 29% after 5 years of treatment in HBeAg-negative patients,⁴⁶ with a corresponding rate of viral breakthrough of 16%, and a genotypic resistance rate as high as 42% after 5 years in HBeAg-positive patients.⁴⁷

Entecavir

With entecavir, a nucleoside analogue with a high genetic barrier to resistance, the 24-week on-treatment HBV DNA level achieved in patients with lamivudine resistance also may be predictive of long-term outcomes and the eventual emergence of resistance to this drug.⁴⁸

Proposed Roadmap Concept for On-Treatment Monitoring and Management of Chronic Hepatitis B

The purposes of monitoring patients during treatment are to assess drug safety, compliance, and the treatment responses. Early virologic response in particular is of value in detecting primary treatment failure (defined later) and in predicting likely outcomes of continued therapy—improved histology, reduced likelihood of clinical disease progression, and/or

the development of drug resistance with viral breakthrough, which in turn may lead to continuing disease progression. After reviewing the available data, there was agreement that quantitative, residual HBV DNA level is the most useful indicator of on-treatment response to therapy, in both HBeAg-positive and HBeAg-negative patients. Although reductions in HBV DNA levels from baseline often are used in clinical trials to report the antiviral potency of drugs for chronic hepatitis B, the panel agreed that residual HBV DNA level was a better marker of therapeutic outcome and the emergence of resistance. Hence, baseline HBV DNA levels were not considered further, although they may be predictive of outcomes before onset of therapy. Figure 1 depicts the roadmap concept. The panel accepted the previously described definition of primary treatment failure, namely failure to reduce HBV DNA by 1 log₁₀ IU/mL or more at week 12 as useful in on-treatment management.¹⁰ It was considered that primary treatment failure is a rare event.¹⁰ For patients in whom compliance is not the likely cause of primary treatment failure, a change in therapy is indicated.

The next time point proposed for monitoring the serum HBV DNA level should be at week 24 of therapy. This measurement was considered essential in the management of both HBeAg-positive and HBeAg-negative patients. Responses at week 24 were categorized as complete, partial, or inadequate virologic responses.

Complete virologic response was defined as HBV DNA levels less than 60 IU/mL (<300 copies/mL) (ie, the lower limit of detection of standard polymerase chain reaction assays). Because most of the available data have used levels of less than

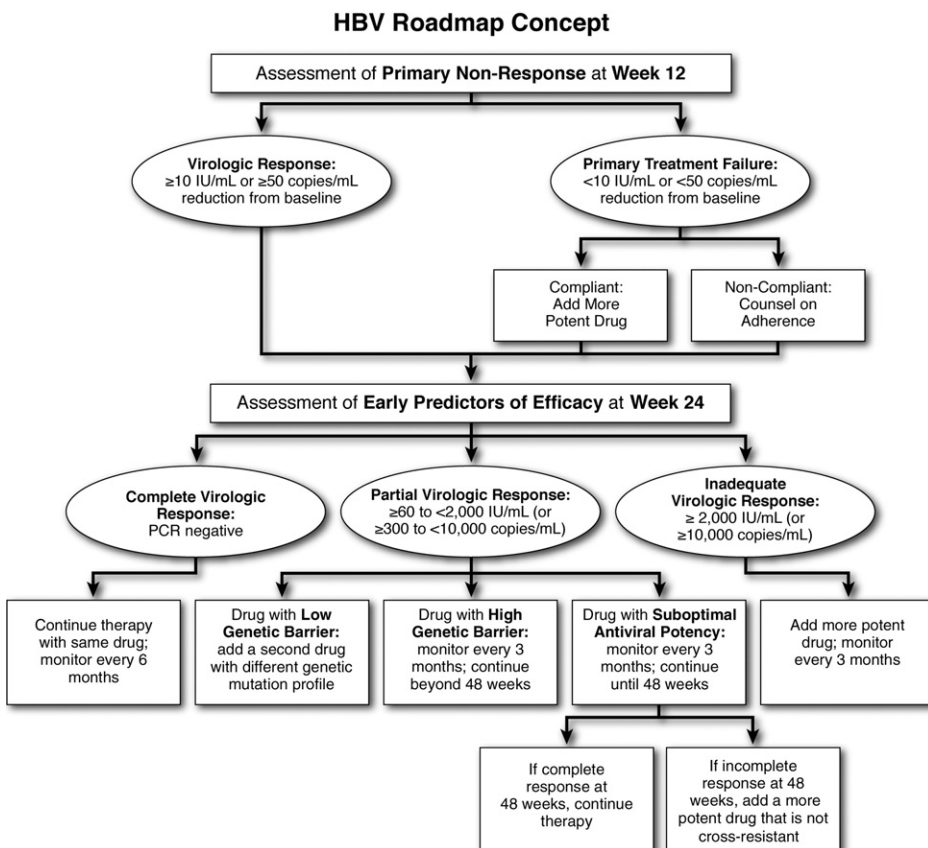


Figure 1. HBV treatment roadmap: on-virologic responses and their management in patients receiving oral therapy for chronic hepatitis B.

300 copies/mL as the threshold for undetectable HBV DNA, the panel favored the use of this level in this classification. For patients with a complete virologic response, continued therapy with the same drug, with repeat testing lengthened to 6-month intervals at the physician's discretion, was recommended (Figure 1).

Partial virologic response was defined as residual HBV DNA levels less than 2000 IU/mL ($<4 \log_{10}$ copies/mL) at week 24. In patients with such a partial response who are treated with a drug with a low genetic barrier to resistance (eg, lamivudine), adding an appropriate non-cross-resistant second drug should be considered to prevent the emergence of resistance and viral breakthrough (Figure 1). Patients with a partial response who are being treated with a potent drug with a high genetic barrier (eg, entecavir), should have repeated monitoring at 3-month intervals and continued beyond 48 weeks. In patients with a partial virologic response who have been treated with a drug with a delayed antiviral effect and a relatively high barrier to resistance (eg, adefovir), monitoring should be repeated at 3-month intervals, and if the response remains partial or becomes inadequate at week 48, a change in therapy should be undertaken unless HBV DNA has been decreasing steadily and is nearly undetectable. If the response becomes complete at week 48, therapy can be continued.

Inadequate virologic responses were defined as residual HBV DNA levels of 2000 IU/mL or higher ($\geq 4 \log_{10}$ copies/mL) at week 24. This threshold for a suboptimal response was accepted because of the reviewed evidence that disease progression is likely with such levels and that viral resistance and breakthrough are much more common in treated patients in whom these levels persist. Patients with an inadequate virologic response require a change in therapy either to a more efficacious drug, if such a drug is available, or the addition of a second drug, preferably one without cross-resistance to the continued drug (Figure 1). Once that change has been made, continued monitoring at 3-month intervals seems appropriate. The intervals between monitoring beyond week 48 should be based on results of testing and may be lengthened from 3 to 6 months, at the physician's discretion, if serum HBV DNA levels decrease to undetectable levels. Patients with advanced disease should be monitored at 3-month intervals independent of virologic response.

Caveats Regarding the Roadmap Concept

The international panel identified a number of potential limitations to this roadmap concept.

1. The applicability of this roadmap concept to treatment with pegylated or conventional interferon was not considered; management of on-treatment early viral kinetic responses to nucleos(t)ides was the focus of the panel's deliberations.
2. Whether the roadmap is applicable to treatment with nucleos(t)ides after failure of treatment with interferon also is uncertain because there are very little available data.
3. Strategies for monitoring patients in whom initial therapy comprises 2 or more drugs were not addressed.
4. The panel speculated that the roadmap concept might apply differently depending on the stage of disease (ie, mild vs advanced).
5. The panel was uncertain whether inclusion of other baseline factors with HBV DNA testing might improve the predictability of the testing strategy.
6. The panel did not consider the role of HBV genotyping, which may become important in guiding changes in therapy in the future. Because the assays for HBV DNA are becoming increasingly sensitive, with very low limits of detection, the precise levels used for definition of virologic response may change over time, and are being recorded in IU/mL rather than copies/mL (1 IU \approx 5.6 copies).
7. The panel did not consider strategies for monitoring patients on long term, continuous suppressive therapy.
8. The panel did not consider the use of monitoring patients to shorten therapy.

The panel recommended that the value of on-treatment monitoring should be assessed in future prospective trials of both approved and new drugs. Until such data are available, on-treatment monitoring at 3- to 6-month intervals should be encouraged in clinical practice. As new information evolves through studies of the use of the current proposals, modification and refinements of the roadmap concept is anticipated.

Conclusions

The expert panel agreed that the natural history of chronic hepatitis B is determined in large part by the level of HBV replication, as reflected in circulating levels of HBV DNA. Profound and sustained inhibition of viral replication is therefore the most important goal of treatment and if achieved will reduce the likelihood of subsequent disease progression and emergence of viral resistance.

In summary, early monitoring of the virologic response to therapy in chronic hepatitis B treated with oral nucleos(t)ides is essential to identify primary treatment failure at week 12 and suboptimal responses at week 24 to modify management accordingly. Prospective testing of this strategy is necessary. If its use can be confirmed, this roadmap should be increasingly helpful as further potent antiviral therapies with superior viral suppressive abilities and high genetic barriers to resistance are developed. The use of this roadmap should permit improved individualized on-treatment management designed to enhance long-term patient outcomes.

References

1. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73.
2. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on level of circulating hepatitis B viral load. *Gastroenterology* 2006; 130:678-686.
3. Chen G, Lin W, Shen F, et al. Past HBV viral load as a predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006;101:1797-1803.
4. Liaw YF. Hepatitis B virus replication and liver disease progression: the impact of antiviral therapy. *Antivir Ther* 2006;11:669-679.
5. Yuen MF, Yuan HJ, Wong DK, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005; 54:1610-1614.
6. Yuan HJ, Yuen MF, Wong DK, et al. The relationship between HBV-DNA levels and cirrhosis-related complications in Chinese with chronic hepatitis B. *J Viral Hepat* 2005;12:373-379.

7. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–117.
8. Lok ASF, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714–1722.
9. Fung SK, Andreone P, Han SH, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. *J Hepatol* 2005;43:937–943.
10. Locarnini S, Hatzakis A, Heathcote J, et al. Management of antiviral resistance in patients with chronic hepatitis B. *Antiviral Ther* 2004;9:679–693.
11. Keeffe E, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol* 2006;4:936–962.
12. Lok ASF, McMahon BJ. AASLD practice guidelines. Chronic hepatitis B. *Hepatology* 2007;45:507–539.
13. EASL Jury. EASL international consensus conference on hepatitis B. 13–14 September, 2002: Geneva, Switzerland. Consensus statement (long version). *J Hepatol* 2003;39:S3–S25.
14. Liaw YF, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. *Liver Int* 2005;25:472–489.
15. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22,707 men in Taiwan. *Lancet* 1981;2:1129–1133.
16. Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. *Hepatology* 1986;6:167–172.
17. Hoofnagle J, Shafritz D, Popper H. Chronic type B hepatitis and the “healthy” HBsAg carrier state. *Hepatology* 1987;7:758–763.
18. McMahon BJ, Holck P, Bulkow L, et al. Serologic and clinical outcomes of 1536 Alaska natives chronically infected with hepatitis B virus. *Ann Intern Med* 2001;135:759–768.
19. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168–174.
20. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of interferon therapy in HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422–1427.
21. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol* 2001;34:306–313.
22. Lin SM, Yu ML, Lee CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol* 2007;46:45–52.
23. van Zonneveld M, Honkoop P, Hansen BE, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004;39:804–810.
24. Di Marco V, Marzano A, Lampertico P, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virologic response to lamivudine. *Hepatology* 2004;40:883–891.
25. Papatheodoridis GV, Dimou E, Dimakopoulos F, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology* 2005;42:121–129.
26. Schiff ER, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-transplantation patients. *Hepatology* 2003;38:1419–1427.
27. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–1531.
28. Yuen MF, Seto W, Chow D, et al. Long-term beneficial outcome of Chinese asymptomatic patients with HBeAg-positive chronic hepatitis B on continuous lamivudine therapy: 7-year experience (abstr). *Hepatology* 2005;42:583A.
29. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1–9.
30. Heijttink RA, Kruining J, Honkoop P, et al. Serum HBeAg quantitation during antiviral therapy for chronic hepatitis B. *J Med Virol* 1997;53:282–287.
31. Park NH, Shin SH, Park JH, et al. Monitoring of HBeAg levels may help to predict the outcomes of lamivudine therapy for HBeAg positive chronic hepatitis B. *J Viral Hepat* 2005;12:216–221.
32. Gauthier J, Bourne EJ, Lutz MW, et al. Quantitation of hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. *J Infect Dis* 1999;180:1757–1762.
33. Mommeja-Marin H, Mondou E, Blum MR, et al. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003;37:1309–1319.
34. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673–2681.
35. Farci P, Marcellin P, Lu ZM, et al. On-treatment predictors of sustained biochemical and virological response in patients with HBeAg-negative chronic hepatitis B (CHB) treated with peginterferon alfa-2a (40KD)(Pegasys) (abstr). *J Hepatol* 2005;42(Suppl 2):175.
36. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med* 2006;355:2444–2451.
37. ter Borg MJ, van Zonneveld M, Zeuzem S, et al. Patterns of viral decline during peg-interferon alpha-2b therapy in HBeAg-positive chronic hepatitis B: relation to treatment response. *Hepatology* 2006;44:721–727.
38. Yuen MF, Sablon E, Hui CK, et al. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology* 2001;34:785–791.
39. Zollner B, Schafer P, Feucht HH, et al. Correlation of hepatitis B virus load with loss of e antigen and emerging drug-resistant variants during lamivudine therapy. *J Med Virol* 2001;65:659–663.
40. Lai CL, Leung N, Teo EK, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* 2005;129:528–536.
41. Gane E, Lai CL, Liaw YF, et al. Phase III comparison of telbivudine vs lamivudine in HBeAg-positive patients with chronic hepatitis B: efficacy, safety, and predictors of response at 1 year (abstr). *J Hepatol* 2006;44(Suppl 2):S183–S184.
42. Zeuzem S, Lai CL, Gane E, et al. Optimal virologic and clinical efficacy at one year is associated with maximal early HBV suppression in nucleoside-treated hepatitis B patients (abstr). *J Hepatol* 2006;44(Suppl 2):S24.
43. DiBisceglie A, Lai CL, Gane E, et al. Telbivudine GLOBE trial: maximal early HBV suppression is predictive of optimal two-year efficacy in nucleoside-treated hepatitis B (abstr). *Hepatology* 2006;44(Suppl 1):230A–231A.
44. Bzowej N, Chan H, Lai CL, et al. A randomized trial of telbivudine (LdT) vs. adefovir for HBeAg-positive chronic hepatitis B: final week 52 results (abstr). *Hepatology* 2006;44(Suppl 1):563A.
45. Locarnini S, Qi X, Arterburn S, et al. Incidence and predictors of emergence of adefovir resistant HBV during 4 years of adefovir dipivoxil (ADV) therapy for patients with chronic hepatitis B (CHB) (abstr). *J Hepatol* 2005;42(Suppl 2):17.
46. Hadziyannis S, Tassopoulos N, Chang T, et al. Long-term adefovir dipivoxil treatment induces regression of liver fibrosis in patients with HBeAg-negative chronic hepatitis B: results after 5 years of therapy (abstr). *Hepatology* 2005;42(Suppl 1):754A.

47. Hepsera (adefovir dipivoxil), package insert. Foster City, CA: Gilead Sciences, Inc., 2006.
48. Colonna RR, Levine S, Baldick J, et al. Entecavir two year resistance update: no resistance observed in nucleoside naive patients and low frequency resistance emergence in lamivudine refractory patients (abstr). *Hepatology* 2005;42(Suppl 1):573A.

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Supported by an unrestricted educational grant from Idenix Pharmaceuticals and Novartis to Axioned, Inc., who coordinated the workshop meeting. E.B.K. is a consultant to and member of the speakers' bureau for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Novartis, and Roche, and receives grant support from Roche and Romark. S.Z. is a consultant, member of the speakers' bureau, and/or a clinical investigator for Gilead, GlaxoSmithKline, Idenix, Novartis, Roche, and Schering-Plough. R.S.K. is a consultant to Idenix and Roche and a member of the speakers' bureau for Roche and Bristol-Myers Squibb. D.T.D. is a consultant, member of the speakers' bureau, and receives grant support from Bristol-Myers Squibb, Idenix, Gilead, and Roche. R.E.-M. is a consultant and member of the speakers' bureau for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Novartis, Schering-Plough, and Vertex. E.J.G. is a consultant on advisory boards for GlaxoSmithKline, Idenix, and

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