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SUPPLEMENT ARTICLE

On-treatment monitoring of HBV DNA levels: predicting response and resistance to oral antiviral therapy at week 24 versus week 48

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Abstract The suppression of hepatitis B viral (HBV) load correlates with favorable histologic, biochemical, and serologic responses in clinical trials of patients with chronic hepatitis B (CHB). The ability to identify patients who will not experience durable viral suppression in response to a specific antiviral regimen affords the opportunity for early treatment modification to optimize outcomes and avoid the development of antiviral resistance. Substantial evidence demonstrates that on-treatment serum HBV DNA levels are predictive of virologic response and risk of resistance. Regional clinical practice guidelines for the management of CHB universally recommend monitoring serum HBV DNA levels at treatment week 24. However, the value of this time point as a predictor of long-term success may not be applicable to all types of antiviral therapy. Indeed, each oral nucleos(t)ide analog (NA) antiviral therapy has a unique profile of potency, genetic barriers to resistance, and viral kinetics that may affect the optimal time point for on-treatment monitoring. This review discusses available data for appropriate predictors for long-term response and antiviral resistance for patients receiving specific oral NA antiviral therapy. Guidelines for on-treatment monitoring are also discussed.

Keywords Antiviral therapy · Chronic hepatitis B · Treatment monitoring

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Introduction

Over the past decade, an increased understanding of the cellular and molecular pathophysiology, natural history, and the risk of developing antiviral resistance to oral nucleos(t)ide analog (NA) antiviral therapy has led to efforts to optimize treatment paradigms for patients with chronic hepatitis B (CHB). Profound and sustained suppression of hepatitis B virus (HBV) replication to below the level of detectability is a critical factor in achieving the primary goal of treatment: the prevention of progression to cirrhosis, hepatic decompensation, and hepatocellular carcinoma [1–3]. Several effective oral NA agents are now available that induce profound suppression of serum HBV DNA levels. However, clinical experience has shown that long-term NA therapy is required to achieve treatment goals and is often hindered by the emergence of viral resistance [4]. The development of highly sensitive polymerase chain reaction-based assays for the quantification of serum HBV DNA has facilitated the investigation of the relationship between early virologic response to oral NA therapy and treatment outcomes. Early virologic response to oral NA therapy has been shown to correlate with favorable outcomes to therapy [5–16]. More specifically, substantial evidence has established that serum HBV DNA levels at week 24 or 48 of treatment are predictive of sustained virologic response, normalization of alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) seroconversion, and the risk of developing antiviral resistance [5–16]. On the basis of these findings, the "roadmap" treatment strategy was developed, advocating the monitoring of serum HBV DNA levels at weeks 12 and 24 of treatment to identify primary nonresponse and partial virologic response, respectively, and to modify treatment accordingly [17]. More recently, this strategy has been

incorporated into regional clinical treatment guideline recommendations [1–3]. Despite these recommendations, the universal applicability of week 24 as the optimal time point for evaluating treatment response to all oral NAs remains unclear, particularly for agents with low genetic barriers to resistance [18–20].

This article reviews the available clinical data regarding the on-treatment monitoring of HBV DNA levels as a predictor of sustained virologic response in patients receiving oral NA therapies, as well as the application of monitoring HBV DNA levels as a means of improving response to antiviral therapy. The impact of the use of specific NAs with differing potencies and viral kinetics on on-treatment monitoring protocols is discussed.

On-treatment HBV DNA levels as predictors of response and resistance

A better understanding of early viral kinetics during pegylated interferon and ribavirin therapy and on-treatment monitoring of predictors of response have been shown to be important tools in optimizing the management of hepatitis C [21, 22]. Similarly, the identification of on-treatment predictors of response and resistance to oral NA therapy has gained considerable interest as a means of optimizing treatment regimens and therapeutic outcomes [23–25]. Substantial data regarding on-treatment predictors of response and resistance to lamivudine, adefovir, and telbivudine in patients with CHB have been reported in the literature [5–7, 10–14]. Limited data on predictors of response for entecavir and tenofovir have been published [9, 16].

Nucleoside analogs

Lamivudine

Lamivudine is a nucleoside reverse transcriptase inhibitor used for the treatment of patients with the human immunodeficiency virus (HIV) and CHB infection. Resistance to lamivudine is conferred by single-site mutation (M204V/I) in the C domain of the HBV DNA polymerase. Several studies have demonstrated that on-treatment serum HBV DNA levels are predictive of resistance to lamivudine [5, 11, 13, 26, 27]. In a 2001 study of 159 patients with HBeAg-positive CHB, who were treated with lamivudine and evaluated for a median period of 30 months, those with HBV DNA levels of more than 10^3 copies/ml at week 24 had a 63% chance of developing the YMDD mutation whereas those with HBV DNA levels of 10^3 copies/ml or less had only a 13% chance of developing the mutation [13]. Another study, involving 139 HBeAg-negative patients treated with lamivudine for 2 years, demonstrated that serum HBV DNA levels at treatment week 24 were predictive of the likelihood for resistance to lamivudine at 2 years [26]. A correlation was observed between the 2-year lamivudine resistance rates and serum HBV DNA levels at week 24. The 2-year resistance rates were 1%, 46%, and 67% in patients with week 24 HBV DNA levels of less than 10^2 copies/ml, 10^2–10^3copies/ml, and more than 10^4 copies/ml, respectively. Similar findings were reported in a randomized, double-blind, multicenter trial comparing telbivudine monotherapy, telbivudine plus lamivudine, and lamivudine monotherapy in HBeAg-positive patients [28]. Data from the pooled analysis of the telbivudine- and lamivudine-treated patients showed that undetectable serum HBV DNA levels at treatment week 24 were associated with a lower rate of virologic breakthrough than serum HBV DNA levels of more than 3–4 $\log_{10}$ copies/ml at week 24 ($P < 0.05$). These findings were subsequently confirmed in the randomized phase III GLOBE trial comparing telbivudine and lamivudine in 1,367 HBeAg-positive and HBeAg-negative patients with CHB [5, 6]. Resistance rates at 1 year of lamivudine treatment were lowest among those patients who had undetectable serum HBV DNA levels at week 24 of treatment (Fig. 1) [5]. More recently, Thompson et al. [27] prospectively studied 85 patients with CHB who were treated with lamivudine and reported resistance rates of 6%, 31%, and 51% at 12, 24, and 48 months, respectively. Multivariate analysis identified the precore variant, high baseline ALT levels, and persistent viremia at 24 weeks as independent predictors of early lamivudine resistance, with rate ratios of 4.93 (95% confidence interval [CI] = 1.32–18.5), 1.22 (95% CI = 1.08–1.49), and 4.73 (95% CI = 1.49–15.00), respectively ($P < 0.05$).

On-treatment serum HBV DNA levels have also been shown to be predictive of long-term virologic outcomes with lamivudine [11, 12, 14, 28, 29]. Early studies of lamivudine found that only patients with undetectable serum HBV DNA levels by week 24 of treatment achieved loss of HBeAg and HBeAg seroconversion [11, 12]. Pooled analyses of data from a phase II study comparing lamivudine and telbivudine showed that undetectable serum HBV DNA levels at week 24 of treatment were associated with high rates of undetectable serum HBV DNA levels (100%), ALT normalization (90%), and HBeAg loss (43%) at week 52 compared with rates of 7%, 55%, and 7%, respectively, in patients with week 24 HBV DNA levels of more than 10^4 copies/ml [28].

Hadziyannis et al. [14] investigated the predictive value of on-treatment serum HBV DNA levels in a study involving 156 HBeAg-negative patients who received prolonged lamivudine treatment. In this analysis, undetectable

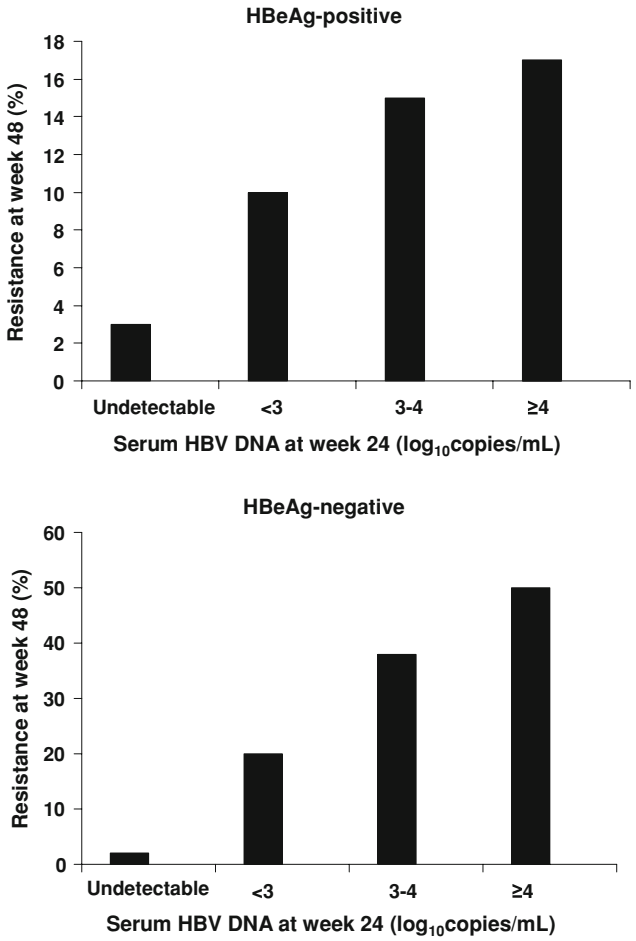

Fig. 1 The effect of early viral suppression on resistance to lamivudine at 1 year in patients with hepatitis B e antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B. Reprinted with permission from Lai et al. [5]

HBV DNA levels at 12 and 24 weeks of lamivudine treatment had a 93% and 72% predictive value for maintained response at 2 and more than 4 years, respectively. On-treatment serum HBV DNA levels as early as week 4 of lamivudine treatment were predictive of long-term outcomes at 5 years in patients with HBeAg-positive CHB [29]. In this study, serum HBV DNA levels were assessed at baseline, weeks 2, 4, 8, 12, 16, 24, and 32, and at yearly intervals until year 5 in 74 HBeAg-positive patients with chronic HBV infection. All the patients with serum HBV DNA levels of less than 2,000 IU/ml at week 4 of lamivudine treatment had an ideal response at 5 years, including HBeAg seroconversion, ALT normalization, and serum HBV DNA levels of less than 400 IU/ml and no lamivudine resistance mutations. In contrast, 83.8% of patients who had serum HBV DNA levels of more than 2,000 IU/ml by treatment week 4 did not achieve long-term ideal response [29]. Although serum HBV DNA levels at week 24 were also predictive of outcomes at 5 years, the emergence of mutations conferring resistance to lamivudine and adefovir was detected by week 24.

Entecavir

Entecavir is a nucleoside analog that demonstrates potent antiviral activity and low rate (1.2–1.7%) of resistance in nucleoside-naive patients at 6 years of treatment [30–33]. In contrast to lamivudine, multiple mutations in the HBV polymerase gene are required to confer resistance to entecavir, contributing to the high genetic barrier of this agent [32]. Continuous treatment with entecavir for up to 6 years is associated with an increasing proportion of patients achieving undetectable serum HBV DNA levels and/or HBeAg seroconversion without a concomitant increase in resistance rate [30, 34, 35]. Thus, limited data are available regarding the predictive value of week 24 serum HBV DNA levels on resistance and virologic response because of the low probability of developing resistance at this time point. The relationship between week 24 serum HBV DNA levels and therapeutic response at week 48 in entecavir-treated patients with CHB has been reported recently [9, 36]. Ma et al. [36] investigated the predictive value of week 24 serum HBV DNA levels on week 48 virologic response in 33 lamivudine-refractory patients treated with entecavir 1.0 mg/day for 48 weeks. Patients who had undetectable HBV DNA levels at week 24 were more likely to have undetectable HBV DNA levels, ALT normalization, and lower rates of viral breakthrough at week 48. In a retrospective analysis involving 109 treatment-naive patients treated with entecavir 0.5 mg/day, ALT levels at baseline and undetectable serum HBV DNA levels at week 24 of treatment were found to be predictive of undetectable HBV DNA levels and ALT normalization at week 48 [9]. In a large, randomized, double-blind, multinational, phase III trial designed to characterize the efficacy of entecavir in HBeAg-positive patients, week 24 serum HBV DNA levels were associated with outcomes at 52 weeks of treatment [8]. Specifically, a higher proportion of patients with HBV DNA levels of less than 10^3 copies/ml, compared with patients whose HBV DNA levels were more than 300 copies/ml at 24 weeks of entecavir treatment, had undetectable serum HBV DNA levels (96% vs. 50%) and underwent HBeAg seroconversion (30% vs. 17%) at week 52 [8].

Telbivudine

Telbivudine is an L-nucleoside with potent and specific anti-HBV activity that demonstrates an intermediate resistance profile compared with other oral NAs. As with lamivudine, resistance is conferred by a single-site substitution (M204I) in the HBV DNA polymerase gene. In a

phase III lamivudine-controlled registration trial of telbivudine in patients with CHB, resistance rates of 5.0% and 2.2% have been reported in intent-to-treat HBeAg-positive and HBeAg-negative individuals, respectively, after 1 year of telbivudine therapy [5]. At 2 years, resistance rates of 25.8% and 10.8% have been reported with telbivudine in HBeAg-positive and HBeAg-negative patients [6]. However, the resistance potential is mitigated in patients who achieve undetectable serum HBV DNA levels at week 24 of treatment. Lower rates of resistance at 1 year (1% HBeAg positive and 0% HBeAg negative) and 2 years (4% HBeAg positive and 2% HBeAg negative) of telbivudine therapy were observed among patients who achieved undetectable serum HBV DNA levels at treatment week 24 [5, 6].

The utility of on-treatment monitoring in patients undergoing treatment with telbivudine has been well characterized in the GLOBE study, a 2-year, multinational, randomized, phase III trial that compared telbivudine 600 mg/day with lamivudine 100 mg/day in 1,367 patients with CHB. In this study, HBV DNA levels at week 24 were the best predictor of clinical and virologic efficacy responses at week 52, irrespective of HBeAg serostatus [5]. HBeAg-positive patients with undetectable HBV DNA levels at week 24 had higher rates of undetectable HBV DNA levels (90% vs. 54%) and HBeAg seroconversion (41% vs. 4%) at week 52 than patients with week 24 serum HBV DNA levels of more than 10^4 copies/ml. Similarly, HBeAg-negative patients with undetectable HBV DNA levels at week 24 had higher rates of undetectable HBV DNA levels (83% vs. 36%) at week 52 than those with week 24 serum HBV DNA levels of more than 10^4 copies/ml. Two-year data from this trial showed a similar relationship between viral suppression at week 24 and virologic outcomes at week 104 (Fig. 2), [6]. A separate multivariate analysis of pretreatment and early on-treatment factors identified undetectable serum HBV DNA levels at treatment week 24 as the strongest predictor for optimal outcomes at 2 years in telbivudine-treated patients [7].

More recently, undetectable serum HBV DNA levels at week 24 were shown to be predictive of optimal outcomes in patients treated with telbivudine for up to 3 years [37]. Among the 293 HBeAg-positive patients who received continuous telbivudine treatment, higher rates of undetectable serum HBV DNA levels (87% vs. 59%), ALT normalization (86% vs. 79%), and cumulative seroconversion (65% vs. 40%) were achieved at 3 years in patients who had undetectable HBV DNA levels at week 24 than in the overall patient population. Similarly, higher rates of undetectable serum HBV DNA levels (87% vs. 71%) and ALT normalization (86% vs. 77%) were observed at 3 years in HBeAg-negative patients who had undetectable HBV DNA levels at week 24 than in the overall patient population.

Nucleotide analogs

Adefovir dipivoxil

Adefovir dipivoxil is an oral nucleotide analog that demonstrates durable suppression of HBV replication, particularly in the setting of lamivudine-resistant CHB. Although adefovir effectively suppresses HBV replication, it has a slower suppressive effect on HBV replication and has been shown to be less potent than other oral NAs in randomized clinical trials [38–40]. Locarnini et al. [41] investigated the

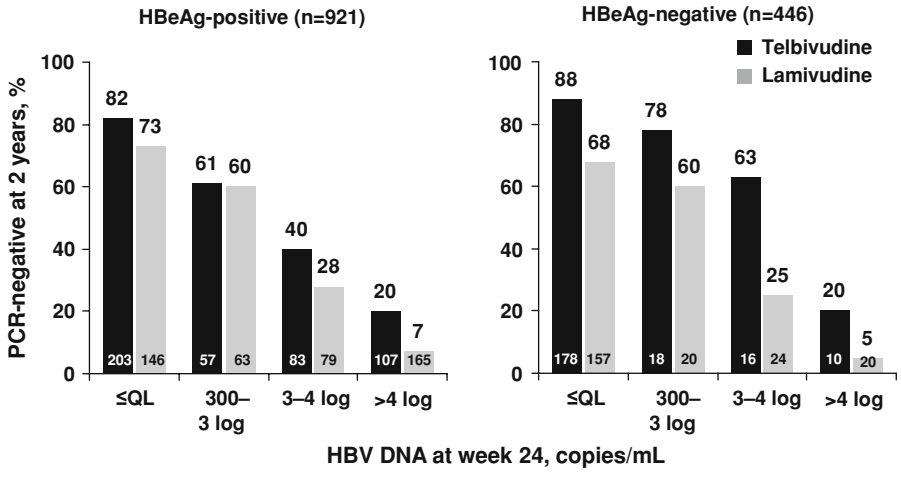

Fig. 2 HBV DNA suppression at 2 years compared with antiviral effect at week 24 in patients receiving telbivudine or lamivudine. Reprinted with permission from Liaw et al. [6]

rate of adefovir resistance and factors associated with adefovir resistance in a pooled analysis of more than 1,000 patients who received adefovir treatment with or without lamivudine for 48–192 weeks. Resistance rates of 4%, 26%, and 67% were observed in patients who had serum HBV DNA levels of more than 10^3 copies/ml, 10^3–10^6 copies/ml, and more than 10^6 copies/ml, respectively, at week 48 of adefovir treatment. Logistic regression analysis of baseline HBV DNA and ALT levels, race, age, gender, body mass index, liver histology, prior HBV therapy, and treatment week 4, 12, and 48 serum HBV DNA levels identified only serum HBV DNA level at week 48 as a predictor of adefovir resistance. Hadziyannis et al. [42] investigated the efficacy, safety, and resistance profile of adefovir dipivoxil treatment for up to 240 weeks in 125 patients with CHB. In a stepwise logistic regression analysis that included demographics, genotype, and baseline fibrosis, only detectable serum HBV DNA level at week 48 was a significant predictor of resistance over 192 weeks ($P = 0.0003$). Seventeen (49%) out of the 35 patients with serum HBV DNA levels of 3 log copies/ml or more after 48 weeks of adefovir therapy developed adefovir resistance at 192 weeks of treatment compared with only 5 (6%) out of the 89 patients with serum HBV DNA levels of less than 3 log copies/ml at 48 weeks [42].

More recently, several studies have shown that serum HBV DNA levels at 24 weeks of adefovir are predictive of favorable outcomes in patients with CHB receiving adefovir [10, 15, 40]. In an adefovir-controlled, randomized, open-label trial of telbivudine involving 135 treatment-naive, HBeAg-positive adults with CHB, undetectable serum HBV DNA levels at week 24 were associated with high rates of virologic response at week 52 [40]. Specifically, a higher proportion of patients with undetectable HBV DNA levels at 24 weeks had undetectable serum HBV DNA levels (90% vs. 25%), ALT normalization (90% vs. 83%), and HBeAg seroconversion (50% vs. 9%) at week 52 than the proportion of patients who had detectable HBV DNA levels at week 24 of adefovir treatment. In addition, Pritchett et al. [15] reported that lamivudine-resistant patients who had a more than 50% reduction in serum HBV DNA levels at week 24 of adefovir treatment were more likely to have undetectable serum HBV DNA levels at 1 year. In a single-center cohort study involving 76 patients with CHB treated with long-term adefovir monotherapy, serum HBV DNA levels at week 24 demonstrated a higher predictive value for virologic response at week 122 than serum HBV DNA levels at week 48 [10]. Of note, patients without undetectable serum HBV DNA levels at week 24 demonstrated a trend toward the emergence of adefovir resistance ($P = 0.07$). The findings from these studies appear to indicate that virologic response to adefovir therapy can be assessed at 24 weeks instead of the generally recommended 48 weeks.

Tenofovir

Tenofovir, an acyclic NA with a molecular structure similar to that of adefovir, is approved for the treatment of patients with HIV infection and CHB. No resistance to tenofovir has been reported in patients with HBeAg-positive and HBeAg-negative CHB at 1 and 2 years of treatment [38, 43–45]. Consequently, no predictors of tenofovir resistance have been identified to date. However, the value of on-treatment serum HBV DNA levels in predicting virologic response to tenofovir has been reported [43, 44]. In the adefovir-controlled phase III trial of tenofovir in treatment-naive HBeAg-positive and HBeAg-negative patients, the majority of tenofovir-treated patients with an incomplete response (HBV DNA levels >400 copies/ml) at week 24 subsequently had a complete response at weeks 48 and 72, suggesting that week 24 response is not a robust predictor of virologic response to tenofovir [43, 44].

On-treatment HBV DNA monitoring strategies

Clinical experience to date confirms that on-treatment serum HBV DNA levels are an important tool for predicting the risk of developing resistance and therapeutic outcomes in patients with CHB. Several strategies for the on-treatment monitoring of oral NA therapy have emerged in an effort to reduce the emergence of antiviral resistance and improve therapeutic outcomes. Some groups have proposed practical recommendations based on experimental data. For example, in the pooled analysis of predictors of response to lamivudine therapy discussed above, Yuen et al. [29] noted that HBV DNA levels at 4 and 16 weeks were the best indictors of ideal response at 5 years. On the basis of these data, the investigators recommended a continuation of lamivudine therapy in patients who achieve HBV DNA levels of less than 4 log copies/ml (<2,000 IU/ml) at week 4. For those who do not achieve this level, the authors advise that therapy be modified. Alternatively, one can allow a later second HBV DNA measurement to be made at week 16 because their data suggested that this does not increase the probability of developing drug resistance.

On the basis of the available evidence supporting the predictive value of on-treatment serum HBV DNA levels, a "roadmap" algorithm of practical guidelines that recommended quantitative HBV DNA monitoring at weeks 12 and 24, during which decisions may be made for optimizing therapeutic outcomes, has been proposed (Fig. 3) [17]. This strategy involves measuring HBV DNA levels at week 12 to determine *primary treatment failure* (defined as

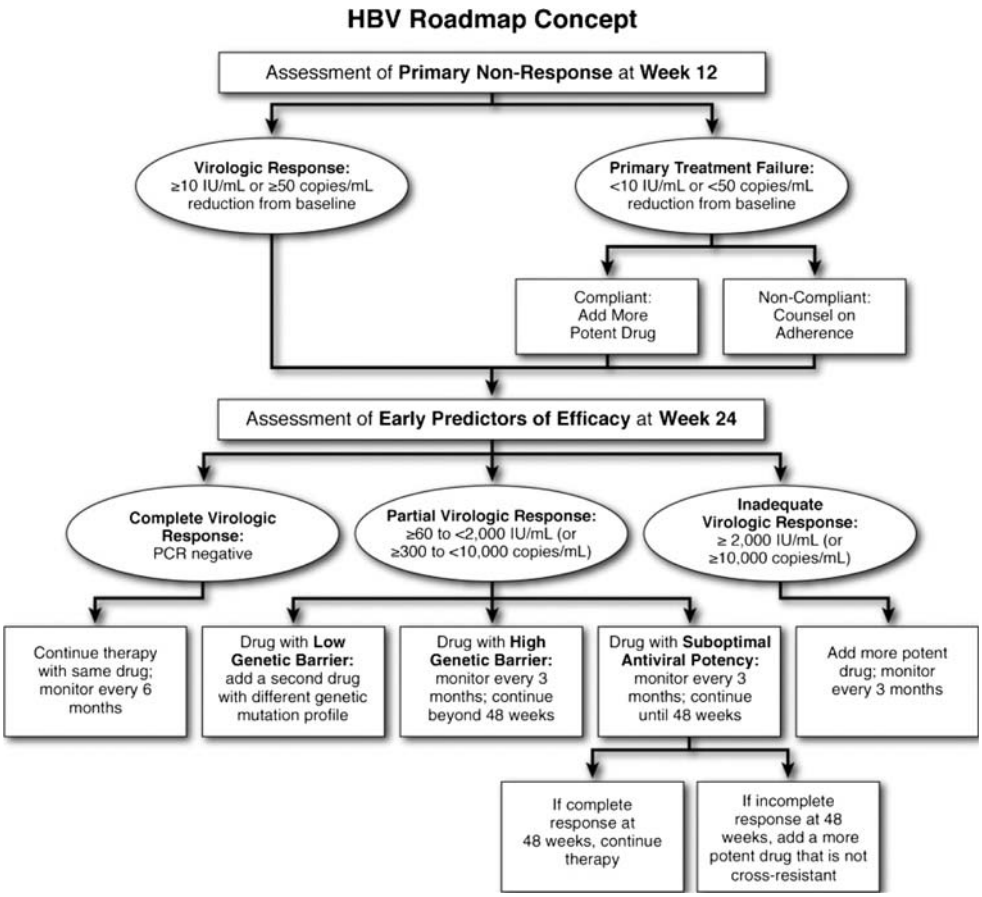

Fig. 3 HBV treatment roadmap: on-virologic responses and their management in patients receiving oral therapy for chronic hepatitis B. *Abbreviation*: PCR, polymerase chain reaction. Reprinted with permission from Keeffe et al. [17]

a decline in HBV DNA levels of <1 $\log_{10}$ IU/ml), and again at treatment week 24 to determine whether adjustment to therapy is required. Virologic response at treatment week 24 is categorized using the following definitions: complete (HBV DNA level <60 IU/ml), partial (HBV DNA level 60 to <2,000 IU/ml), and inadequate (HBV DNA level ≥2,000 IU/ml).

For patients with a complete virologic response, continued therapy with the same drug is recommended, with repeat testing at 24-week intervals at the physician's discretion. The addition of an appropriate non-cross-resistant second drug should be considered to prevent the emergence of resistance and viral breakthrough in patients with a partial response who are treated with a drug with a low genetic barrier to resistance (e.g., lamivudine). In contrast, patients who demonstrate a partial response while receiving treatment with a potent drug with a high genetic barrier (e.g., entecavir) should undergo repeated monitoring at 12-week intervals to be continued beyond 48 weeks. In patients with a partial response who have been treated with a drug with a delayed antiviral effect and a relatively high barrier to resistance (e.g., adefovir), monitoring should be repeated at 12-week intervals. If the response remains partial or becomes inadequate at week 48, a change in therapy should be undertaken unless HBV DNA levels have been decreasing steadily and are nearly undetectable. If the response becomes complete at week 48, therapy can be continued. Finally, patients with an inadequate virologic response require a change to a more efficacious drug or the addition of a second drug, preferably one without cross-resistance to the continued drug. Once this change has been made, patients should undergo monitoring at 12-week intervals.

The "roadmap" algorithm of practical guidelines for HBV DNA monitoring is in alignment with on-treatment monitoring and treatment adjustment recommendations by regional liver society guidelines for the management of CHB [1–3]. Previous treatment guidelines have provided some limited discussion of on-treatment monitoring. The 2008 Asian Pacific Association for the Study of the Liver practice guidelines recommended that, during therapy, HBV DNA levels should be monitored at least every 12 weeks, regardless of the treatment modality used [1]. Similarly, the recently published 2008 European Association for the Study of the Liver guidelines recommended that serum HBV DNA levels should be assessed every 12 weeks in patients treated with an NA [3]. Finally, the 2007 American Association for the Study of Liver Diseases

practice guidelines recommended that patients receiving NA therapy should have their HBV DNA levels measured every 12–24 weeks [2]. Collectively, these guidelines published by the world's three largest liver societies concur that the first assessment point for on-treatment monitoring of HBV DNA levels should occur at week 12 after treatment initiation and continue every 12–24 weeks thereafter.

Conclusion

Durable HBV DNA suppression is a critical determinant of treatment outcome, and evidence from clinical studies of CHB shows that on-treatment HBV DNA levels can predict response to oral antiviral therapy. Substantial evidence from clinical studies has validated 24 weeks as a useful time point for on-treatment monitoring for lamivudine, adefovir, entecavir, and telbivudine. The optimal time for on-treatment monitoring of tenofovir remains to be determined. Based on clinical evidence, regional liver society guidelines recommend that on-treatment monitoring of HBV DN levels should occur at week 12 to assess compliance and every 12–24 weeks thereafter to ascertain virologic response to treatment. Additional studies are needed to investigate the value of earlier time points in predicting successful outcomes.

Ultimately, optimal time points for on-treatment monitoring are dependent on the unique properties of each individual NA (e.g., potency, viral kinetics, genetic barrier/resistance profile), and further study will help refine recommendations for on-treatment monitoring based on these variables. Regardless, on-treatment monitoring represents a powerful tool to identify patients at risk of treatment failure and provides an opportunity for early treatment modification to improve outcomes and reduce the risk of antiviral resistance.

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