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REVIEW ARTICLE

Hepatitis B viral factors and treatment responses in chronic hepatitis B

Chih-Lin Lin [a,b], Jia-Horng Kao [c,d,e,f,*]

[a] Department of Gastroenterology, Ren-Ai Branch, Taipei City Hospital, Taipei, Taiwan
[b] Department of Psychology, National Chengchi University, Taipei, Taiwan
[c] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[d] Graduate Institute of Clinical Medicine, National Taiwan University, College of Medicine, Taipei, Taiwan
[e] Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan
[f] Department of Medical Research, National Taiwan University, College of Medicine, Taipei, Taiwan

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Baseline and on-treatment hepatitis B viral factors are reported to affect treatment responses. A lower baseline hepatitis B virus (HBV) DNA level is a strong predictor of the response to antiviral therapy. HBV genotype A/B patients have better responses to interferon-based therapy than those with genotypes C/D. Regarding the association of HBV mutants with responses to antiviral therapy, current evidence is limited. On-treatment viral suppression is the most important predictor of response to nucleoside analogs. On-treatment hepatitis B surface antigen decline is significantly associated with response to pegylated interferon. In the future, individualized therapy should be based on treatment efficacy, adverse effects, baseline and on-treatment predictors of antiviral therapy.
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Introduction

Hepatitis B virus (HBV) is an important public health problem and the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) worldwide. The long-term outcomes of chronic HBV infection vary widely. For example, the annual incidence rate of cirrhosis is estimated to be 2–6% for hepatitis B e antigen (HBeAg)-positive and 8–10% for HBeAg-negative patients. The lifetime risk of HBV carriers to develop cirrhosis, liver failure, or HCC may be as high as 15–40%.[1–3] Therefore, the development of effective antiviral agents to delay or even halt the progression from chronic hepatitis to cirrhosis and

* Corresponding author. Graduate Institute of Clinical Medicine, National Taiwan University, College of Medicine, 1, Chang-Te Street, Taipei 10002, Taiwan.
E-mail address: kaojh@ntu.edu.tw (J.-H. Kao).

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eventually HCC is urgently needed. According to the recommendations of the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver (EASL), and the Asian Pacific Association for the study of liver (APASL), the evaluation tests for the indications of HBV therapy include quantitative serum HBV DNA level, alanine aminotransferase (ALT) level and/or histological severity. The clinical assessment to monitor treatment responses entails sustained suppression of HBV replication, biochemical remission, histological improvement, HBeAg/hepatitis B surface antigen (HBsAg) loss or seroconversion for HBeAg-positive patients, and ideally HBsAg loss or seroconversion for HBeAg-negative patients.[4–6] Previous investigations into the molecular epidemiology of HBV and therapeutic development have led to significant advances in the treatment of chronic hepatitis B (CHB). In this article, hepatitis B viral factors influencing responses to anti-HBV therapy will be reviewed and discussed.

Therapeutic efficacy of current antiviral agents

At present, seven agents have been globally approved for the treatment of CHB, they are standard interferon (IFN)-α or polyethylene glycol (PEG)ylated IFN-α (PEG-IFN-α), with mainly immune modulatory effects, and five nucleos(t)ide analogs (NAs) with direct antiviral effects, including lamivudine (LAM), telbivudine (LdT), entecavir (ETV), adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF). Recent updates of AASLD, EASL, and APASL management guidelines recommended PEG-IFN-α, ETV and TDF as the preferred first-line agents.[4–6] Clinical effectiveness of these agents in treatment-naïve patients is summarized in Table 1.

Immunomodulatory agents

Standard IFN-α

The first approved antiviral agent for CHB, induces dual antiviral effects through the degradation of viral messenger RNA to inhibit protein synthesis and the enhancement of host natural killer as well as cytotoxic T cell activities.[7] The mechanisms of IFN-α response for HBeAg-positive and -negative patients are different. For HBeAg-positive patients, IFN-α induces an early reduction of HBV replication and a late (about 2 months later) increase in serum ALT levels. Thus, HBeAg seroconversion can be achieved, following a hepatitis flare-up, before or within 6 months of the end of IFN-α therapy.[8] However, HBeAg-negative CHB patients have replicating HBV DNA in the presence of anti-HBe immunity. In those patients, efficient control of HBV infection is achieved through sustained suppression of HBV replication.[9] A meta-analysis showed that standard IFN-α therapy can induce serum ALT normalization, loss of HBeAg, sustained suppression of serum HBV DNA as measured by non-polymerase chain reaction (PCR) assays and clearance of HBsAg by 25%, 25%, 23%, and 6%, respectively, in HBeAg-positive patients.[10] In HBeAg-negative patients treated with standard IFN-α, the combined persistent serum ALT normalization and suppression of serum HBV DNA as measured by non-PCR assays was achieved in 10—47% of patients.[11,12] However, viral relapse occurred in about half of initial responders after cessation of IFN treatment.[13]

PEG-IFN-α

With an attachment of inert PEG polymer to standard IFN, PEG-IFN-α shows a longer half-life than standard IFN-α.[14] In HBeAg-positive patients, 1 year of PEG-IFN α-2a and -2b

Table 1 Clinical efficacy of 1-year (48 weeks or 52 weeks) antiviral agent therapy in treatment-naïve CHB in a randomized controlled trial.

Efficacy	LAM	ADV	LdT	ETV	TDF	PEG-IFN-α
HBeAg-positive patients						
Log_{10}HBV DNA decline	5.54	3.5	6.45	6.9	6.4	4.5
HBV DNA undetectable (%)	36—40	13—21	60	67	76	14[a]
ALT normalization (%)	60—75	48—54	77	68	68	41[b]
Histologic improvement (%)	56—62	53—68	64.7	72	74	38[b]
HBeAg seroconversion (%)	18—21.5	12—18	22.5	21	21	32[b]
HBsAg seroconversion (%)	1	0	NA	2	3.2	3—5[b]
HBeAg-negative patients						
Log_{10}HBV DNA decline	4.5	3.9	5.2	5.0	4.7	4.1
HBV DNA undetectable (%)	72	51—63	88.3	90	93	19[a]
ALT normalization (%)	71—79.3	72—77	74.4	78	76	59[b]
Histologic improvement (%)	61—66	64—69	66.6	70	72	48[b]
HBsAg loss (%)	<1	0	<1	NA	0	4[b]

ADV = adefovir dipivoxil; ALT = alanine aminotransferase; CHB = chronic hepatitis B; ETV = entecavir; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; LAM = lamivudine; LdT = telbivudine; NA = not available; PEG-IFN-α = pegylated interferon-α; TDF = tenofovir disoproxil fumarate.

[a] Rates of suppression of HBV DNA to below 400 copies/mL at 24 weeks after 48 weeks of treatment.

[b] Efficacy was assessed at 24 weeks after 48 weeks of treatment.

monotherapy led to HBeAg seroconversion in 32% and 29% of patients at 6 months after therapy cessation, respectively. In addition, HBsAg seroconversion was achieved in 3—5% of patients at 6 months after therapy.[15,16] Regarding HBeAg-negative patients, a recent large multinational trial revealed that combined response with serum ALT normalization and <400 copies/mL of HBV DNA occurred in 15% of patients treated for 1 year with PEG-IFN α-2a, and HBsAg loss was reported in 4% at 6 months after therapy.[17] After 4 years of follow-up, 17% of HBeAg-negative patients had <400 copies/mL of HBV DNA as assessed by PCR assay. In addition, HBsAg seroclearance progressively increased to 11%.[18] The cumulating data suggest that PEG-IFN-α tends to be superior to standard IFN-α for the treatment of CHB, irrespective of HBeAg status.

Direct antiviral agents

LAM

As the first approved NA with intermediate antiviral potency, LAM is the most widely used anti-HBV agent worldwide. For HBeAg-positive patients, the HBeAg seroconversion rate was improved from 18% to 65% after 1—5 years of LAM therapy.[19—23] LAM therapy for 3 years also reduced necro-inflammatory activity and reversed bridging fibrosis in 57% and 65% of CHB patients, respectively.[24] For HBeAg negative patients, LAM achieved HBV DNA undetectability in as many as 75% of CHB patients after 1 year of therapy.[25—27] However, due to the low genetic barrier to the development of drug resistance, the incidence of LAM resistance with subsequent virological breakthrough accumulates with increasing duration of treatment, in 14%, 38%, 57%, 67%, and 70% of people after 1, 2, 3, 4, and 5 years, respectively.[19—22,28] Drug resistance to LAM sometimes induces marked flare of serum ALT level or acute exacerbation.[29] However, a recent meta-analysis showed that the risk of developing long-term complications including decompensated cirrhosis, liver-related death or HCC was substantially reduced in patients with long-term LAM therapy than those without [relative risk (RR): 0.26, 95% confidence interval (CI): 0.15—0.47]. Even in patients with LAM resistance, the incidence of long-term complications was also lower than those without treatment (RR: 0.55, 95% CI: 0.40—0.76).[30] In addition, Fasano et al recently reported that HBsAg clearance was observed in 11.7% of patients responding to 5-year LAM monotherapy (undetectable HBV DNA and without LAM-resistant mutations) who continued to receive LAM monotherapy.[31] Therefore, although the risk of LAM resistance-related hepatitis flare-up may limit the popular use of LAM, long-term LAM therapy still significantly achieves HBsAg clearance, improves survival of CHB patients, and reduces the risk of major complications compared with no antiviral treatment.[32]

ADV

As a second proved NA for the treatment of CHB, ADV results in sustained reductions of serum HBV DNA level and is associated with histological improvement in both HBeAg-positive and -negative patients. In HBeAg-positive patients, 21% of patients had undetectable serum HBV DNA after 48 weeks of ADV treatment. Rates of HBeAg loss and HBeAg seroconversion were 24% and 12%, respectively.[33] After 5 years of ADV treatment, rates of HBeAg loss and seroconversion increased to 58% and 48%, respectively.[34] In HBeAg-negative patients, 51% of patients had undetectable serum HBV DNA after 48 weeks of ADV treatment.[35] After 5 years of ADV treatment, 67% of patients had serum HBV DNA levels of <1000 copies/mL.[36]

Compared with the low genetic barrier of LAM, ADV has an intermediate genetic barrier to the development of drug resistance. For treatment-naïve CHB patients, no ADV-associated resistant mutation was identified after 1 year of treatment, regardless of HBeAg status.[33,35] However, the 5-year cumulative probability of ADV resistance was 20% and 29% for HBeAg-positive and HBeAg-negative patients, respectively.[34,36] Regarding the profile of adverse effects, renal toxicity with an increase in serum creatinine level of >0.5 mg/dL from baseline was observed in 8% of patients treated with 5-year ADV.[34]

LdT

LdT is a potent anti-HBV agent with no fetal toxic effects in preclinical studies.[37] Patients treated with LdT, including HBeAg-positive and -negative patients, had a significantly greater reduction of serum HBV DNA level than those treated with LAM.[27] Among HBeAg-positive patients, HBeAg seroconversion was reached in 22.5% and 29.6% of patients after 1 and 2 years of LdT therapy, respectively.[27,38] Of particular note, 57% of HBeAg-positive patients who maintained undetectable serum HBV DNA during 3-year LdT treatment could achieve HBeAg seroconversion, and 6% of them lost serum HBsAg at the end of 3-year LdT therapy.[39]

Nevertheless, like LAM, virological response rates decrease over time due to the emergence of drug resistance to LdT. The frequency of LdT resistance increased from 5.0% and 2.3% at 1 year to 25% and 11% at 2 years in HBeAg-positive and HBeAg-negative patients, respectively.[27,38] In addition, LdT-resistant mutations have cross-resistance with LAM,[40] thus LdT is limited for the treatment of patients with proven LAM resistance.

ETV

ETV is a highly potent nucleoside inhibitor of HBV polymerase with a high genetic barrier to drug resistance.[41,42] For treatment-naïve HBeAg-positive patients, cumulative rates of HBV suppression increased from 67% to 94% at 1 and 5 years of ETV treatment, respectively.[43,44] HBeAg seroconversion occurred in 21% and 31% of patients at 1 and 2 years of ETV therapy, respectively.[43,45] Of note, HBsAg loss was confirmed in 5.1% HBeAg-positive patients after 2 years of treatment.[46] Similarly, 90% of HBeAg-negative patients had undetectable serum HBV DNA after 48 weeks of ETV treatment.[26] In particular, histological evaluation after long-term treatment with ETV (median time of biopsy: 6 years, range: 3—7 years) showed necro-inflammatory and

fibrosis score improvement in 96% and 88% of patients, respectively.[47]

In addition to a high potency of viral suppression, the high barrier to drug resistance leads to a sustained virological response from ETV therapy. Among nucleoside-naïve patients treated with ETV, 7% of patients had viremia (≥300 copies/mL of HBV DNA) in year 5. However, the 5-year cumulative probability of genotypic resistance and genotypic resistance-associated virologic breakthrough was only 1.2% and 0.8%.[48] However, the genetic barrier to drug resistance was substantially reduced and the rate of genotypic resistance was 51% of patients with prior LAM resistance at 5-year ETV treatment.[48]

TDF

TDF is the latest licensed agent for the treatment of chronic HBV infection. The therapeutic effect remained durable at 5 years of TDF treatment, 83% of HBeAg-negative and 65% of HBeAg-positive patients had HBV DNA undetectability. Overall histologic improvement occurred in 85% of patients, including 75% of patients with cirrhosis at entry who had regression of histologic cirrhosis at 5 years.[49] The virological breakthrough and persistent viremia on TDF monotherapy were infrequent over 3 years (3% and 0.8%, respectively). However, neither of them were associated with virological resistance to TDF.[50] Furthermore, no NA-naïve patients developed amino acid substitutions associated with drug resistance to TDF during 5 years of treatment.[49] By using systematic review and meta-analyses, Woo et al reported that for HBeAg-positive patients, TDF was most effective in inducing undetectable serum HBV DNA, ALT normalization, HBeAg seroconversion, and HBsAg loss with the predicted probability of 88%, 66%, 20%, and 5%, respectively. Additionally, for HBeAg-negative patients, TDF was most effective in inducing undetectable serum HBV DNA and improving liver histology with the predicted probability of 94% and 65%, respectively.[51]

Combination of NAs with low genetic barrier

The major limitation of long-term NA therapy is the development of drug resistance. For patients with drug resistance to LAM and LdT, both are L-NAs with low genetic barrier, the optimal treatment includes add-on TDF or shift to TDF. The alternative treatment is add-on ADV.[52] Several studies further supported that add-on ADV to LAM in patients with LAM-resistance could result in effective HBV suppression and induce maintained biochemical remission with rare emergence of ADV-resistance as compared with switching to ADV monotherapy.[53–56] A recent meta-analysis revealed that ADV in combination with LAM as a salvage therapy for patients with LAM-resistance had lower emergence rates of ADV-resistant HBV strains than ADV monotherapy (RR: 0.15, 95% CI: 0.03–0.74, $p = 0.02$). In addition, compared with ADV monotherapy, ADV plus LAM had greater virological response rates (RR: 1.28, 95% CI: 1.10–1.49, $p = 0.002$) as well as biochemical response rates (RR: 1.18, 95% CI: 1.04–1.35, $p = 0.01$).[52]

Factors influencing the response to antiviral therapy

The mechanisms of antiviral activity have led to different characteristics and suitability of patients for each type of antiviral agent. Therefore, it is necessary to find out the predictors of each medicine to improve its clinical outcomes and tailor individualization of treatment. Currently, several hepatitis B viral factors, which can be divided into baseline and on-treatment factors, have been identified to influence responses to antiviral therapies (Table 2).[57]

Baseline viral factors

Hepatitis B viral load. Serum HBV DNA level is the known predictor of adverse clinical outcomes (cirrhosis, HCC, and

Table 2 Hepatitis B viral factors associated with response of antiviral agent therapy in chronic hepatitis B.

	IFN-based therapy		NA therapy	
	HBeAg-positive	HBeAg-negative	HBeAg-positive	HBeAg-negative
Baseline				
Viral load	Low	Low	Low	Low
Quantitative HBsAg	No correlation	No correlation	Controversial	Controversial
Genotype	A>D and B>C	A>non-A	No correlation	No correlation
HBV mutants				
PC/BCP mutants	Controversial	Controversial	Controversial	Controversial
On-treatment				
HBV DNA decline	No correlation	≥2 $\log_{10}$ IU/mL at week 12	Undetectable at week 24	Undetectable at week 24
Quantitative HBsAg decline	<1500 IU/ml at week 12	≥10% decline from baseline at week 12	≥1 $\log_{10}$ IU/mL at year 1[a]	No correlation

BCP = basal core promoter; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IFN = interferon; NA = nucleoside analog; PC = pre-core.

[a] Telbivudine treatment.

death from liver disease) in adults with chronic HBV infection.[58–60] An earlier study using a summative analysis of the literature also showed that pretreatment serum HBV DNA level was significantly associated with efficacy of antiviral therapy, including histological grading, serum ALT normalization and incidence of HBeAg seroconversion.[61] Furthermore, several clinical trials confirmed that a lower baseline HBV DNA level was predictive of HBeAg loss or seroconversion as well as viral suppression in patients receiving antiviral therapy.[15,16,62–66]

Quantitative HBsAg levels. A quantitative assay for serum HBsAg levels is currently available.[67] The relationships between HBsAg, intrahepatic HBV DNA and serum HBV DNA concentration were quite distinct by HBeAg status. In HBeAg-positive CHB, HBsAg level was positively correlated with intrahepatic HBV DNA and serum HBV DNA concentration. On the contrary, HBsAg level correlated poorly with serum HBV DNA and did not correlate with intrahepatic HBV DNA in HBeAg-negative CHB.[68] With regard to clinical phenotypes, HBsAg levels were much higher in HBeAg-positive patients in the immune tolerance and immune clearance phase than HBeAg-negative patients.[69,70] Our recent study showed that HBeAg-negative patients with lower levels of HBsAg have higher chances of losing HBsAg than those with high levels.[71] High levels of HBsAg increase the risk of HCC in HBeAg-negative patients with low levels of serum HBV DNA (<2000 IU/mL). The hazard ratio for HCC in patients with levels of HBsAg $\geq$ 1000 vs. < 1000 IU/mL was 13.7 (95% CI: 4.8–39.3).[72] In addition, high HBsAg level ($\geq$1000 IU/mL) was also associated with HBeAg-negative hepatitis development in those patients.[73] These lines of evidence indicate that there is a correlation between serum HBsAg level and liver disease progression. Therefore, serum HBsAg levels may serve as a predictor of efficacy during antiviral therapy.

In two large multinational studies of patients treated with PEG-IFN-α-2a, the baseline HBsAg level was not correlated with antiviral response, regardless of HBeAg status.[74,75] Most recently, two studies on naïve HBeAg-positive patients treated with ETV for 2 years showed that the association of baseline HBsAg level and treatment response still remained controvesial.[76,77] These lines of evidence indicate that further studies are warranted to validate the predictive value of baseline HBsAg levels for responses to antiviral therapies.

HBV genotype. According to strains exhibiting an entire genome sequence, divergence of >8% or 4–8%, at least 10 HBV genotypes (A–J), and several subtypes have been identified.[78] The clinical and virological implications of HBV genotypes bear geographic differences. The impact of HBV genotype on the responses to both IFN-based and NA treatments has been increasingly recognized.[78] In HBeAg-positive patients treated with standard IFN-α, the sustained response rate of serum ALT level normalization and HBeAg seroconversion post-treatment, is significantly better in genotype A and B patients than genotype C and D patients.[79–81] A multicenter study on PEG-IFN-α for HBeAg-positive patients also showed that the rate of HBeAg clearance and durable loss of HBeAg at 3 years post-treatment were higher in genotype A and B patients than genotype C and D patients.[82] In addition, genotype A and B patients had a significant decline of serum HBsAg level compared with genotype C and D patients ($p < 0.001$) during PEG-IFN-α therapy for HBeAg-positive patients.[83] Among HBeAg-negative patients treated with PEG-IFN-α, a long-term follow-up study further showed that HBsAg seroclearance was significantly higher in genotype A (20%) than non-A (6–9%) patients.[84] A meta-analysis also confirmed that HBV genotype A patients have better responses to IFN-α treatment than genotype D patients, regardless of HBeAg status. Similarly, HBeAg-positive genotype B patients have a higher response rate to IFN-α treatment than genotype C patients.[85] Recently, pooled data from two large global trials of HBeAg-positive patients treated with PEG-IFN-α showed that genotype A patients with higher ALT levels or lower HBV DNA levels, as well as genotype B and C patients having both higher ALT levels and lower HBV DNA levels had a high predicted probability of a sustained treatment response. On the contrary, genotype D patients had the lowest chance of sustained response, irrespective of ALT or HBV DNA levels.[86]

In sharp contrast to IFN-based therapy, differential responses to NAs among patients with different HBV genotypes remain controversial.[87–92] Although HBV genotype seems to have no impact on the response to NA treatment, our retrospective study showed that HBV genotype B was independently associated with earlier emergence of LAM-resistant strains than genotype C. In addition, genotype B was significantly associated with development of LAM-resistance within the first 12 months of LAM therapy compared with genotype C (odds ratio (OR): 8.27; $p = 0.004$).[93] Whether a given genotype is associated with emergence of LAM resistance remains unclear, frequent monitoring of genotypic resistance should be performed for all patients during LAM therapy.

HBV mutants. Several common HBV mutant strains such as mutations in the pre-core, core promoter and deletion mutation in the pre-S/S genes have been reported to be associated with progressive liver disease, including cirrhosis and HCC.[60] However, their impact on HBV treatment remains largely unknown. A recent review showed that half of the studies suggested that pre-core G1896A mutation or basal core promoter (BCP) A1762T/G1764A mutation were associated with the response to IFN-α or NA therapy.[94] A previous study on 116 HBeAg-positive CHB patients receiving short-term LAM therapy showed that pre-core G1896A mutation, compared with wild-type (75% vs. 52%, $p = 0.045$), correlated with the loss of HBeAg at the end of therapy.[95] Our recent study on 115 HBeAg-positive patients receiving PEG-IFN-α-2a for 6 months indicated that BCP A1762T/G1764A mutation was associated with a combined response defined as HBeAg seroconversion, HBV DNA level < 20,000 IU/mL as well as ALT normalization at 6 months after therapy cessation (OR: 8.04, 95% CI: 2.00–32.28).[66] On the contrary, recent analysis of 214 HBeAg-positive patients receiving PEG-IFN-α with or without LAM for 1 year revealed that patients without presence of pre-core and BCP mutants at baseline were more likely to achieve HBeAg loss with HBV DNA of <10,000 copies/mL (response, 34% vs. 11%, $p < 0.001$) and HBsAg clearance (18% vs. 2%, $p < 0.001$) at 6 months after therapy cessation than patients with the presence of pre-core or BCP mutants. The wild-type of pre-core and BCP region of virus at baseline was an independent predictor of response

(OR: 2.90, 95% CI: 1.15−7.31, $p = 0.023$) and HBsAg clearance (OR 5.58, 95% CI: 1.26−24.63, $p = 0.013$).[96] Recently, we developed a new assay, PCR-pyrosequencing, to quantify the pre-core G1896A and BCP A1762T/G1764A mutant percentages. The correlation between dynamic changes of these mutants and IFN-induced HBeAg seroconversion was further determined in 203 HBeAg-positive CHB patients. We found that the chance of HBeAg seroconversion increased by 2.2% (OR: 1.022, 95% CI: 1.009−1.034, $p = 0.001$) and 2.3% (OR: 1.023, 95% CI: 1.010−1.037, $p = 0.001$) per 1% increase in the pretreatment pre-core G1896A and BCP A1762T/G1764A mutants, respectively.[97] As relevant data are limited, additional large-scale studies are required to examine the association of common HBV mutants with treatment response to currently available antiviral agents.

On-treatment viral factors

Reduction of HBV DNA level. In recent years, early viral suppression has been found to be the most important predictive factor of the antiviral efficacy of NAs. It was confirmed that patients with a DNA level of <2000 IU/mL at 4 weeks of LAM therapy had the highest probability to reach the ideal response (HBV DNA level < 400 IU/mL, HBeAg seroconversion, normal ALT levels, and absence of LAM resistance) after 5-year LAM treatment.[98] Similar findings were observed in both HBeAg-positive and -negative patients with LdT or LAM therapy, that undetectable serum HBV DNA level at week 24 was associated with favorable outcomes at week 52 in terms of virological, biochemical responses and drug resistance.[27] In patients with LAM resistance who were treated with ADV, early viral suppression was also a predictor for long-term favorable outcomes. Patients with undetectable serum HBV DNA at 24 weeks had significantly higher virological response than those with HBV DNA > 2000 IU/mL.[99] For NA-naïve, HBeAg-positive patients on long-term ADV therapy, HBV DNA level of <10,000 copies/mL at week 24 was predictive of virological response, as well as HBeAg seroconversion.[100] In addition, in patients with LAM resistance, achievement of an on-treatment initial virological response at 6 months (serum HBV DNA levels of <2000 copies/mL) was one of the predictive factors for virological response after 5-year ADV monotherapy.[101] Unlike agents with modest antiviral potency, the impact of early viral suppression on treatment effect for highly potent NAs, such as ETV and TDF, is not confirmed. For patients treated with ETV, early rapid decline of viral load at day 10 was found to be predictive of virological response with serum HBV DNA of <300 copies/mL at week 48.[102] All the evidence indicates that HBV viral kinetics are the most important predictor of response and drug resistance during NA therapy.[103]

Kinetics of quantitative HBsAg level. Recently, the on-treatment decline of quantitative serum HBsAg level has been proven to be useful as a predictor of response after antiviral treatment. For HBeAg-positive patients, 1 year of PEG-IFN-α with or without LAM resulted in a significantly sustained decline of serum HBsAg level in patients with HBeAg loss and HBV DNA of <10,000 copies/mL at 26 weeks post-treatment compared with non-responders (decline at week 52: 3.3 vs. 0.7 log IU/mL, $p < 0.001$). Patients without any decline of serum HBsAg level at week 12 had a 97% probability of non-response and no chance of HBsAg loss at the end of follow-up.[74] A recent randomized controlled trial also showed that on-treatment decline of serum HBsAg level was significantly associated with post-treatment HBeAg seroconversion in HBeAg-positive, genotype B and C patients treated with PEG-IFN-α-2a. The highest rates of HBeAg seroconversion were achieved by patients with HBsAg of <1500 IU/mL at week 12 (58%) or week 24 (57%), whereas patients with HBsAg > 20,000 IU/mL did not respond.[104] In a multinational study of 386 HBeAg-negative patients (mainly with HBV genotype B or C infection) treated for 48 weeks with PEG-IFN-α-2a with or without LAM, end-of-treatment serum HBsAg level $\leq$ 10 IU/mL and on-treatment decline of serum HBsAg level > 1 $\log_{10}$ IU/mL were significantly associated with sustained HBsAg clearance at 3 years post-treatment.[105] Of particular note is that early decrease of serum HBsAg levels at week 12 was highly predictive of sustained virological response to PEG-IFN-α-2a.[106,107] Similarly, in HBeAg-negative patients with genotype A and D infection, those with decrease of serum HBsAg level and decline of HBV DNA > 2 log copies/mL at week 12 of PEG-IFN-α-2a treatment achieved the highest probability of sustained virological response.[75] In a long-term follow-up study of HBeAg-negative patients receiving PEG-IFN-α-2a with or without LAM for 48 weeks, an on-treatment decline in serum HBsAg level $\geq$ 10% from baseline at weeks 12 or 24 was significantly associated with sustained immune control (HBV DNA $\leq$ 2000 IU/mL) at 1 year post-treatment as well as HBsAg clearance 5 years post-treatment.[108] These results indicate that the on-treatment serum HBsAg level is useful not only to identify patients who are not likely to benefit from IFN-α earlier, but also guide optimized treatment duration.[109,110] In addition, serum HBsAg level monitoring after the end of therapy can help track progress towards sustained response, and even eventual HBsAg clearance. However, the prediction rules for PEG-IFN-α therapy based on serum HBsAg level have not been confirmed across all HBV genotypes patients, therefore more cohort studies are needed to prove HBsAg prediction rules for the treatment of chronic hepatitis B.

In contrast to IFN-based therapy, the role of serum HBsAg level in patients receiving NA therapy remains controversial. In a study of 168 HBeAg-positive patients treated with daily LdT at 600 mg for 3 years, serum HBsAg level progressively reduced from baseline to year 3 of therapy ($P < 0.0001$). In addition, 25% of patients with rapid HBsAg decline ($\geq$1 $\log_{10}$ IU/mL at year 1) achieved HBsAg seroclearance at year 3 of therapy compared with none of those with steady serum HBsAg levels ($p = 0.0024$).[39] In a recent study on HBeAg-positive patients treated with ETV, the majority of patients (60%) had no significant decline in serum HBsAg levels during 2 years of ETV treatment. Furthermore, early decline of serum HBsAg levels at 12/24 weeks was not associated with HBV DNA suppression or HBeAg seroconversion.[76] In addition, serum HBsAg levels at baseline and during antiviral therapy in a limited number of patients treated with ETV and PEG-IFN-α were compared. In HBeAg-negative patients, PEG-IFN-α therapy resulted in a significant reduction in serum HBsAg level, whereas serum

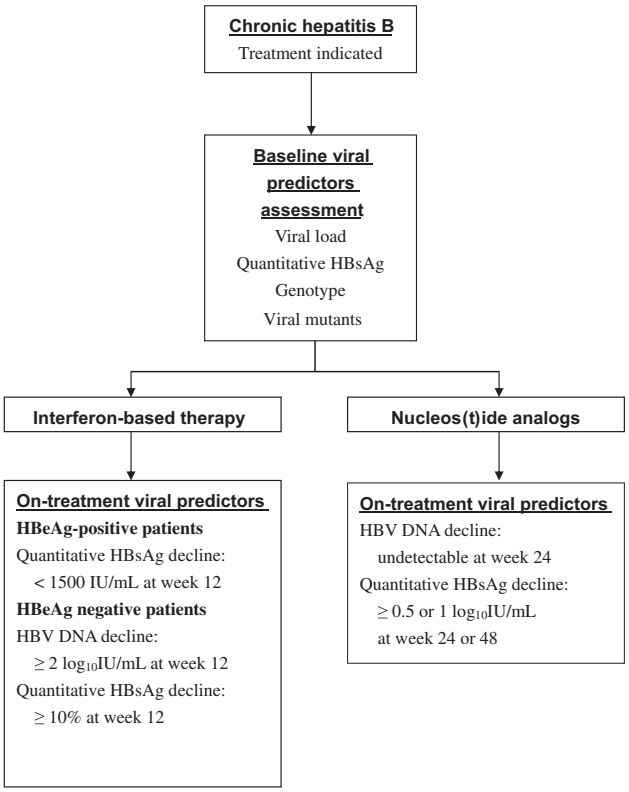

Figure 1 Hypothetical algorithm for predicting antiviral treatment response in chronic hepatitis B.

HBsAg level did not decrease in ETV-treated patients.[111] Therefore, whether different antiviral therapies have different HBsAg kinetics remains unknown. Furthermore, the time of HBsAg decline during treatment is uncertain. Therefore, further prospective studies are warranted to determine the predictive value of HBsAg kinetics for efficacy as well as the optimal time points to measure the HBsAg level during antiviral treatment.

Conclusions

Accumulating data indicate that long-term HBV suppression significantly reduced the degree of liver damage and risk of end-stage liver diseases such as cirrhosis and HCC. A recent meta-analysis showed that both short-term IFN-based therapy and long-term NA therapy could improve adverse outcomes of CHB patients.[30,112] During antiviral therapy, baseline and on-treatment hepatitis B viral factors are important for the prediction of therapeutic effects (Fig. 1). On the basis of baseline viral factors, clinicians may select candidates for IFN-based or NA therapy. Furthermore, on-treatment predictors may be helpful in making decisions to stop IFN-based therapy or shift to an alternative therapy. Although antiviral therapy of CHB has dramatically improved, eradication of HBV infection is still a challenge. With the implementation of universal hepatitis B vaccination, interruption of possible transmission routes and development of more effective HBV eradication therapy, HBV eradication is likely to be achieved in the foreseeable future.

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