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TOPIC HIGHLIGHT

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Optimization therapy for the treatment of chronic hepatitis B

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Abstract

Chronic hepatitis B (CHB) is currently medically managed with either interferon-alpha or one of the five nucleos(t)ide analogs. However, there are still a large number of CHB patients whose response to the above therapies remains less than satisfactory, and their incomplete or non-response to antiviral therapies has plagued clinicians worldwide. In recent years, a newly proposed optimization therapy has provided us with a new approach to solve this problem. The key points in this optimization therapy are to initiate antiviral therapy with an appropriate agent at the correct time point, and to adjust treatments in patients with poor early responses by adding a second agent or switching to another more potent agent. In this review, we summarize recent developments in optimization therapy for the treatment of CHB, and provide an outlook for future research in this field.

Key words: Chronic hepatitis B; Nucleos(t)ide analog; Interferon; Suboptimal response; Optimization therapy

Core tip: Optimization therapy is a personalized strategy, and it aims to achieve profound and sustained inhibition of hepatitis B virus replication, and to reduce the likelihood of subsequent disease progression. The key points of optimization therapy are to initiate antiviral therapy with an appropriate agent at the correct time point based on baseline characteristics, and to timely adjust the treatment by dynamic monitoring of the on-treatment response. However, the current understanding of optimization therapy is still very limited, and many issues still need further research.

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INTRODUCTION

An estimated 350 million people are infected with hepatitis B worldwide, and up to 1 million deaths annually can be attributed to hepatitis B virus (HBV)-related complications, including cirrhosis and hepatocellular carcinoma (HCC)[1]. Currently, both interferon-α (IFN-α) and oral nucleos(t)ide analogs (NAs) are used to treat chronic hepatitis B (CHB) patients[2], and a profound and sustained inhibition of viral replication is the most important goal of any CHB treatment, as only such inhibition can reduce the likelihood of subsequent disease progression and viral resistance[3,4].

However, due to the large variation in hosts (gender, age, genetic background, disease duration, extent of liver damage) and viral (genotype and quasispecies complexity) factors[5-8], a considerable number of CHB patients do not have a satisfactory response to therapy. These patients usually have suboptimal response, viral resistance or a lack of sustained curative response. Thus, optimizing existing treatment strategies to maximize efficacy and reduce the emergence of resistance has become a hot research topic over the past few years[9]. In this review, we summarize recent developments in optimization therapy for the treatment of CHB, and provide an outlook on this topic.

IMPORTANCE OF OPTIMIZATION THERAPY FOR CHB

Definition of optimization therapy

The concept of optimization therapy can be traced back to the roadmap approach[10], in which on-treatment adjustment and strategies were proposed for patients with suboptimal responses to antiviral therapy. As there is no uniform definition of suboptimal response, some published reports refer to suboptimal response as poor response or partial response. This definition of optimization therapy has been further broadened to include any therapy with the following two aspects: (1) selecting appropriate drugs for the initial treatment at the correct time point based on baseline characteristics of the patients including serum alanine aminotransferase (ALT) levels, HBV DNA titers, HBV genotypes, and severity of liver damage; and (2) making timely therapeutic changes in CHB patients with poor early response to initial therapy. As an individual measure, more and more clinical trials have demonstrated that the application of optimization therapy can achieve better long-term treatment efficacy[11,12].

For a long time, there was no consensus on the time point for assessing the suboptimal response to NAs. However, recently the European Association for the Study of the Liver (EASL) guideline recommended that suboptimal response should be assessed at the 24th week of treatment for moderately potent agents including agents with a low genetic barrier to resistance [including lamivudine (LAM) and telbivudine (LdT)] and at the 48th week for highly potent agents including agents with a higher genetic barrier to resistance or agents with late emergence of resistance [including entecavir (ETV), adefovir (ADV) and tenofovir disoproxil (TDF)][13].

Why optimization therapy should be considered

TDF and ETV are the currently preferred antiviral agents, given their potent anti-HBV activity and high barrier to resistance. However, these drugs are expensive and their long-term use is often unaffordable for many patients, especially low-income patients from developing countries[14]. Thus, affordable drugs such as LAM, ADV and LdT are still used by a significant number of patients[2]. However, due to the low genetic barrier to resistance and ineffective inhibition of virus replication, these cheaper agents often lead to suboptimal responses and the emergence of viral resistance. An efficacy analysis of different NAs showed that suboptimal virological response (HBV DNA > 300 copies/mL at week 24) was 51%-88% for HBeAg positive patients and 20%-64% for HBeAg negative patients[15], and that the suboptimal virological response to NAs always had a high incidence of resistance and high risk of HCC[16]. In addition, the persistent positive status of HBV DNA caused by the suboptimal virological response also led to extended duration of therapy and increased medical costs, and therefore lowered patient adherence to antiviral therapy[17]. In addition, the baseline HBV DNA levels, ALT levels and histological changes also affected the on-treatment virological response to NAs. Thus, the development of individualized and optimized treatments with NAs is widely accepted by clinicians in clinical practice[6,7,18,19].

Although IFN has both antiviral and immunomodulatory properties against HBV, and a slight serologic advantage over NAs, its strength in suppressing HBV DNA replication is relatively weak. The majority of CHB patients have a low viral response to IFN after completing their full course of treatment, and 65%-80% of them may develop virological rebound in the 6th month after discontinuing therapy, which inevitably diminishes the beneficial effects of the previous therapy. In addition, the antiviral efficacy of IFN is also affected by HBV genotypes[20], and patients with similar clinical characteristics infected with different HBV genotypes may respond differently to the same IFN therapy[21]. Thus, the current NAs and IFN-based antiviral strategies need to be optimized during the course of treatment. Timely and reasonable optimization strategies would help to achieve sustained suppression of HBV replication and remission of liver disease, and to prevent or decrease the occurrence of life-threatening cirrhosis and HCC.

OPTIMIZATION STRATGIES FOR NAS THERAPY

Currently, five NAs are approved for the treatment of CHB, including LAM, ADV, ETV, LdT, and TDF. As NAs only suppress HBV replication at the level of DNA synthesis, most patients require long-term (even lifelong) treatment. In addition, the antiviral strength and genetic barrier to resistance are quite different among these NAs, and non-response, suboptimal response and resistance all limit the use of long-term NAs therapies. Thus, it is necessary to optimize the current antiviral strategies to improve patient responses during and after treatment[22].

Optimization therapy according to baseline characteristics

In the past decade, several factors (including gender, duration of infection, baseline HBeAg level, HBV DNA level, and ALT level) have been used to predict the vi-

rological responses of HBeAg-positive patients to NAs treatments. According to international guidelines, high ALT levels, low HBV DNA levels and high histological activity index prior to NAs treatments can lead to good HBeAg seroconversion[23,24]; and high baseline HBV DNA level was found to be the most important factor associated with virologic breakthrough[7,25-27]. For patients with HBV DNA levels higher than 6.6 log10 copies/mL, virologic breakthrough during LAM monotherapy was as high as 19% at year 1 and 45% at year 2; and was only 6.7% and 18% at years 1 and 2, respectively, for patients with HBV DNA levels lower than 6.6 log10 copies/mL[7], which indicated that LAM may be an effective first-line therapy for HBeAg-positive patients with lower baseline HBV DNA levels. However, further studies are needed to confirm that the baseline HBV DNA level of 6.6 log10 copies/mL is an ideal cutoff value in selecting initial treatment with LAM. The LdT 2-year GLOBE trial results showed that baseline serum ALT and HBV DNA levels could be used to predict the 2-year response in patients treated with LdT. For HBeAg-positive patients with ALT equal to or higher than 2 × ULN and HBV DNA less than 9 log10 copies/mL, more than 47% achieved HBeAg seroconversion at year 2[28]. We previously compared the 2-year efficacy of initial ADV and ETV treatments[29], and found that the efficacy of ADV was inferior to that of ETV in HBeAg-positive patients, however, in HBeAg-negative patients, ADV and ETV achieved similar biochemical and virological responses. Thus, ADV should be considered for HBeAg-negative patients with low baseline HBV DNA.

Considering that high baseline viral load was highly associated with failure to achieve virologic suppression, we recently determined the 96-wk efficacy of highly potent ETV in the treatment of HBeAg-positive patients with baseline HBV DNA higher than 9 log10 copies/mL, and found that the virological response rate was significantly lower in this cohort than in patients with HBV DNA lower than or equal to 9 log10 copies/mL (unpublished data). This suggested that high baseline HBV DNA may be a negative factor influencing the likelihood of virological responses with initial ETV monotherapy. The optimization of treatment for patients with high baseline HBV DNA has become a new challenge, and de novo combination therapies may be good options in solving this problem, however, further research is required.

TDF is a very potent antiviral agent for maintaining long-term HBV DNA suppression, with very low rates of resistance development and a good safety profile. Recently, Gordon *et al*[30] investigated the efficacy of TDF in CHB patients with high baseline HBV DNA (≥ 9 log10 copies/mL), and they found that patients with high baseline HBV DNA could achieve a similar virological response (HBV DNA < 400 copies/mL) to patients with low baseline HBV DNA (< 9 log10 copies/mL), although this tended to take longer in patients with high baseline viral load. Thus, TDF is a good therapeutic option in patients with high baseline HBV DNA.

Recent studies showed that different HBV genotypes also show different sensitivities to NAs therapy. For example, HBV genotype B shows a better virological response to ADV therapy than genotype C[31], and TDF therapy can induce a significant decrease in HBsAg in HBeAg negative patients infected by HBV genotype D. However, the antiviral response of different HBV genotypes to NAs is still unclear[32]. Thus, it remains to be clarified whether optimization strategies of initial NAs therapies should consider HBV genotypes.

Optimization therapy according to on-treatment responses

Suboptimal response is associated with all NAs therapies, and persistent viremia can greatly increase resistance and inevitably lead to aggravation of the disease. Thus, a rapid decrease in HBV DNA to undetectable levels is highly correlated with long-term treatment efficacy[33,34]. In recent years, there has been tremendous progress in the use of on-treatment HBV DNA levels at different time points to predict clinical outcomes in patients[25]. An earlier study of 74 HBeAg-positive patients treated with LAM showed that an HBV DNA level below 4 log10 copies/mL at week 4 can be used to predict the ideal response at year 5 (undetectable HBV DNA level, HBeAg seroconversion, and normal ALT levels)[35]; while patients with HBV DNA levels equal to or higher than 3 log10 copies/mL after 6 mo of LAM therapy had a 63.2% chance of developing resistance[36]. In addition, an early reduction in HBV DNA before week 24 in predicting long-term response was also observed in LAM-treated HBeAg-negative patients[37]. Thus, for LAM-treated patients who fail to achieve this early target, the addition of (such as ADV or TDF or IFN add-on) or a switch to (such as IFN) alternative antiviral agents should be considered. However, data on optimization strategies in LAM suboptimal responders are still limited, especially for IFN add-on or the switch to IFN treatments.

One study from Spain showed that 77% of patients with early virological responses (reduction in HBV DNA ≥ 4 log10 IU/mL at month 6) on ADV therapy achieved undetectable HBV DNA level at month 12 compared to only 5% in those without early virological responses[38]. In China, it was observed that HBV DNA levels at week 24 (HBV DNA < 1000 copies/mL *vs* HBV DNA ≥ 1000 copies/mL) were highly related to the 48-wk virological response, and the rates of 48-wk virological and serological responses were also significantly different between patients with primary non-response and those with virological response at week 12[25]. Currently, the common optimization strategies for suboptimal response to ADV are LAM, LdT and ETV add-on treatments. The IFN add-on or switch to IFN can also be considered in theory. Among 31 HBeAg-positive patients with HBV DNA equal to or higher than 4 log10 copies/mL after 48 wk of ADV monotherapy, the levels of HBV DNA were significantly reduced after 24-wk combination therapy with LAM plus ADV[39]. We further evaluated the combination

strategies of LAM plus ADV or LdT plus ADV for patients with suboptimal responses to ADV, and found that both combination therapies led to a significant decrease in HBV DNA, however, HBeAg serological outcomes were significantly higher in patients treated with LdT plus ADV than those treated with LAM plus ADV[11].

The on-treatment HBV DNA levels for predicting long-term antiviral responses were also determined with LdT treatment. Among HBeAg-positive patients with HBV DNA lower than 300 copies/mL at week 24, the proportions who achieved 2-year undetectable HBV DNA, cumulative HBeAg seroconversion or resistance were 82%, 46% and 9%, respectively[6]; and at year 3, the cumulative HBeAg seroconversion further increased to 54%[40]. A recent study also reported that serum HBV DNA level at week 12 was better than the viral response at week 24 in predicting long-term treatment outcome with LdT[41]. Thus, either ADV or TDF add-on therapy should be used in patients with suboptimal viral response to LdT as early as possible. It is worth mentioning that we recently participated in a large national cohort to evaluate the efficacy and safety of optimization strategy with ADV add-on for suboptimal responders to LdT, and found that change in treatment strategy was essential for suboptimal virological responders at week 24, and ADV add-on optimization therapy increased antiviral potency and lowered resistance without increasing side effects (unpublished data).

Despite the high potency of ETV, some patients treated with ETV only have a suboptimal response (detectable HBV DNA after 12-mo treatment)[42]. The add-ons of ADV, TDF, or IFN, and a switch to TDF or IFN are both considered alternative optimization therapies. One retrospective study from United States compared three different optimization strategies (ADV add-on, switch to TDF, or TDF add-on) in patients with a partial response to ETV, and showed that the TDF add-on therapy and the switch to TDF monotherapy appeared to have similar efficacy in most patients, but the efficacy of ADV add-on therapy was much less than that of either switch to TDF or TDF add-on therapy[43]. However, studies also showed that the vast majority of patients with primary non-response or suboptimal responses to initial ETV treatment (for more than 12 mo) would achieve virological response through prolonged ETV treatment without any other adjustments, and would have only a 1.4% chance of viral resistance[44]. As there are relatively limited data available, more studies are required to determine whether and which optimization therapies are necessary for patients with suboptimal responses to ETV.

There is increasing evidence to show that the change in serum HBsAg titer during antiviral treatment is correlated with changes in covalently closed circular DNA (cccDNA) levels[45]. Monitoring serum HBsAg titer is a reasonable on-treatment indicator of long-term response to pegylated IFN-α therapy. However, the decline in serum HBsAg titer is not significant in patients treated with NAs[46], and its value in predicting responses to NAs therapy is still controversial[47,48]. Thus, further investigation and analysis are needed to determine whether the absolute HBsAg titer or a reduction in HBsAg titer could be used to optimize NAs treatment.

OPTIMIZATION STRATGIES FOR INTERFERON THERAPY

Optimization therapy according to baseline characteristics

IFN therapy results in sustained responses in only a minority of CHB patients, and both host and viral characteristics significantly affect the response to INF. Most recent studies suggest that HBV genotypes, high levels of ALT [$\geqslant 2 \times$ upper limit of normal (ULN)], low levels of HBV-DNA ($< 2.0 \times 10^8$ IU/mL), and female sex predict a long-term viral response with IFN treatment[49]; and patients who can achieve a long-term response to INF are genotype A patients with high ALT and/or low HBV-DNA levels, and genotype B patients with both high ALT and low HBV-DNA levels. However, genotype C and D patients have a low chance of long-term response, regardless of ALT or HBV-DNA levels[21]. In addition, baseline ALT level is also a reliable predictor of HBeAg seroconversion, and the cumulative HBeAg seroconversion rate is significantly high in patients with high ALT levels. For example, the HBeAg seroconversion rate is 22.5% in patients with baseline ALT $> 2 \times$ ULN, and is only 12.5% in patients with baseline ALT $\leqslant 2 \times$ ULN[49].

Thus, determining the correct time and patients for IFN therapy is the core of optimization strategies. A consensus has been reached on the correct time of IFN therapy. The best time to start an appropriate IFN therapy is when patients have changed from the state of immune tolerance to the immune clearance phase, accompanied by increased ALT and decreased HBV DNA[50]. Patients with HBV genotype C and D infection may be considered for NAs treatment, but not IFN treatment[2].

Optimization therapy according to on-treatment responses

Recently, monitoring serum HBV DNA and HBsAg levels has helped to differentiate patients who will quickly respond from those who will require longer treatment and those who are unlikely to respond and therefore need alternative medicines[5]. Thus, monitoring the changes and trends of these indicators during treatment is necessary to develop optimization strategies for IFN therapy.

There is a correlation between HBsAg titer and the levels of cccDNA and total intra-hepatic HBV DNA[45], and the elimination of cccDNA and levels of HBsAg are associated with long-term virological response. Thus, HBsAg and HBV DNA levels may be used to predict long-term responses to IFN therapy. For example, a recent international multicenter trial investigated the role of early on-treatment serum HBsAg levels in predicting long-term response (HBV DNA level < 10000 copies/mL and normal ALT levels at week 72) to IFN in HBeAg-nega-

tive patients[51]. However, other studies showed that a decrease in HBsAg alone was of limited value in predicting long-term responses, but decreases in both HBsAg and HBV DNA (≥ 2 log10 copies/mL) were good indicators of long-term response[51]. Importantly, patients without a change in HBsAg or a significant decline in HBV DNA (< 2 log10 copies/mL) at week 12 are unlikely to have an ideal response[51]. Therefore, a decline in both serum HBV DNA and HBsAg levels at week 12 of IFN therapy have been recommended to determine the choice of subsequent therapies. The absence of a decrease in HBsAg together with a reduction in HBV DNA to below 2 log10 copies/mL at week 12 could serve as the stopping point in HBeAg-negative patients with genotype D HBV infection[52]. Thus, on-treatment HBV DNA and HBsAg kinetics are useful for individual IFN treatment optimization.

A recent report from China showed that extended treatment with pegylated IFNα-2a in combination with LAM or ADV for 96 wk was a promising strategy for achieving high rates of sustainable HBeAg and HBsAg seroconversion and HBV DNA suppression in HBeAg-positive patients[12]. In addition, there is an ongoing multicenter randomized trial in China, which aims to investigate the optimization strategy for pegylated IFNα. In this study, patients with a rapid response (both HBsAg < 1500 IU/mL and HBV DNA < 1.0×10^5 copies/mL at week 24 after treatment) would complete 48 wk of PegIFN monotherapy; while patients with a slow response (both HBsAg ≥ 1500 IU/mL and HBV DNA ≥ 1.0×10^5 copies/mL at week 24) would receive either extended IFN monotherapy to 96 wk or combination therapy of IFN and NAs. The findings of this study will provide further evidence for the combined usage of HBsAg and HBV DNA levels for predicting long-term antiviral efficacy and guiding the choice of optimal treatment strategies (extended treatment *vs* NAs add-on therapy).

CONCLUSION

The primary goal of the above-mentioned optimization therapy is to enable these patients to achieve maximum treatment benefits from current NAs and IFN therapies. At present, optimization therapy is an individualized treatment approach. To establish a rational optimization strategy, patients should be thoroughly assessed for demographic, lifestyle, income and clinical characteristics before starting treatment. Appropriate drugs should be selected according to a patient's baseline host and viral characteristics, followed by timely adjustments of medicines by dynamic monitoring of on-treatment responses. However, research on optimization therapy for CHB is still very limited, and many issues still need to be investigated such as: (1) the concept of poor early response should be strictly defined with unified standards and the difference between various antiviral drugs should be taken into account; (2) besides HBV DNA and quantitative HBsAg, more parameters (including immunology and host genomic-related indicators) should be determined to help develop optimization therapy; (3) broadening drug selection for optimization therapy (not just confined to NAs and IFN-α), and the agents of therapeutic hepatitis B vaccine and immunomodulators should also be considered for use in combination with existing antiviral drugs; and (4) optimization strategies for special populations (including pregnant women, liver transplant patients, viral reactivation during immunosuppression) should also be developed.

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