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REVIEW OF THE TREATMENT PROBLEM AND DRUG GROUPS FOR THE TREATMENT OF VIRAL HEPATITIS B

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Abstract

Current treatment of chronic hepatitis B virus (HBV) infection, pegylated interferon-α (pegIFN-α) and nucleos(t)ide analogue (NA), can suppress HBV replication, reverse liver inflammation and fibrosis, and decrease risks of cirrhosis and hepatocellular carcinoma, but hepatitis B surface antigen (HBsAg) loss is rare. Functional HBV cure is defined as undetectable HBsAg and unquantifiable serum HBV DNA for at least 24 weeks after a finite course of therapy. This requires suppression of HBV replication and viral protein production as well as restoration of immune response to HBV. Direct-acting antivirals targeting virus entry, capsid assembly, viral protein production and secretion are in clinical trials. In parallel, immune modulatory therapies to stimulate HBV-specific immune response and to remove immune blockade are being tested. Clinical trials of direct-acting antivirals alone or immune modulatory therapies alone have not been successful in achieving HBV cure. Recent combinations of direct-acting antivirals and immune modulatory therapies have shown promising results particularly with combinations that included pegIFN-α. These results need to be confirmed in larger studies with longer follow-up, and further work is needed to develop simpler regimens with fewer drugs that can be administered orally and safely. While there is a strong desire to develop finite therapies that can achieve HBV cure, safety is paramount and new therapies must provide incremental value compared to standard of care, which is predominantly long-term NA therapy.

Keywords: Direct-acting antivirals, Hepatitis B surface antigen loss, Immune modulatory therapies, Nucleos(t)ide analogues, Pegylated interferon-α.

Introduction

Current treatment of chronic hepatitis B virus (HBV) infection comprises pegylated interferon-α (pegIFN-α) or nucleos(t)ide analogues (NAs), used as monotherapy. Both pegIFN-α and NA can suppress HBV DNA replication, decrease liver inflammation, reverse liver fibrosis, and decrease risk of cirrhosis, hepatocellular carcinoma, and liver-related deaths. However, HBV remains in the liver and hepatitis B surface antigen (HBsAg) remains in the circulation even after HBV DNA has been undetectable in serum for many years, and virological relapse is universal when treatment is stopped. This review article will describe the challenges in eradicating HBV, summarize the efficacy of new HBV direct-acting antivirals and immune modulatory therapies in clinical trials, and discuss the strategies needed to achieve HBV cure.

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PROBLEMS OF CURE VIRAL HEPATITIS B

HBV replicates at a rapid rate with daily production of HBV virions estimated to be 1 trillion. In addition to complete virions, HBV produces subviral particles that consist of surface proteins only. These subviral particles are incapable of replication or infection, but they are >1,000-fold more abundant than complete virions and the vast amount of circulating HBsAg has been attributed to cause immune exhaustion in chronic HBV infection. Recovery of HBV-specific T-cell immune responses had been demonstrated in patients with spontaneous, pegIFN-α- or NA-induced hepatitis B e antigen (HBeAg) or HBsAg loss and more recently in some patients who experienced marked decrease in HBsAg levels during treatment with short interfering RNA (siRNA). These data suggest that HBV-specific immune responses can be restored at least in some patients after HBV DNA replication and HBsAg production are suppressed.

A major challenge to HBV cure is the presence of covalently closed circular DNA (cccDNA), which can be derived both from incoming virions and from intracellular recycling of nucleocapsids. The cccDNA serves as a transcriptional template for all HBV RNAs including pregenomic RNA (pgRNA) which is reverse transcribed into HBV DNA and messenger RNAs which are translated into viral proteins. *In vitro* studies suggest IFN has direct effects on cccDNA enhancing its degradation and/or decreasing its transcription, accounting for a higher rate of HBeAg and HBsAg loss compared to NA therapy. NAs do not have direct inhibitory effects on cccDNA; thus, cccDNA concentrations are minimally decreased even after many years of NA therapy.

A further challenge is that HBV DNA can be integrated into host DNA. Integrated HBV DNA is not replication competent, but full-length S gene is usually preserved and can be a source of circulating HBsAg, particularly in HBeAg-negative patients.Thus, HBV cure will require sustained suppression of both cccDNA and integrated HBV DNA transcription as well as restoration of HBV-specific immune response to maintain immune control.

Apart from the biological challenges, HBV cure therapies must demonstrate incremental value and comparable safety to standard of care which is predominantly long-term NA monotherapy. The second-generation NAs, entecavir and tenofovir, are administered orally once daily, have excellent safety profile and <1% risk of antiviral drug resistance after ≥10 years of continuous therapy. Entecavir and tenofovir disoproxil fumarate are available as generics and are readily available and affordable in most countries. Thus, the bar for new therapies to show incremental value is high. In addition, there is a risk of hepatic decompensation when all drugs including NA are discontinued as had been reported in a recent trial of HBV cure therapy.

DEFINITION OF HBV CURE

HBV cure has been categorized as sterilizing, functional, and partial. Sterilizing cure, defined as the elimination of cccDNA as well as integrated HBV DNA is considered an ideal but unrealistic endpoint. Functional cure, defined as sustained (≥24 weeks posttreatment) HBsAg loss with or without seroconversion to hepatitis B surface antibody (anti-HBs) and undetectable HBeAg and serum HBV DNA after a finite course of therapy, is considered an achievable endpoint and the goal to strive for. Partial HBV cure, defined as HBsAg positive, HBeAg negative with undetectable serum HBV DNA after discontinuation of a finite course of treatment, is considered a suboptimal endpoint for HBV cure therapies. These definitions were first proposed at the 2016 American Association for

the Study of Liver Diseases and European Association for the Study of the Liver HBV Treatment Endpoint Conference, reaffirmed at the 2019 conference, and refined at the 2022 conference. At the 2022 conference, very few new therapies had resulted in HBsAg loss at the end of treatment raising concerns that sustained HBsAg loss off-treatment might be aspirational. Thus, a revised definition of partial cure, HBsAg decreased to <100 IU/mL, HBeAg negative, and HBV DNA below quantification, sustained for at least 24 weeks off-treatment was embraced as an acceptable intermediate step toward functional HBV cure.

Low end-of-treatment HBsAg level is the best predictor of HBsAg loss after NA withdrawal and on-treatment HBsAg decline is a strong predictor of HBsAg loss during pegIFN-α therapy. Low baseline HBsAg level is a predictor of HBsAg loss with many new HBV therapies in clinical trials. However, there are no data on the likelihood of HBsAg loss after HBsAg level is reduced to low levels when treatment that directly targets HBsAg production, secretion or binding is stopped. Follow-up week 24 was selected as the timepoint to assess sustained response because durability of spontaneous, pegIFN-α- or NA- associated HBsAg loss is ~90% if undetectable HBsAg is confirmed on follow-up testing ≥24 weeks later but this timepoint may not be appropriate for treatments with long duration of action. Indeed, among the small number of patients who had achieved HBsAg loss at the end of treatment in ongoing trials of new antivirals, 50% or more reverted back to HBsAg positive by follow-up week 24.

New HBV markers such as HBV RNA and hepatitis B core-related antigen had been shown to be inferior to HBsAg level as predictors of HBsAg loss in studies of pegIFN-α and NA. The utility of these markers in predicting HBsAg loss with HBV cure therapies has not been demonstrated in part due to the limited number of patients achieving HBsAg loss.

MODERN TREATMENT RARELY RESULTS IN LOSS OF HBSAG

1. Interferon monotherapy

After a 48-week course of pegIFN-α treatment, 20% to 25% of patients achieve a sustained decrease in HBV DNA levels, with HBsAg loss increasing from 2%–3% at the end of treatment to 8%–14% after 3 to 5 years posttreatment follow-up. However, HBsAg loss is mainly observed in genotype A which is rare in endemic regions.

2. NA Monotherapy

NAs are more effective than pegIFN-α in inhibiting HBV DNA replication but only 2% to 5% of patients lost HBsAg after 10 years of continuous treatment. Although virologic relapse is universal when NA is stopped prior to HBsAg loss, not all patients experience clinical relapse. Furthermore, some studies found that discontinuation of NA in HBeAg-negative patients who have completed more than 2 to 3 years treatment with undetectable serum HBV DNA have higher rates of HBsAg loss compared to those who continued NA. This paradoxical finding first reported in retrospective studies has now been confirmed in two prospective randomized controlled trials in Europe with almost exclusively White patients but not in two other trials in North America with predominantly Asian patients. Indeed, Asian patients with HBsAg level <100 IU/mL at the time of NA discontinuation have lower likelihood of HBsAg loss than White patients with HBsAg level <1,000 IU/mL at the

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time of NA discontinuation. Thus, NA withdrawal will have minimal global impact as a strategy toward HBV cure.

3. Combination of IFN and NA

Conclusion

Most studies evaluating de novo combination of IFN-α and NA have not shown an improvement in HBsAg loss. Two meta-analyses showed that IFN-α add-on to NA or switching from NA to IFN-α in selected patients may increase HBsAg loss but IFN-α is associated with many side effects and contraindicated in some patients, and the results in these selected patients may not be generalized.

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