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HBV 2021: New therapeutic strategies against an old foe

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Abstract

Hepatitis B virus (HBV) affects more than 250 million people worldwide, and is one of the major aetiologies for the development of cirrhosis and hepatocellular carcinoma (HCC). In spite of universal vaccination programs, HBV infection is still a public health problem, and the limited number of available therapeutic approaches complicates the clinical management of these patients. Thus, HBV infection remains an unmet medical need that requires a continuous effort to develop new individual molecules, treatment combinations and even completely novel therapeutic strategies to achieve the goal of HBV elimination. The following review provides an overview of the current situation in chronic HBV infection, with an analysis of the scientific rationale of certain clinical interventions and, more importantly, explores the most recent developments in the field of HBV drug discovery.

KEYWORDS

antiviral agents, cccDNA, combination therapy, HBV, immune modulation

1 | INTRODUCTION

With more than 250 million patients with chronic hepatitis B virus (HBV) infection worldwide, this disease is still a clear and ever-present public health burden.[1] Indeed, phylogenetic analysis of HBV genomes suggests that certain subgenotypes originated more than 50,000 years ago.[2] We have only recently understood how such a small non-cytopathic DNA virus could be of great clinical relevance, as HBV-associated complications are the seventh highest cause of mortality worldwide. Indeed, chronic HBV infection is one of the major aetiological factors in the development of cirrhosis and hepatocellular carcinoma (HCC).[3] On the molecular level, the mechanism behind chronic HBV infection is based on the persistence of the viral genome as an episomal structure referred to as covalently closed circular DNA (cccDNA), which remains in the nucleus as a viral reservoir and template for viral replication.[4] As a by-product of viral replication, HBV DNA can be randomly integrated into the host cell genome. Although integrated HBV sequences cannot sustain viral replication, they can generate viral proteins, namely hepatitis B surface antigen (HBsAg) and the transcriptional regulator HBV x protein.[4]

Despite the implementation of universal vaccination programs, chronic HBV infection remains a major public health problem worldwide. Moreover, existing therapeutic compounds against HBV are

Abbreviations: ALT, alanine aminotransferase; ASO, antisense oligonucleotide; CAM, capsid assembly modulator; CAR, chimeric antigen receptor; cccDNA, covalently closed circular DNA; CHB, chronic HBV infection; CRISPR, clustered regularly interspaced short palindromic repeats; DAA, direct-acting antiviral; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; HTA, host-targeting agent; NAP, nucleic acid polymer; NK, natural killer; NTCP, sodium taurocholate cotransporting polypeptide; NUC, nucleos(t)ide analogue; PD1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; Peg-IFN-α, pegylated interferon α; RIG-I, retinoic acid-inducible gene I; RISC, RNA-induced silencing complex; siRNA, small-interfering RNA; TCR, T-cell receptor; TDF, tenofovir disoproxil fumarate; TLR, Toll-like receptor; WHV, woodchuck hepatitis virus.

limited and mainly include nucleos(t)ide analogues (NUCs) (eg entecavir, tenofovir) and pegylated interferon α (Peg-IFN-α). As beneficial as they may be, these treatments do not usually achieve eradication of the virus and HBsAg loss is still rare.[5] Thus, these regimens require indefinite treatment to maintain viral suppression and prevent the virological relapse that usually occurs after treatment discontinuation.[6] Moreover, it is unrealistic to expect all patients to adhere to long-term or lifelong non-curative treatment and there is a strong patient preference for finite therapy. Drug resistance is still a concern in low-income settings that use early generation NUCs and while there is no resistance with IFN treatment, the use of this agent is rare because of problems with tolerability. The cost of lifelong therapy and monitoring is also an important economic issue in highly endemic areas. Thus, the aim of new therapeutic strategies is to achieve a "functional cure" for chronic hepatitis B (CHB), defined as sustained off-treatment loss of HBsAg, undetectable HBV DNA in serum, normalization of liver enzymes and improvement in liver histology (Figure 1). HBsAg loss is a sign of profound suppression of HBV replication and is the only existing indicator for safe treatment discontinuation. Moreover, HBsAg loss is associated with a decreased risk of developing inflammation-driven hepatic complications such as HCC.[7,8]

Thus, CHB is an unmet medical need which requires a continuous effort to develop new individual molecules, combinations therapies and completely novel therapeutic strategies to achieve the goal of HBV elimination.[9] The search for these compounds is a highly dynamic field that has grown considerably in recent years owing to the close collaboration between academic research and industry. This has led to renewed interest in the development of novel direct-acting antivirals (DAAs) and host-targeting agents (HTAs) for HBV infection. Thus, the aim of this review is to analyse the scientific rationale for potential treatments and more importantly, to describe the most recent clinical developments in the field to understand future therapies against HBV.

Key points

- HBV infection is a major public health burden with more than 250 million individuals with chronic infection worldwide.
- The clinical management of patients with HBV infection is difficult and costly, as it involves close monitoring for long periods of time.
- Improving the treatment of patients with HBV infection will require the development of new direct-acting antivirals and host-targeting agents.
- The evaluation of novel drug combinations will also be essential to achieve the goal of HBV elimination.
- Further efforts should be made to improve HBV animal models and continue the development of preclinical stage treatments.

2 | NOVEL DIRECT-ACTING ANTIVIRALS AGAINST HBV INFECTION

Based on the particularities of the HBV viral cycle, DAA-based therapeutic strategies can be classified according to the process they target. These include: 1) drugs targeting the HBV replicative cycle, in particular, inhibitors of entry, capsid assembly/disassembly, HBsAg secretion and reverse transcriptase; and 2) drugs targeting HBV gene expression, which are compounds designed to decrease the levels of viral transcripts and antigens. Both classes of drugs indirectly target the intracellular pool of cccDNA. Targeting viral expression can decrease HBsAg levels and therefore help restore antiviral immune responses. Strategies directly targeting viral cccDNA for degradation or silencing should be a priority. This review will discuss selected examples of these compounds under clinical investigation (Table 1).

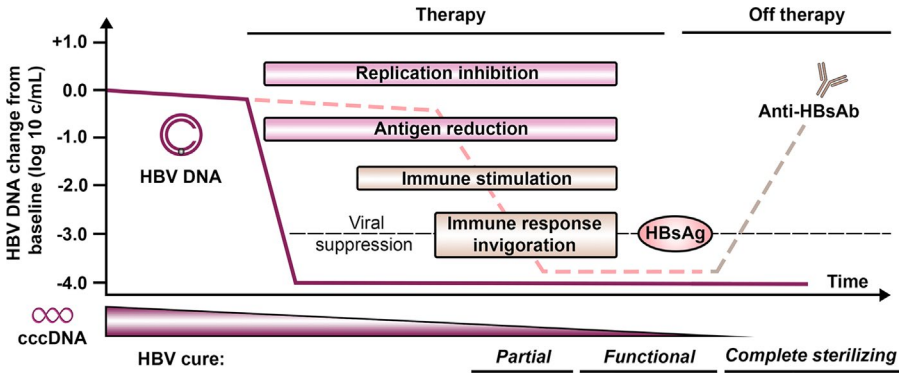

FIGURE 1 New antiviral strategies aimed to achieve HBV cure. The goal of anti-HBV therapy is to achieve a functional cure, defined as sustained off-treatment loss of HBsAg, undetectable HBV DNA, normalization of liver enzymes and improvement in liver histology. Current antiviral regimens require indefinite treatment and do not usually achieve virus eradication. Future therapies directed against the virus (inhibition of replication and antigen production) or the host (immune response stimulation and reinvigoration) and their combination may improve upon current treatments and increase the rate of patients achieving a sustained response or even allow HBV elimination. Abbreviations: cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; HBsAb, HBs antibodies; HBV, hepatitis B virus

TABLE 1 HBV antiviral compounds currently under clinical evaluation

Compound	Mechanism of action	Clinical stage	Reference/clinical trial
Entry inhibitors			
Myrcludex B (bulevirtide)	Blocks NTCP	II	[11]
CRV431	Blocks NTCP and protein folding	I	NCT03596697
Capsid assembly modulators			
ABI-H0731 (Vebicorvir)	Core binding	II	NCT04454567 [14]
JNJ-6379	Core binding	II	NCT03361956
GLS4	Core binding	II	NCT04147208
RO7049389	Core binding	II	NCT04225715
HBsAg secretion inhibitors			
REP 2139 and REP 2165	HBsAg binding	II	NCT02565719 [17]
Nucleos(t)ide analogues			
HS-10234	Polymerase inhibitor	III	NCT03903796
Viral expression inhibitors			
JNJ-3989 (ARO-HBV)	siRNA targeting HBV transcripts	II II I/II	NCT04439539 NCT04535544 NCT03365947 [20]
VIR-2218	siRNA targeting HBV transcripts	II II	NCT04507269 NCT04412863 [21]
GSK3228836 (ISIS 505358)	ASO targeting HBV transcripts	IIa	NCT04449029 [22]
RO7062931	ASO targeting HBV transcripts	I	NCT03038113 [23]
RG6346 (DCR-HBVS)	siRNA targeting HBV transcripts	I	NCT03772249
Innate immunity activators			
GS-9688 (Selgantolimod)	TLR8 agonist	II II	NCT03615066 NCT03491553 [30]
Adaptive immunity activators			
ASC22 (Envafolimab)	Anti-PD-L1 antibody	II	NCT04465890
HepTcell (FP-02.2)	Therapeutic vaccine	I, cleared for phase II	NCT02496897
TG-1050/T101	Therapeutic vaccine	II	NCT04189276 [35]
GS-4774	Therapeutic vaccine	II	[36]

Abbreviations: ASO, antisense oligonucleotide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NTCP, sodium taurocholate cotransporting polypeptide; PD-L1, programmed cell death 1 ligand 1; siRNA, small-interfering RNA; TLR8, Toll-like receptor 8.

2.1 | Targeting the HBV replicative cycle

2.1.1 | Entry inhibitors

Because de novo infection is a central factor in the maintenance of the cccDNA pool and thus the persistence of HBV infection, targeting viral entry would be a sensible approach to prevent progression of the viral cycle.[10] Moreover, hepatitis delta virus (HDV) uses the HBV envelope and thus also uses sodium taurocholate cotransporting polypeptide (NTCP) as an entry receptor. Therefore, this approach could also help manage HBV/HDV co-infected patients. Myrcludex B (bulevirtide), a peptide containing

47 amino acids of the pre S1 domain of the HBV large surface protein, was developed to compete with HBsAg for binding to NTCP and thus inhibit virion uptake in the cell. Myrcludex B was recently evaluated for HBV/HDV co-infection, showing that the combination of Myrcludex B + Peg-IFN-α was associated with both a decline in HDV RNA titres as well as HBsAg decline/loss, which is also relevant for HBV mono-infections.[11]

CRV431 is a cyclophilin inhibitor that has been shown to prevent HBV entry in vitro by targeting NTCP.[12] The effect of CRV431 in vivo was then explored in a study using HBV transgenic mice, reporting significantly reduced hepatic HBV DNA levels and an additive inhibitory effect in combination with the prodrug tenofovir exalidex.[13] CRV431 is being evaluated in a phase I clinical trial (NCT03596697).

2.1.2 | Capsid assembly modulators

Similar to entry inhibitors, capsid assembly modulators (CAMs) could be a viable strategy to reduce HBV viral load. Depending on their chemical structure, this type of drug can induce either the production of misassembled non-capsid core polymers or morphologically normal capsids that lack HBV nucleic acid. The rationale behind their use is based on the action of these compounds on several steps of the viral cycle. Indeed, besides their capacity to alter the correct formation of new nucleocapsids (and, thus, infectious virions), they have been shown to block transport of HBV nucleocapsids to the nucleus, their disassembly and the release of viral particles, thus reducing cccDNA formation in newly infected cells. Moreover, since the core protein has been proposed as a transcriptional regulator of cccDNA, these drugs could affect HBV RNAs expression. ABI-H0731 (Vebicorvir), one of these compounds, is currently being evaluated in a phase II clinical study to assess its antiviral activity in combination with NUCs (NCT04454567). Preliminary results have confirmed the favourable safety profile of ABI-H0731. Moreover, after 24 weeks of treatment, a higher proportion of hepatitis B e antigen (HBeAg)-negative patients receiving ABI-H0731/NUC achieved undetectable HBV DNA levels compared to the placebo/NUC group.[14] The results of at least three other CAMs, JNJ-6379, GLS4 and RO7049389, have been favourable in phase I trials and are being evaluated in phase II studies (NCT03361956, NCT0414720 and, NCT04225715).[15,16]

2.1.3 | HBsAg secretion inhibitors

The most recent members of this family of drugs are nucleic acid polymers (NAPs), a class of broad-spectrum viral attachment or entry inhibitors that also prevent the release of HBsAg from HBV-infected hepatocytes. Because the immune exhaustion caused by a high viral antigen load is a key process in the progression towards CHB, this type of antiviral compound could decrease circulating levels of HBsAg and thus potentially favour clearance of the virus by the immune system. Indeed, recently published results from a phase II trial (NCT02565719) have shown that addition of the NAPs REP 2139 and REP 2165 to a regimen including tenofovir disoproxil fumarate (TDF) and Peg-IFN-α resulted in significantly increased rates of HBsAg loss and HBsAg seroconversion during therapy (60%) and a functional cure after therapy (35%).[17]

2.1.4 | Nucleos(t)ide reverse transcriptase inhibitors

Although new-generation NUCs do not eliminate HBV, they are highly efficient in suppressing viral DNA synthesis and are therefore the current backbone of treatment for CHB. There are several compounds being developed to improve available NUCs. One example is HS-10234, a 5' deoxyadenosine triphosphate analogue that is being evaluated in a phase III clinical trial to compare its efficacy and safety against TDF for CHB (NCT03903796).

2.2 | Targeting HBV gene expression

As previously mentioned, high antigen load is thought to play a role in maintaining chronic HBV, so preventing HBsAg production by both cccDNA and integrated DNA is of interest. Moreover, targeting viral expression is not limited to HBsAg because the characteristics of the HBV genome allow selection of target sequences in overlapping coding regions and thus simultaneous degradation or translation inhibition of multiple transcripts can be achieved. Most of the HBV antiviral strategies under clinical evaluation are small-interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs). At the molecular level, ASOs are distinct from siRNAs as they are not incorporated into the RNA-induced silencing complex (RISC) to silence its target, but they induce RNase H-mediated RNA cleavage by binding to target RNA.[18] Some of the molecules under evaluation include the siRNAs JNJ-3989, VIR-2218 and RG6346, and the ASOs GSK3228836 and RO7062931.

siRNAs were first tested a few years ago in CHB patients. Results showed a stronger decline in HBsAg levels in NUC-suppressed HBeAg-positive than in HBeAg-negative patients. Additional studies in chimpanzees showed that in the HBeAg-negative chronic infection phase, HBsAg may be mainly expressed from integrated viral sequences instead of cccDNA, and that integration may delete the target sequence of siRNA in the 3' end of viral transcripts.[19] Thus, siRNAs were re-designed to target the 3' end of all transcripts upstream from the integration site to be re-evaluated in clinical trials while improvements were made in delivery modes. Preliminary results of the new generation of siRNAs showed that JNJ-3989 (ARO-HBV) is well tolerated in CHB patients and induces a significant HBsAg reduction in most cases. A subset of patients also had sustained suppression of HBsAg for up to 9 months after the last treatment dose.[20] JNJ-3989 is now in phase II evaluation (NCT03365947). VIR-2218, a siRNA targeting HBV transcripts, is being evaluated in phase II studies as

monotherapy (NCT04507269) or in combination with Peg-IFN-α (NCT04412863). Preliminary results have shown VIR-2218 to be well tolerated in patients with CHB and that this agent induces marked reductions in HBsAg in both HBeAg-positive and -negative patients.[21] A third siRNA of interest is RG6346 (DCR-HBVS), which is currently in phase I clinical trials (NCT03772249).

GSK3228836 (ISIS 505358) is an ASO targeting all HBV RNAs which is being evaluated in a phase II trial (NCT04449029). Recent results from this clinical study have shown that after 4 weeks of treatment with GSK3228836 there was a significant reduction in HBsAg levels associated with alanine aminotransferase (ALT) elevation in patients. This was observed in both NUC-treated and -naïve patients. Significant reductions in HBV DNA were also reported in treatment-naïve patients.[22] In addition, preliminary results are available from a phase I clinical trial evaluating the ASO RO7062931, a locked nucleic acid targeting HBV transcripts (NCT03038113). This report showed that the compound is well tolerated with potential antiviral activity, suggested by a decrease in HBsAg levels following 4 weeks of treatment.[23]

Finally, it is worth mentioning a third category of small molecules targeting HBV antigen production via RNA destabilization (eg AB-452 and RG7834). Although these compounds are not in clinical development, drugs such as RG7834 have been shown to reduce HBsAg levels and HBV viraemia in animal models.[24]

3 | NOVEL HOST-TARGETING AGENTS AGAINST HBV INFECTION

The development of antiviral agents has mainly focused on compounds targeting viral components. The rationale behind this is that these compounds would be less likely to cross react with human molecules and thus induce less toxicity. However, because the control of HBV infection is mainly immune-mediated,[25] approaches to boost innate and/or adaptive immunity are also an area of research. Moreover, this approach is based on 1) the observation that no matter how virus specific the design of DAAs might seem, off-target and side effects may occur, 2) the fact that drug resistance often appears after extended use of DAAs and 3) the limit that the small HBV genome imposes on drug design. Therefore, HTAs appear to be an option to overcome these issues and several of them are currently under clinical evaluation (Table 1).

3.1 | Stimulating the innate immune response

Although there is still a debate about whether HBV escapes or actively suppresses the innate immune system, it is clear that it is a weak inducer of these antiviral responses. However, HBV replication can be suppressed by reactivating innate signalling pathways in hepatocytes, such as during co-infection with HDV, in which a reduction in HBV is observed. These antiviral responses are not limited to HBV-infected hepatocytes, as cytokines produced in non-parenchymal cells (eg IFN-γ, IL-1β) also play a role in controlling infection. Indeed, this is the rationale for IFN-α because it not only presents direct antiviral action but also boosts natural killer (NK) and T-cell responses. Therefore, direct activation of innate immunity in hepatocytes via retinoic acid-inducible gene I (RIG-I) or in neighbouring cells via Toll-like receptor (TLR) signalling has been explored as possible immunostimulatory therapy against CHB.

For example, Inarigivir, a RIG-I agonist was reported to inhibit HBV replication via induction of IFN-α in hepatocytes, however, results were not confirmed in the clinical evaluation. Despite an initial assessment concluding that Inarigivir was well tolerated following 12 weeks of administration, a second longer clinical trial reported severe toxicity in several patients and the development of organ failure and death in one.[26] Similarly, results with the TLR7 agonist GS-9620 were highly promising in the woodchuck hepatitis virus (WHV) and chimpanzee models,[27] however, the clinical evaluation was disappointing, with no significant decreases in HBsAg despite target engagement, demonstrated by increased ISG15 expression.[28]

More recent results with GS-9688 (Selgantolimod), a TLR8 agonist that favours production of IL-12, IFN-γ and stimulation of T-cell function, have been encouraging in the WHV model.[29] GS-9688 is under evaluation in a phase II trial to determine its safety, tolerability and antiviral activity in untreated patients (NCT03615066). Preliminary results have shown that GS-9688 is well tolerated after 24 weeks of treatment, with HBsAg loss and HBsAg decline more apparent in the GS-9688-treated group.[30]

3.2 | Stimulating the adaptive immune response

An interesting observation has shown that patients with CHB who received a bone marrow transplant from donors with resolved HBV infection may become HBsAg negative. This highlights the efficacy of HBV-specific immunity via the action of memory B and T cells. A similar situation is observed in patients with controlled HBV infection, showing coordinated activation of humoral and cellular immunity against HBV. However, this is not observed in most patients, as T cells progressively become dysfunctional and lose their proliferative and cytotoxic activity owing to continued exposure to HBV antigens (*T-cell exhaustion*).[31] Thus, activating HBV-specific responses could be another option in antiviral regimens, which could be achieved with checkpoint inhibitors or therapeutic vaccines.

Checkpoint inhibitors reinvigorate pre-existing antiviral immunity by preventing the action of signalling pathways that limit the duration and amplitude of immune responses. This type of negative regulatory mechanism is induced to reduce tissue damage. One strategy, for example, is to prevent the inhibitory signals generated from the interaction between programmed cell death 1 ligand 1 (PD-L1) and its receptor programmed cell death 1 (PD1). This PD-L1/PD1 interaction regulates the activity of T cells in peripheral tissues, playing a key role during inflammatory responses directed to control infection.[32] ASC22

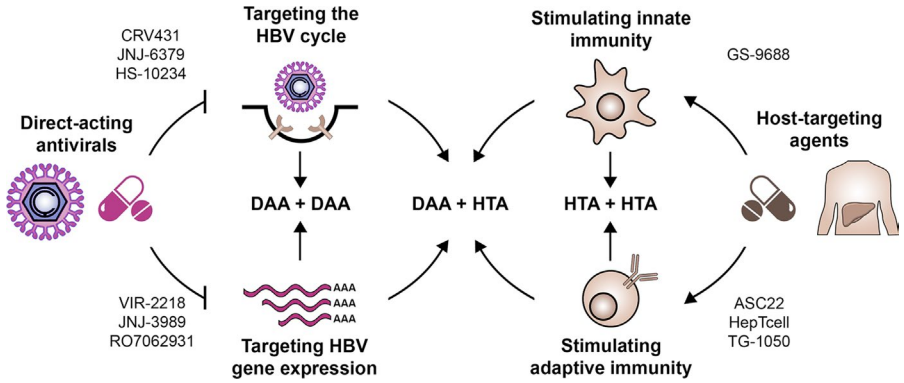

FIGURE 2 Combination of drugs with different mechanisms of action as a strategy against HBV infection. DAAs are divided into 1) drugs targeting the HBV replicative cycle and 2) drugs targeting HBV gene expression. HTAs are divided into 1) drugs that stimulate the innate response and 2) drugs that stimulate the adaptive immune response. Selected examples from table 1 are displayed alongside each category. The development of new compounds allows the potential combination of DAAs, HTAs or both, as a means of increasing the likelihood of HBV elimination. Abbreviations: HBV, hepatitis B virus; DAA, direct-acting antiviral; HTA, host-targeting agent

(Envafolimab) is an anti-PD-L1 antibody currently in phase II clinical trial to evaluate its safety and efficacy in CHB patients (NCT04465890).

Unlike checkpoint inhibitors, therapeutic vaccines boost immunity by priming new antiviral responses. This type of intervention mainly relies on the induction of effective CD4 and CD8 T-cell immunity and to a lesser extent on B cells and antibody responses. It is interesting to note that intrahepatic presentation of HBV antigens to T cells has been reported to result in their inappropriate activation.[33] Thus, it is preferable for these antigens to be present in other organs such as lymph nodes to undergo processing by professional antigen-presenting cells (eg dendritic cells). In this context, HepTcell (FP-02.2), a peptide-based immunotherapeutic, has recently completed a phase I trial and been cleared to initiate phase II evaluation (NCT02496897). TG-1050 is a replication-defective adenovirus serotype 5 expressing multiple HBV-specific antigens which has been shown to induce a significant reduction in circulating viral parameters in a mouse model. A phase I trial has confirmed a good safety profile with this agent which has been shown to induce HBV-specific cellular immune responses.[34,35] T101, a therapeutic vaccine based on the TG-1050 technology, is currently undergoing evaluation in a phase II trial (NCT04189276).

Finally, GS-4774, a therapeutic T-cell vaccine containing epitopes derived from HBs, x and core protein, has been shown to induce IFN-γ and IL-2 by CD8 T cells in TDF-treated patients. Although the use of GS-4774 was not significantly associated with a decrease in HBsAg levels, its strong immune stimulatory effect could be useful in combination with other antiviral agents or immune modulators to boost the immune response against HBV.[36]

4 | OPENING THE POSSIBILITY FOR NEW DRUG COMBINATIONS

Based on the knowledge of the mechanisms of HBV persistence, it is now clear that elimination of HBV will probably require combination therapies. Moreover, these therapies will probably include the combined effect of DAAs with HTAs. These approaches must obtain complete suppression of virus production, de novo infection and circulating HBsAg levels, while boosting the immune system to increase and maintain HBV-specific adaptive responses. This has been previously evaluated by a combination of NUCs and IFN, with practically no improvement compared to monotherapy. However, the new therapeutic agents under development such as those mentioned, represent interesting options to explore the efficacy of novel combination strategies.

The evaluation of these drug combinations will need to have a solid scientific basis with careful monitoring of potential drug-drug interactions and to be initially performed in patients without advanced liver disease.[6] We will now discuss some of these potential combinations (Figure 2).

4.1 | DAA combinations with or without inhibition of HBV expression

The goal of combining multiple DAAs is to target the HBV replicative cycle to reduce the pool of cccDNA by inducing more potent inhibition of viral genome replication and decreasing the rate of intracellular cccDNA recycling and/or of new rounds of hepatocyte infection. The combination of DAAs with different mechanisms of action would also prevent the development of drug resistance. Combining an entry inhibitor with a NUC could also be an option to reduce the cccDNA pool maintained by de novo infection. Similarly, the combination of NUCs with a potent CAM could provide stronger suppression of viral replication, leading to a decrease in intracellular recycling of cccDNA and its impaired formation in de novo-infected hepatocytes, thus reducing the pool of intrahepatic cccDNA. Whether this type of approach can achieve a functional cure or high rate of virological control after cessation of therapy needs to be evaluated in clinical trials.[37]

The idea of combining drugs that target the HBV replicative cycle with compounds targeting HBV expression is based on the hypothesis that reducing not only viral replication but also expression

of viral proteins and antigens to much lower levels than those obtained with NUC monotherapy could increase HBV-specific immune reconstitution in patients with CHB. Clinical trials are underway to evaluate this approach using siRNA JNJ-3989 in combination with the CAM JNJ-6379 and NUCs for the treatment of CHB patients (NCT04439539),[38] or in combination with NUCs in HBV/HDV co-infected individuals (NCT04535544).

4.2 | DAA combinations with immunotherapy

It has been suggested that combination strategies including NUCs and new immunological therapies could be promising for the management of CHB patients. This based on the observation that NUC treatment not only reduces the production of new virions but also because it resolves hepatic inflammation, thus increasing the accessibility and functionality of HBV-specific immune cells. This approach will be evaluated with HepTcell as an add-on therapy to entecavir or tenofovir in CHB patients (NCT02496897). Similarly, GS-9688 will be evaluated in patients receiving a variety of NUCs (NCT03491553).

Because of the limited efficacy of therapeutic vaccines up to now, it is thought that they may need to be given in combination with other immune therapies. This approach has been explored in preclinical models (ie WHV-infected woodchucks) which have shown that a combination of therapeutic vaccines and checkpoint inhibitors might have a beneficial effect against HBV infection.[39] Although there are no clinical investigations of this option as yet,[40] a combination of immunotherapeutic agents against CHB is an important field that warrants further investigation.

Finally, the combination of siRNAs with a therapeutic vaccine was recently evaluated in an animal model, which showed that reducing the HBV antigen load is highly relevant to overcome immune tolerance and achieve a cure for HBV in mice.[41]

5 | CONCLUSION AND PERSPECTIVES

With only 10 years until the 2030 deadline for the elimination of viral hepatitis,[9] we can see how much progress has been made in the development of new therapeutic agents against CHB. However, there are several challenges that must be addressed if this goal is to be met. In particular, the scientific community will need to focus on the development of better animal models for the study of HBV infection and antiviral drug discovery.[42] These models could help overcome the challenges of HBV cccDNA targeting, evaluating immune stimulation and preclinical testing of drug combinations.

Although this review has focused on drugs under clinical evaluation, we must highlight the investigations that are at early stages of development. Examples of promising strategies in this category are chimeric antigen receptor (CAR) T cells, HBV T-cell receptor (TCR)-designed CD8 T cells and soluble TCRs, to redirect HBV-specific T cells to infected hepatocytes and gene editing approaches to directly target cccDNA by clustered regularly interspaced short palindromic repeat- (CRISPR)/Cas9-based approaches.[43,44]

In summary, HBV eradication will require a thorough understanding of HBV biology, the specificities of the liver microenvironment and their interactions with the immune system. The design of future therapeutic approaches against HBV will need to take these factors into account, as they will probably pave the way for the next generation of antiviral agents and their combinations.

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CONFLICT OF INTEREST

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