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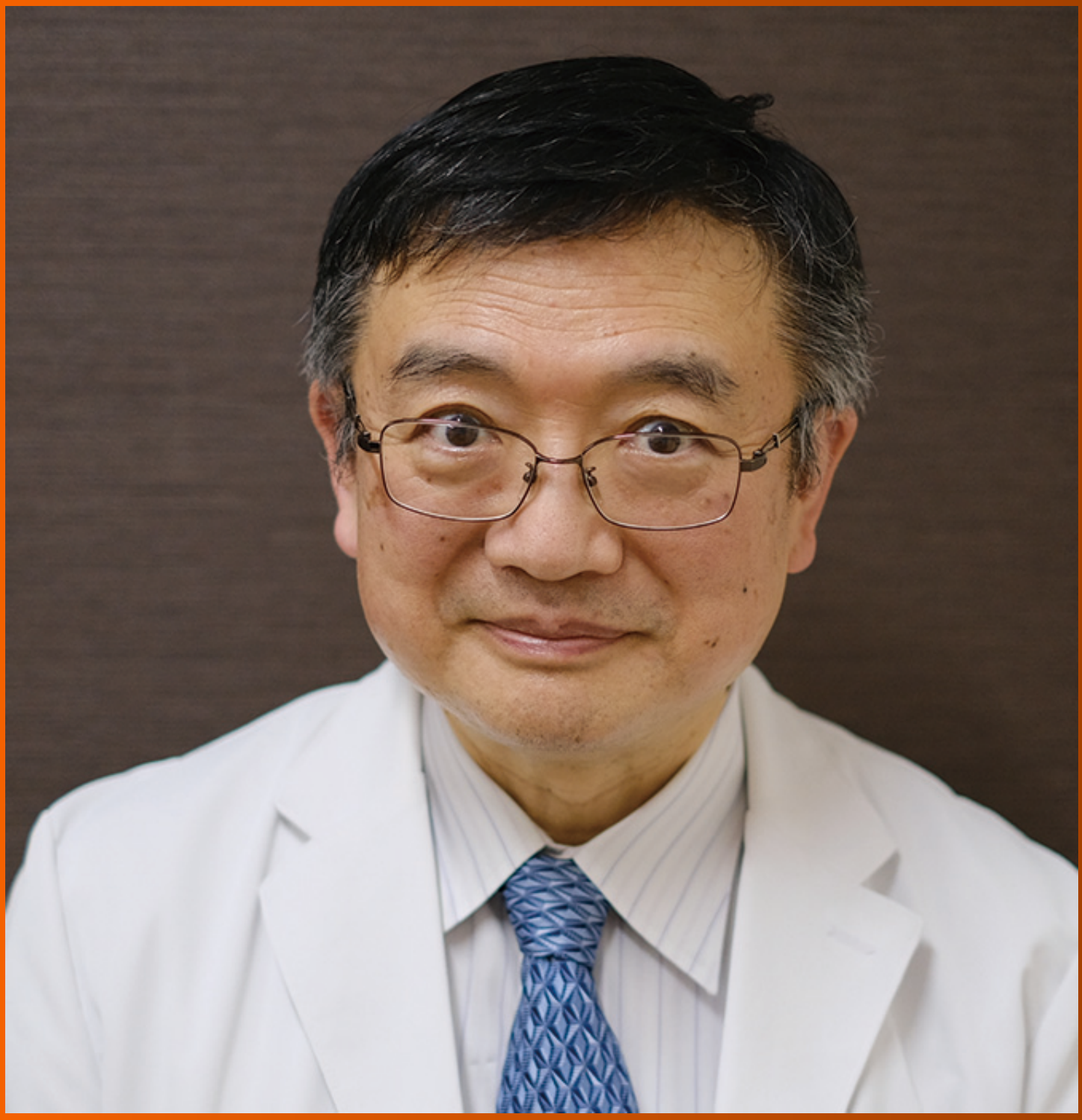

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REVIEW

Past, present, and future of long-term treatment for hepatitis B virus

Teresa Broquetas, José A Carrión

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Abstract

The estimated world prevalence of hepatitis B virus (HBV) infection is 316 million. HBV infection was identified in 1963 and nowadays is a major cause of cirrhosis and hepatocellular carcinoma (HCC) despite universal vaccination programs, and effective antiviral therapy. Long-term administration of nucleos(t)ide analogues (NA) has been the treatment of choice for chronic hepatitis B during the last decades. The NA has shown a good safety profile and high efficacy in controlling viral replication, improving histology, and decreasing the HCC incidence, decompensation, and mortality. However, the low probability of HBV surface antigen seroclearance made necessary an indefinite treatment. The knowledge, in recent years, about the different phases of the viral cycle, and the new insights into the role of the immune system have yielded an increase in new therapeutic approaches. Consequently, several clinical trials evaluating combinations of new drugs with different mechanisms of action are ongoing with promising results. This integrative literature review aims to assess the knowledge and major advances from the past of hepatitis B, the present of NA treatment and withdrawal, and the future perspectives with combined molecules to achieve a functional cure.

Key Words: Hepatitis B; Therapy; Antigen; Functional cure; Antiviral agents; Drug development

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Core Tip: Treatment for chronic hepatitis B has been used for decades, showing a good safety profile and high virological and clinical efficacy, decreasing hepatocellular carcinoma, clinical decompensation, and mortality. However, the low probability of hepatitis B virus surface antigen seroclearance with therapy made necessary indefinite treatment in a majority of patients. With the new insights about the immune system role in hepatitis B virus infection and the knowledge of the viral cycle phases, there has been in recent years increased activity in new therapeutic approaches. This review focuses on the past, present, and future of chronic hepatitis B therapy.

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INTRODUCTION

The hepatitis B virus (HBV) was identified in 1963 when the modern research history of viral hepatitis began. The Nobel Prize winner Baruch S. Blumberg (1925-2011) discovered, 60 years ago, an enigmatic serum protein named "Australia" antigen (AuAg)[1]. Some years later, the recognition of the HBV surface antigen (HBsAg) allowed for the first-time screening of blood donors. The HBsAg was the first marker assessed by a highly sensitive immune analysis, the HBV genome the first identified by deoxyribonucleic acid (DNA), the antibody against HBV core (anti-HBc) the first evaluated by the anti-μ capture technique, and the HBV vaccine the first produced by gene technology[2].

Infection by HBV may lead to acute or chronic hepatitis. Chronic hepatitis B (CHB) infection is defined as HBsAg serum detection for at least six months. The estimated world prevalence of CHB was 316 million in 2019, a major cause of cirrhosis and hepatocellular carcinoma (HCC)[3]. The treatment of choice during the last decades has been the long-term administration of nucleos(t)ide analogues (NA) with a high barrier to resistance. However, the low probability of HBsAg seroclearance made necessary an indefinite therapy.

This integrative literature review aims to review the major advances from the past of hepatitis B, the present of NA treatment and withdrawal, and the future perspectives for the new combined molecules to achieve a functional cure.

PAST

Virus detection: The "Australia" antigen and "Dane" particle

In the 1960s, virology was a young science, and techniques for the diagnosis of most viral diseases were complicated and suboptimal. The most often used method was the complement fixation reaction, which required four complex biological component mixtures from four different animal species. The first hint came from the American physician and geneticist Baruch S. Blumberg who used an immunological approach in 1967[1]. Blumberg's co-worker, Harvey J. Alter, discovered a new antigen in Australian aborigines named the AuAg.

Dane *et al*[4] were inspecting AuAg immune complexes under the electron microscope and identified virus-like particles of 42 nm in size. In 1971, Almeida *et al*[5] were able to free the core particles from the "Dane" particle and showed that patients formed, against this core antigen (HBcAg), antibodies (anti-HBc) suggesting that the Dane particle was the cause of hepatitis B, and the AuAg was the surface antigen of the HBV envelope (HBsAg)[5].

Many scientists, including Blumberg, recognized that the HBsAg did not allow to assess the severity of the disease. Magnius *et al*[6] discovered an additional marker when looking for HBsAg subtypes, the HB e antigen (HBeAg), which helped to distinguish highly infectious from less infectious HBV carriers. However, direct detection of the nucleic acid within HBV was not possible at that time since the HBV still could not be grown in cell cultures, and patient sera contained a few nanograms of Dane particles/mL. It was in 1974 when Robinson *et al*[7] identified the polymerase activity, and the HBV-DNA. The nucleic acid of HBV was a small circular double-stranded DNA but not covalently closed such as the polyoma- or papillomaviruses. Therefore, the ability of the HBV-DNA polymerase to transcribe both RNA and DNA was similar to retroviruses[2,8].

After more than half a century, current international guidelines have recommended using these three viral markers, HBsAg, HBeAg, and HBV-DNA for characterizing HBV infection[9-11].

Hepadnaviral life cycle: The journey of Dane particle

HBV is a partially double-stranded virus that belongs to the *Hepadnaviridae* family[12]. The virus replicates in the host's hepatocytes. The first step is viral cell entry *via* the bile acid transporter sodium taurocholate cotransporting polypeptide (NTCP)[13,14]. The HBV is transported to the nucleus to release the relaxed circular DNA (rcDNA) genome[15] and becomes a covalently closed circular DNA (cccDNA) that uses the host-cell DNA repair mechanism and can serve as a template for all viral transcripts that are translated into viral proteins. The HBV genome can be integrated into the host genome with the risk of hepatocyte transformation and carcinogenesis[16]. The pre-genomic RNA (pgRNA) is packaged and reversely transcribed to begin replication. The pgRNA is also enveloped and secreted. The HBV-integrated DNA encodes three HBsAg proteins: Large (L), middle (M), and small (S) HBs which are especially important in HBeAg-negative patients[17]. The viral capsids will be enveloped with the HBsAg and released as infectious virions, non-infectious sub-viral spherical or filamentous particles[18], empty virions (HBsAg and core proteins), and RNA virions[19]. The role of subviral particles in the pathogenesis of chronic HBV infection is not fully understood, but they could act as an immune evasion mechanism by blocking the host's neutralizing antibodies (anti-HBs) and promoting the spread and persistence of the infection[20,21].

Pathogenesis and phases of HBV infection

The first step in HBV infection is a highly replicative phase before immune recognition begins, after weeks or months of delay. A vigorous cellular immune response suppresses viral replication and eliminates most of the HBV-infected hepatocytes resulting in acute hepatitis. During acute hepatitis B, HBsAg disappears within six months. If HBsAg persist longer than this period, is considered a CHB infection. CHB is a dynamic interaction between HBV and the host's immune system.

Infection of newborns or infants results in a persistent infection because of an ineffective immune response. After a long anergic phase, immune defense emerges and leads to the selection of escape mutants. The cellular immune responses against HBcAg appear and HBeAg loses its immunomodulatory function. Therefore, the HBeAg-positive chronic infection usually occurs in younger patients during the first years. Patients have a high viral load with normal liver function tests. The HBeAg-negative chronic infection is characterized by low levels of HBV-DNA with normal liver function and without significant fibrosis. Generally, treatment is not recommended in these two phases, but guidelines advocate treating older than 30-40 years HBeAg-positive patients[9-11]. Chronic hepatitis, defined by the elevation of transaminases and high viral load, induces liver fibrosis progression to cirrhosis and risk of developing HCC, being antiviral treatment recommended in these phases (Figure 1).

Antiviral treatments: Interferon and nucleos(t)ide analogues

In 1976, William Robinson and Thomas Merigan reported that interferon alpha suppressed HBV replication and cured some patients suffering from CHB[22]. However, further clinical studies showed that only a minority of the patients achieved the clearance of HBsAg while the majority showed a viral breakthrough under treatment or a relapse after the end of therapy (EoT). Conventional interferon alpha was approved in 1992 and one year later Wong *et al*[23] demonstrated an HBeAg loss rate of 33%. Efficacy in HBeAg-negative patients was very limited and only 15% to 25% showed a sustained biochemical response after 12 mo of treatment[24]. In 2005, pegylated interferon (Peg-IFN) replaced the standard form due to its improved pharmacokinetics and prolonged half-life. In HBeAg-positive patients, 12 mo of therapy achieved the sustained response (HBeAg loss with HBV-DNA < 2000 IU/mL, 6 mo after therapy) in 20% to 30% and the HBsAg loss in 3% to 7%[25]. The Peg-IFN therapy has important disadvantages, its high variability of response and its unfavorable safety profile with a significant number of patients ineligible or unwilling.

In 1995, Benhamou *et al*[26] reported that HIV-co-infected patients with HBV who received the HIV drug named lamivudine (LAM) lost their HBV-DNA and improved their hepatitis (Figure 2). The same year Jules Dienstag showed the efficacy and safety of LAM in HBV-mono-infected patients[27]. LAM was well tolerated, but resistance soon developed in cases with high replication. After 5 years of therapy, 75% of the LAM-treated patients developed resistant HBV variants. The acyclic nucleotide analog adefovir (ADV) was approved in 2002 for LAM-resistant CHB patients. Unfortunately, its activity was relatively low and was rapidly replaced by the newer drug named tenofovir (TDF). This very similar drug was approved in 2001 for HIV and in 2008 for HBV[28]. The guanosine analog entecavir (ETV) was originally developed against the herpes simplex virus. In 1997, ETV showed its strong activity against HBV in the HepG2.2.15 cell line. In 2001, showed its efficacy in LAM-resistant CHB patients, and in 2005, it was approved over LAM[29]. In 2006, a synthetic thymidine nucleoside analogue named telbivudine (LdT) was approved but its activity was relatively low and was rapidly replaced. In 2015, the prodrug of TDF, tenofovir alafenamide (TAF), was approved for older patients with lower eGFR or lower bone mineral density[30,31].

Safety of long-term treatments

The safety profile of NA is very good even in HBV-infected patients with decompensated liver disease,

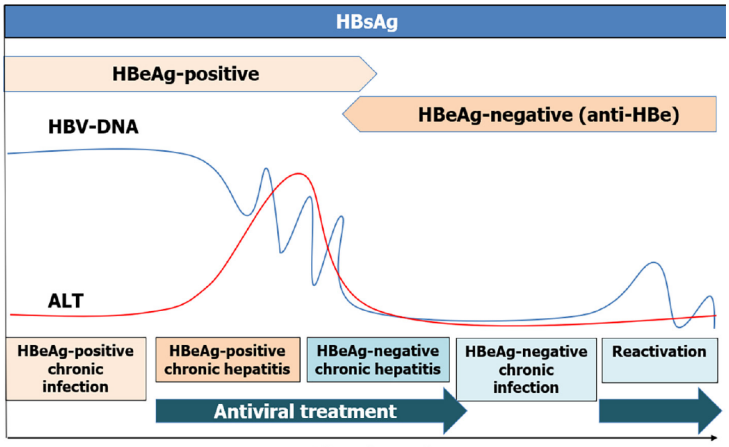

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Figure 1 Phases of hepatitis B virus infection. The persistence of hepatitis B virus surface antigen longer than six months is considered a marker for chronic hepatitis B infection. The HB e antigen (HBeAg)-positive chronic infection occurs in younger patients with high viral load and normal liver function tests. In contrast, HBeAg-negative chronic infection is characterized by low levels of hepatitis B virus-DNA with normal liver function and without fibrosis. Generally, treatment is not recommended in these two phases. Chronic hepatitis is defined by the presence of transaminases and high viral load that can induce liver fibrosis and risk of developing hepatocellular carcinoma, being antiviral treatment recommended[9-11]. HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase.

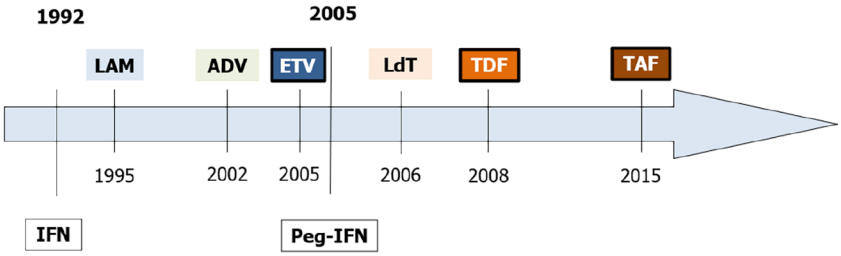

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Figure 2 Hepatitis B virus antiviral treatment history. The figure shows the United States Food and Drug Administration approval dates for hepatitis B virus drugs. IFN: Interferon; Peg-IFN: Pegylated interferon; LAM: Lamivudine; ADV: Adefovir; TDF: Tenofovir; ETV: Entecavir; LdT: Telbivudine; TAF: Tenofovir alafenamide.

liver transplants, extrahepatic manifestations, acute hepatitis, or severe exacerbation[32,33]. However, NA inhibits the HBV polymerase activity only during the time of administration. Long-term therapy with NA can produce a decline in bone mineral density and renal tubular dysfunction[34].

TDF and ETV have renal metabolism and must be adjusted if patients have an estimated glomerular filtration rate (eGFR) of less than 50 mL/min per 1.73 m^2. A multicenter retrospective study including 6189 CHB patients treated with TDF (n = 2482) or ETV (n = 3707) showed that TDF was associated with a higher risk of worsening renal function (adjusted HR 1.26, 95%CI 1.11-1.43)[35]. A systematic review and meta-analysis showed that TDF and ETV can affect renal function and patients with cirrhosis under TDF had a higher risk of renal damage and hypophosphatemia[36]. The effects of TDF on bone mineral density are suspected to be related to an increased tubular phosphate metabolism, but with few clinical implications as they appear to be reversible after withdrawal[34]. Recently, it has been shown an improvement in bone density and renal function in patients previously treated with TDF after switching to TAF[37]. However, TAF is not approved in very low eGFR (below 15 mL/min per 1.73 m^2).

Even if side effects of NA are scarce, CHB patients usually start treatment at young ages, and with NA treatment, they may be treated for decades. Therefore, questions on NA treatment duration and withdrawal have been gaining interest in recent years.

PRESENT

Monitoring HBV infection: Quantification of HBsAg levels

Classically, three viral markers have been used to characterize HBV infection: (1) The qualitative HBsAg; (2) the HBeAg; and (3) the HBV-DNA. However, most patients under NA treatment have

undetectable HBV-DNA and normal alanine aminotransferase (ALT). Therefore, other biomarkers are needed to monitor antiviral activity. The quantified HBsAg is one of the most extensively studied biomarkers because HBsAg negativization, spontaneously or with treatment, has been related to a good prognosis[38]. It has been shown that the decline in HBsAg levels during NA therapy is very slow (around 0.1 Log IU/mL per year)[39-41] suggesting that it would take decades, even long life, to achieve the HBsAg loss[42,43]. Importantly, some patients have shown a faster and larger HBsAg decline during NA therapy achieving low HBsAg levels[41,43]. Importantly, low HBsAg levels after NA withdrawal (below 1000 in Caucasian and below 100 in Asian patients) can be predictors of HBsAg seroclearance[44-47].

Efficacy of long-term antiviral therapy

The NA can be classified as low (LAM, ADV, and LdT) or high (ETV, TDF, and TAF) barrier of resistance. Current international guidelines recommend the use of NA with a high barrier of resistance to prevent the progression of liver disease, decompensation of cirrhosis, the need for liver transplantation, the development of HCC and to improve survival[9-11].

The suppression of HBV-DNA to undetectable levels (virological response) is normally associated with a normalization of transaminases (biochemical response) and an improvement in survival. In the presence of cirrhosis, all patients with detectable HBV-DNA should be treated[9-11]. Indications for HBeAg-positive and HBeAg-negative CHB patients' treatment are generally based on the combination of three main criteria: Liver disease severity, HBV-DNA units, and ALT levels[9-11].

In HBeAg-positive CHB patients, long-term NA therapy can induce HBeAg loss and seroconversion, leading to a low replicative phase with partial immune control[9-11]. In these patients, antiviral treatment with ETV has demonstrated a 5 years cumulative probability with a virological response of 99%, HBeAg loss of 53%, but HBsAg loss of only 1.4%[48]. Similarly, TDF for 10 years has demonstrated an HBeAg loss of 52% but only a 4.9% of HBsAg loss[33].

In HBeAg-negative patients, the 5-year cumulative probability with ETV of virological response was 96%, although HBsAg loss was only achieved in 4.6%[32]. In the TDF registry study with patients treated for 10 years, 100% achieved a virological response, and 83% biochemical response, but only 3.4% succeeded in the HBsAg loss[33].

Similar rates of virological response have been described for TAF in HBeAg-positive[30] and HBeAg-negative patients[31].

This high efficacy in controlling viral replication causes histological and elastographic improvement. The long-term treatment with NA has shown a significant regression of liver fibrosis and even cirrhosis. A study with paired liver biopsies, after a median time of 6 years, in 57 patients receiving ETV[49] showed histological improvement (decrease ≥ 2 points in the Knodell necroinflammatory score) in 96% of patients, and fibrosis improvement (decrease ≥ 1 point in the Ishak fibrosis score) in 88% of them. In a trial with TDF[50], including 348 patients with paired liver biopsies (at baseline and week 240), 87% showed histological improvement and 51% fibrosis regression (decrease ≥ 1 point in the Ishak fibrosis score). Among the 96 patients with cirrhosis at baseline, 74% achieved some degree of fibrosis regression.

A decrease in liver stiffness measurement (LSM) after long-term treatment with NA has been described[51]. After treatment initiation, the LSM decline is faster mainly related to the improvement in necroinflammatory activity. After 6 mo of therapy, the following LSM decrease is slower and could be associated with a true improvement of fibrosis[52,53].

The most important outcome of antiviral therapy is to improve survival. Studies comparing untreated and ETV-treated patients demonstrated that antiviral therapy reduced the incidence of liver-related complications, HCC, and mortality[54,55]. Similarly, a multicenter study in TDF-treated patients with cirrhosis showed a reduced risk of developing, clinical decompensation, HCC or liver transplantation, and death compared to untreated patients[56]. However, patients treated with NA, are still in danger of developing HCC, and high-risk patients stratified by risk scores such as REACH-B or PAGE-B, should continue HCC surveillance[57].

In recent years there has been a debate about the effect of the two main NA on HCC risk. Some data suggest that TDF is associated with significantly lower HCC risk compared to ETV in Asian patients [58]. A Chinese study including 29350 patients, showed a reduced HCC incidence in patients receiving TDF. However, there were differences in HCC risk factors between groups: TDF-treated patients were younger, and more frequently HBeAg-positive, females, without cirrhosis, and without diabetes. Thus, only 1% of patients with cirrhosis had received TDF[59]. Similarly, a recent meta-analysis of individual data including 42939 patients receiving TDF (n = 6979) or ETV (n = 35960) monotherapy, showed a lower risk of HCC with TDF, especially in patients older ≥ than 50, males, HBeAg-positive, and non-diabetic subgroups[60]. In contrast, other studies have failed to demonstrate this association[61,62]. A large study including 1935 Caucasian patients from the PAGE-B cohort did not find differences in 5-year cumulative HCC incidence between ETV (5.4%) or TDF (6.0%) after a median follow-up of 7.5 years[62].

Benefits of functional cure

The "functional" cure defined as the HBsAg loss, with or without seroconversion of antibody against HBsAg (anti-HBs), is considered the optimal goal for antiviral treatments[10,38]. However, even if third-

generation NA are drugs with a high barrier to HBV resistance, and high efficacy, achieving in most patients a virological and biochemical response, the HBsAg seroclearance is anecdotic[63,64]. Table 1 summarizes the efficacy of available treatments to achieve the HBsAg loss.

In patients without advanced fibrosis, the HBsAg loss is associated with an improvement in survival, and minimal risk of developing cirrhosis, decompensation, or HCC[38]. A recent study of 1972 patients with HBsAg loss, showed an HCC annual incidence of 0.38 per 100 person-years (median follow-up of 5.6 years). The study did not show differences between patients who achieved the functional cure spontaneously or with NA[65]. A systematic review showed lower HCC incidence in patients with functional cure (1.86%) compared to those who did not achieve it (6.56%) ($P < 0.001$). Cirrhosis, age ≥ 50, and male gender were the major risks for developing HCC after HBsAg seroclearance[66]. However, the 10-year HBsAg loss rate described in a large multicenter cohort ($n = 4769$) treated with ETV or TDF was only 2.1% with an annual incidence of 0.22%[64].

Rules to consider before treatment withdrawal

International guidelines of the main scientific societies recommend different treatment duration with NA. In non-cirrhotic HBeAg-positive CHB patients, NA treatment can be discontinued when HBeAg seroconversion is achieved and after one year of consolidation[9-11]. However, in non-cirrhotic HBeAg-negative patients, the NA treatment duration has been a matter of debate in recent years[39-43,67].

In 2008 the APASL guideline suggested the possibility of discontinuing NA therapy in HBeAg-negative patients after at least 2 years with undetectable HBV-DNA documented on three separate occasions 6 mo apart[68]. This approach in Asian patients was mostly driven by economics and reimbursement policies. Despite this, in 2012, Hadziyannis *et al*[69] reported in 33 Caucasian patients a high rate of HBsAg seroclearance after stopping ADV (39% at 5.5 years after withdrawal). In 2017, the first randomized controlled trial, the FINITE study, confirmed that the strategy of stopping therapy increased the HBsAg loss rate compared to continuing treatment (19% *vs* 0%)[70]. Based on these studies, in 2017 EASL guideline introduced the possibility of treatment withdrawal in non-cirrhotic HBeAg-negative CHB patients after 3 years of viral suppression[10]. In the last years, several studies have evaluated this strategy with different results (Table 1). Studies in Asian patients have shown a lower HBsAg loss rate compared to Caucasians. The different distribution of HBV-genotypes (especially genotype D), the inclusion or not of patients with advanced liver disease, and the different retreatment rules could explain these dissimilar results[45,71-73].

One of the important points to be considered before stopping treatment is the selection of the best candidates. The initial stopping rules proposed were based on the duration of treatment and virological suppression[9,10]. It has been suggested that NA withdrawal can be successful, only if the transcriptional activity of cccDNA has been silenced during treatment[74]. Additionally, it has been reported that long-term suppression of HBV-DNA can improve CD8 + T cell functions and restore the capacity of immune control by decreasing NK cell killing of HBV-specific T cells and increasing serum cytokines[44,75-77]. This immune restoration can exert control of viral replication after treatment discontinuation, and a large proportion of patients remain as inactive carriers. Moreover, the recurrence of HBV replication after NA discontinuation can represent a trigger for the immune response[78] that can induce an accelerated HBsAg decline and may be beneficial to eradicate residual cccDNA-containing hepatocytes. Our group has recently observed that HBsAg decline was faster during the first year after NA cessation compared to the on-treatment decline[46].

HBsAg and hepatitis B core-related antigen (HBcrAg) levels have been evaluated as surrogate markers to select the patients with a better outcome after NA cessation. It has been shown that not only HBsAg levels at the EoT but also on-treatment HBsAg kinetics are good predictors of HBsAg loss[79,80]. In a study performed by our group, we showed that on-treatment HBsAg kinetics had a high accuracy to predict the HBsAg loss one year after withdrawal[46]. Patients with an HBsAg decline > 1 Log IU/mL during treatment had a probability of 50% of achieving HBsAg loss one year after discontinuation. A large multicenter multiethnic study ($n = 1552$), the RETRACT-B study, showed different cut-offs of HBsAg at EoT in Asian and Caucasian patients. HBsAg levels at EoT < 100 IU/mL in Asian and < 1000 IU/mL in Caucasian patients were associated with a 4-year HBsAg loss probability of 33% and 41%, respectively[47]. Regarding levels of HBcrAg, the CREATE study, including 572 patients with NA discontinuation, showed lower HBcrAg levels at EoT in those with a virological response and HBsAg loss. Patients with undetectable HBcrAg (< 2 Log U/mL) at EoT showed a higher virological response and HBsAg loss rates one year after withdrawal (65% and 12%, respectively). The same group confirmed in 1216 patients that non-Asian ethnicity, HBsAg levels < 100 IU/mL, and undetectable HBcrAg were associated with the highest HBsAg loss rate[81].

Another important point is to define standardized re-treatment criteria. Some authors recommend delaying retreatment, to allow patients with a "beneficial" flare to achieve a functional cure[82]. However, other authors suggested that re-treatment should be initiated in response to significant increases in serum HBV-DNA, regardless of other liver parameters as cases of fulminant hepatitis have been reported[83]. Table 1 summarizes the efficacy of NA withdrawal to achieve the HBsAg loss[84-93].

Table 1 Efficacy of available antiviral treatments and nucleos(t)ide analogues withdrawal to achieve hepatitis B virus surface antigen loss

Ref.	Treatment (duration)	HBeAg	Ethnicity	Follow-up	HBsAg loss (%)
Current antiviral treatments					
Lau *et al*[84], 2005	Peg-IFNα (1 yr)	+	Mainly Asian	6 mo	2.9
Marcellin *et al*[85], 2013	Peg-IFNα (1 yr)	-	Asian	60 mo	12.0
Chang *et al*[48], 2010	ETV (5 yr)	+	Asian	-	1.4
Ahn *et al*[32], 2016	ETV (5 yr)	-	Mixed	-	4.6
Marcellin *et al*[33], 2019	TDF (10 yr)	+	Mixed	-	4.9
Marcellin *et al*[33], 2019	TDF (10 yr)	-	Mixed	-	3.4
Chan *et al*[30], 2016	TAF (3 yr)	+	Mixed	-	4.0
Buti *et al*[31], 2016	TAF (3 yr)	-	Mixed	-	3.0
Combined treatments					
Marcellin *et al*[86], 2016	Peg-IFN + TDF (1 yr)	+/-	Mixed	18 mo	9.1
Bourlière *et al*[87], 2017	ETV, TDF, ADV, and LAM (1 yr)	-	Caucasian	12 mo	7.8
Lim *et al*[88], 2022	NA add-on Peg-IFN (1 yr)	+/-	Asian	6 mo	12.1
Mo *et al*[89], 2022	NAs (HBsAg < 1500 IU/mL, 1 yr)	-	Asian	48 mo	33.2
Lim *et al*[88], 2022	NA switch to Peg-IFN (1 yr)	+/-	Asian	6 mo	9.7
NA discontinuation					
Chen *et al*[90], 2018	2.7 yr	+	Asian	96 mo	19.6
Song *et al*[91], 2021	2.9 yr	+	Asian	73 mo	9.5
Kuo *et al*[92], 2019	3.1 yr	+	Asian	24 mo	4.7 (ETV); 0 (TDF)
Jeng *et al*[72], 2018	2.9 yr	-	Asian	36 mo	13
Chen *et al*[90], 2018	2.9 yr	-	Asian	96 mo	33.1
Kuo *et al*[92], 2019	3.1 yr	-	Asian	36 mo	10 (ETV); 15 (TDF)
Chen *et al*[93], 2020	3.2 yr	-	Asian	58 mo	20.8
Song *et al*[91], 2021	2.7 yr	-	Asian	73 mo	14.6
Hirode *et al*[47], 2022	3.0 yr	-	Mixed	17 mo	15.0

Only studies with more than 100 patients have been included. HBsAg: Hepatitis B virus surface antigen; HBeAg: Hepatitis B e antigen; Peg-IFN: Pegylated interferon; LAM: Lamivudine; ADV: Adefovir; TDF: Tenofovir; ETV: Entecavir; TAF: Tenofovir alafenamide.

Risks of treatment withdrawal

The safety of treatment withdrawal is under discussion because on one hand hepatitis flare after NA cessation can induce hepatic decompensation but on the other hand early initiation of NA retreatment can inhibit the beneficial effect of flare-associated immune activation[47,72,94,95]. A study from Taiwan including 691 patients (44.6% with cirrhosis) showed a clinical relapse in 60.6% (7 developed a hepatic decompensation and 3 died)[72]. Similarly, the RETRACT-B study showed hepatic decompensation in only 1.22% (4.3% in patients with cirrhosis and 0.8% in those without cirrhosis; $P < 0.01$)[47]. In this study, 7 patients died (0.45%) by hepatic decompensation and 4 (0.25%) due to hepatitis B-associated flare.

Another important issue is the risk of developing HCC. The study of Jeng *et al*[72] included patients with (n = 308) and without cirrhosis (n = 383). The HCC incidence at 1, and 3 years after treatment discontinuation (0.15% and 1.00% for non-cirrhotic *vs* 1.30% and 4.00% for patients with cirrhosis) was similar to those during NA therapy (0.08% and 0.30% for non-cirrhotic *vs* 1.50% and 3.40% for patients with cirrhosis). Similarly, in the RETRACT-B study, the HCC incidence at 48 mo after NA withdrawal was 2.2% in patients with cirrhosis and 0.7% in those without cirrhosis[47]. Therefore, NA withdrawal does not seem to increase HCC rates. However, the tolerable level of circulating HBV DNA during long-term follow-up post-NA withdrawal has not been yet elucidated.

The evidence of increased HBsAg loss rates after NA cessation in some HBeAg-negative CHB patients must be balanced with safety. NA withdrawal should be performed only in centers with expertise in CHB management and in adherent patients willing stricter control after carefully discussing the pros and cons[74,96,97].

FUTURE

The need of expanding antiviral treatment criteria

Some recent studies have evaluated, with contradictory results, the use of NA in patients who do not meet strict criteria for treatment. On one hand, two retrospective studies in HBeAg-positive HBV-infected patients from Korea showed a lower risk of HCC and cirrhosis in those treated compared to untreated controls, suggesting a benefit of starting NA treatment at earlier phases[98,99]. Similarly, another Asian study including "minimally active" carriers showed a high risk of HCC (HR 9.9; 95%CI, 1.239-76.923; P = 0.031) when compared to inactive carriers[100]. But, the study included HBeAg-positive patients and those with a LSM > 9 kPa[101].

On the other hand, some European studies have not demonstrated significant benefits. A study from Italy, including patients without treatment with normal ALT and DNA < 20000 IU/mL, showed a benign course during a follow-up longer than 4 years[102]. Another study including Caucasian patients with HBeAg-negative chronic infection showed a high rate of HBsAg loss (15%) and low transition to CHB (6.3%) in patients with normal ALT and DNA < 2000 IU/mL or in the "grey zone" (HBV-DNA < 2000 IU/mL and ALT 40-80 U/L or, HBV-DNA 2000-20000 IU/mL and ALT < 40 U/L or ALT 40-80 U/L) after a median follow-up of 8.2 years[103]. However, a recent study from the United States has shown that patients without treatment indications, according to AASLD guidelines, had twice the risk of developing cirrhosis and/or HCC when compared to treated patients[104].

Simplifying indications for treatment initiation could be cost-effective and associated with survival improvement[105]. Therefore, it is plausible that antiviral treatment criteria will be expanded in the coming years to achieve the Global Hepatitis Elimination Goals, especially when new therapies with higher HBsAg loss rates will be available[106].

New HBV biomarkers to monitor antiviral therapy

The persistence of the cccDNA in the hepatocytes perpetuates HBV infection. So, detection and measurement of cccDNA levels would be the most precise tool to recognize HBV eradication. However, cccDNA can only be measured in liver biopsy samples by non-standardized or semi-automated techniques[107]. In recent years, there has been an effort to identify new biomarkers that could serve as cccDNA transcriptional activity surrogate markers.

The hepatitis B virus core-related antigen (HBcrAg) is an interesting biomarker composed of the hepatitis B core antigen (HBcAg), the HBeAg, and the 22-KDa pre-core protein (p22cr)[108]. These protein components are translated from cccDNA transcripts reflecting the cccDNA transcriptional activity. The HBcrAg is detected by automated chemiluminescence techniques using specific monoclonal antibodies with a limited sensitivity of 3.0 Log U/mL. The HBcrAg kinetics has been analyzed during NA therapy in a cohort of 222 CHB patients (132 HBeAg-negative and 90 HBeAg-positive) receiving ETV[109]. The decline of HBcrAg levels was 0.244 Log U/mL per year. HBcrAg levels were lower in HBeAg-negative patients compared to HBeAg-positive, but no differences were found between TDF or ETV[109,110]. On the other hand, the persistence of detectable HBcrAg at EoT has been related to severe aminotransferase flares after NA treatment cessation[111]. The main limitations of HBcrAg are its low sensitivity and its low levels after a long-treatment period in HBeAg-negative patients. Therefore, a great proportion of treated HBeAg-negative patients can show undetectable HBcrAg[112]. Recently, a new ultrasensitive assay has been described to improve the HBcrAg sensitivity, but further studies are needed to consider it in clinical practice[113].

The HBV-RNA is a newer marker under evaluation. The pgRNA is packaged in nucleocapsids and serves as the template for reverse transcription to HBV-DNA. In patients not receiving antiviral therapy, serum HBV-RNA levels are much lower than serum HBV-DNA levels. It can be detected in serum samples as pgRNA and spliced pgRNA variants produced by transcription of cccDNA as a marker of intrahepatic cccDNA transcriptional activity[114]. However, serum HBV-RNA is usually quantified by in-house assays and there are no commercial tests available for routine clinical practice. During NA therapy, reverse transcription of pgRNA to HBV-DNA is blocked, but cccDNA transcription to pgRNA persists, and HBV-RNA may be detected in the serum of patients with undetectable HBV-DNA. Therefore, the HBV-RNA could be useful to monitor NA-treated patients[115,116]. Recently, it has been shown that serum HBV-RNA reduced after treatment initiation from 1.46 Logs at week 48 to 1.77 Logs at week 96[117]. On one hand, serum pgRNA levels at wk 4 after NA initiation were correlated with low HBsAg levels (≤ 100 IU/mL) and seroclearance during follow-up[118]. On the other hand, high levels of pgRNA have been associated with viral relapse after NA withdrawal[119].

The recognition of HBsAg composition could be an interesting tool for following CHB patients because it changes across the stages of HBV infection. The main HBsAg component is S-HBs. The L-HBs and M-HBs proportion is lower in the inactive carrier stage compared to those in HBeAg-negative or HBeAg-positive CHB patients[120,121]. Interestingly, L-HBs and M-HBs proportions decrease prior to total HBsAg loss in patients receiving antiviral treatment[122].

Nowadays, the quantitative HBsAg is the most used and widely available biomarker as a consequence of its standardized and commercial tests. It includes the HBsAg produced not only from cccDNA but also by the integrated DNA that is the main source of the HBsAg in HBeAg-negative CHB patients, being more representative of the transcriptional activity. Moreover, quantitative HBsAg has shown a better predictive capacity compared to HBrcAg and HBV-RNA[123].

However, despite the potential utility of these new biomarkers for monitoring NA treatment, their usefulness should still be established for monitoring the new treatment strategies.

New drugs in development

After several years without major advances in novel therapies for CHB, currently, a multitude of new molecules are emerging, individually or in combination, as future treatment strategies. The last part of this review summarizes the main groups of evolving molecules evaluated in clinical trials (Table 2) and the combinations that are showing higher rates of sustained HBsAg loss (Table 3).

Several drugs are being evaluated in phase II clinical trials. These new molecules can be classified into two main groups according to their mechanism of action: (1) Molecules targeting different steps in the HBV life cycle; and (2) those acting as immunomodulators.

Molecules targeting HBV life cycle

Molecules targeting different steps in the HBV life cycle are summarized according to their treatment class, mechanism of action, and type in Table 2[124-143].

HBV entry inhibitors

HBV entry inhibitors protect naïve hepatocytes from infection. However, they do not directly target cccDNA. The recent identification of liver-specific bile acid transporter, the NTCP, has allowed exploring new therapeutics to block viral entry and reduce viral spread[144]. Bulevirtide consists of the preS1 domain of the large surface protein, which inhibits NTCP and prevents viral entry. In the phase 2 study, Bulevirtide monotherapy was evaluated in patients with CHB co-infected with the hepatitis D virus (HDV)[124]. HBV-DNA declined by > 1 Log in 32% of patients, although HBsAg was not affected. Its low effect on HBsAg levels made most studies focus on long-term treatment for HBV/HDV co-infected patients.

Capsid assembly modulators

The primary mechanism of action of nucleocapsid assembly modulators (CAMs) is to drive the nucleocapsid misassemble. These molecules interfere with capsid formation and disrupt the encapsidation of pgRNA. They have been classified into two main families (Class I and Class II). These agents have been shown to decrease serum HBV-DNA and RNA levels, although declines in HBsAg levels are negligible. Moreover, it has been shown HBV-RNA and HBcrAg rebounded after discontinuation of treatment [126]. Due to these limitations, to date, the role of CAMs in future treatments for CHB must be defined.

Post-transcriptional control inhibitors (small interfering RNA and antisense oligonucleotides)

RNA molecules, both pgRNA, and mRNAs encoding viral proteins, are essential for HBV replication. Small interfering RNA (SiRNA) is a specific post-transcriptional gene silencing mechanism that can inhibit the translation of viral proteins needed for cccDNA formation. SiRNA is 21-23 nucleotide duplexes processed from large double-stranded RNAs[145]. Chemically synthesized short RNA duplexes were shown to be capable of gene silencing *in vitro* without inducing an interferon response [146]. Different anti-HBV siRNA are being tested in clinical trials. Available clinical data are promising and show that siRNAs are safe and well-tolerated[127]. A study of siRNA therapy that targeted the common 3′ ends of all HBV transcripts showed that while the treatment markedly reduced HBsAg levels in HBeAg-positive patients, it had minimal effects in HBeAg-negative patients[128].

Antisense nucleotides (ASOs) are single-stranded DNAs (8-10 nucleotides) that target HBV mRNA sequences, forming a DNA-RNA hybrid that is rapidly degraded by cytoplasmic ribonuclease-H[147]. Early results of ASOs, alone or in combination, have shown a profound HBsAg decline[130]. The B-Clear Study, a phase 2b clinical trial evaluating bepirovirsen 300 mg subcutaneously once weekly for 24 wk, showed undetectable HBsAg in 9% of patients who received bepirovirsen plus NA and in 10% who received bepirovirsen alone[131].

HBsAg release inhibitors: Nucleic acid polymers

HBsAg plays a major role in HBV infection and is the most abundant HBV antigen. Therefore, blocking its release could potentially prevent the release of new virions, decline the number of subviral particles and restore the HBV-specific immune response[148]. Nucleic acid polymers (NAPs) are amphipathic

Table 2 Mechanisms of action of the new drugs under development

Treatment class	Mechanism of action	Types
Drugs targeting HBV life cycle		
Entry inhibitors	Blockage of liver-specific bile acid transporter (NTCP)	Inhibitors of NTCP[124]; NMAb[125]
Capsid assembly modulators	Interfere with capsid formation and disrupt the encapsidation of pgRNA	CAMs[126]
Post-transcriptional control inhibitors	Post-transcriptional gene silencing by inhibition of the translation of viral proteins	SiRNA[127-129]; ASOs[130,131]
HBsAg release inhibitors	Intracellular degradation of HBsAg *via* proteasomal and lysosomal degradation	NAPs[132,133]
Immunomodulators		
Innate immune activator	Stimulation of innate immunity through TLRs and RIG-I	TLRs agonist[134-137]; RIG-I agonists[138, 139]
Adaptive immune activator	Blocking the PD-1/PD-L1 pathway to reverse T-cell exhaustion; stimulation of host's immune response to generate CD4 and CD8 HBV-specific T cells	Checkpoint inhibitors[140,141]; therapeutic vaccines[142,143]

HBV: Hepatitis B virus; NTCP: Sodium taurocholate co-transporting polypeptide; NMAb: Neutralizing monoclonal antibodies; CAMs: Nucleocapsid assembly modulators; SiRNA: Small interfering RNA; ASO: Antisense oligonucleotides; NAP: Nucleic acid polymers; TLRs: Toll-like receptors; RIG-I: Retinoic acid-inducible gene-1; PD-1: Programmed death receptor 1; PD-L1: Programmed cell death ligand 1; HBsAg: Hepatitis B virus surface antigen; HBeAg: Hepatitis B e antigen.

phosphorothioate oligonucleotides. The antiviral effect of NAPs against HBV infection is the inhibition of HBsAg release, although the exact mechanism is unknown, resulting in rapid clearance of HBsAg [132]. In clinical studies, NAP monotherapy was accompanied by rapid HBsAg decline and seroconversion. Recently, NAP-based combination therapy with TDF and Peg-IFN achieved a functional cure in 35% of patients[133] Interestingly, in HBeAg-negative patients, HBsAg produced by integrated DNA was lost. However, more than 90% of patients experienced immune-mediated transaminase flares during therapy[132].

Immunomodulators

Immunomodulator molecules are summarized according to their treatment class, mechanism of action, and type in Table 2.

Immunomodulatory targets including therapeutic vaccines

The impaired immune response is one of the main barriers to eliminating HBV. T cell immune exhaustion due to the presence of high amounts of HBsAg and a defective response of the innate immune response has a role in HBV persistence. Thus, treatment strategies to restore HBV-specific immune responses with immunomodulatory therapies have been evaluated to achieve viral clearance.

Pegylated interferon: A "second life" for an old friend

Interferon was the first drug approved for CHB treatment. Despite the long use of this treatment, the exact mechanism of action is still unclear. It has been suggested that Peg-IFN has two main effects, acting on the transcriptional activity of cccDNA and also an immunomodulatory effect, enhancing both innate and adaptive immunity[149,150]. Due to its hypothetical immunomodulatory effects, the synergistic effects of combination with NA and Peg-IFN have been evaluated.

A recent meta-analysis found that NA and Peg-IFN combination improved HBsAg seroclearance rates (RR: 4.52, 95%CI: 1.95-10.47 for adding-on and RR: 12.15, 95%CI 3.99-37.01 for switching-to) compared to NA monotherapy. One of the strongest predictors of HBsAg seroclearance was the HBsAg level at the start of IFN therapy[151]. Our group also showed that the addition of Peg-IFN to NA produced a faster and larger decrease in HBsAg levels compared to NA monotherapy, especially in those patients with IL28CC polymorphism[112]. A better Peg-IFN response in patients with IL28CC polymorphism has been described especially in those infected with genotype D[152,153]. More recently, a Chinese real-world study (n = 3988), the Everest Project (NCT04035837), has reported that the addition of Peg-IFN alpha 2b to NA in HBeAg-negative patients achieved a 4-year HBsAg loss rate of 33%[89].

The main concerns on the use of Peg-IFN are side effects, poor tolerability, and major contraindication such as decompensated cirrhosis. These explain the preference to use NA in routine clinical practice. However, in selected patients with good tolerance, the adding-on or switching-to strategy may improve the HBsAg seroclearance. Indeed, some of the phase 2 trials evaluating new antivirals, have included concomitant treatment with Peg-IFN and have shown better outcomes.

Table 3 Efficacy of drug combinations to achieve sustained hepatitis B virus surface antigen loss

Drug class	Drug	Patients	Time therapy (wk)	Efficacy	Safety
NA +/- CAM	NA *vs* NA + JNJ-6379 (bersacapavir)	232	24-48	HBsAg decline 0.25 log IU/mL *vs* 0.41 log IU/mL	No major AE
SiRNA +/- NA	AB-729 *vs* NA + AB-729	43	8	HBsAg decline 2.03 log IU/mL monotherapy *vs* 2.16 log IU/mL combination	Injection site reactions; ALT flares
ASO + NA	ASO-GSK3228836 (bepirovirsen) ± NA	457	12-24	HBsAg < LoQ in 28%-29% and HBsAg loss in 9%-10% after 24 wk of EoT	Injection site reactions; few cases of grade 3-4 ALT flares
Inhibitor of NTCP + Peg-IFN	Bulevirtide + Peg-IFN in HDV-HBV co-infection	90	48	HBsAg loss 26.7% in one arm *vs* 0% in the other	Related to Peg-IFN; injection site reactions
NA + TLR agonists	NA + TLR7 agonist (vesatolimod, GS-9620)	162	24	No changes in HBsAg	Some grade 3 AE with higher doses (few treatment discontinuations)
NA + TLR agonists	NA + TLR8 agonist (selgantolimod)	48	24	HBsAg loss 5% at week 48	Mild and transient gastrointestinal AE
NA + checkpoint inhibitors	NA + PD-1 inhibitor (nivolumab)	12	1 dose (24 follow-up)	HBsAg reduction 0.48 log IU/mL (HBsAg loss in 5%)	No major AE
NA + checkpoint inhibitors	NA + PD-L1 inhibitor (ASC22, Menvafolimab)	48	24	HBsAg decline 0.38 log IU/mL (HBsAg loss in 19%)	Grade 1 and 2 ALT flares
NA + SiRNA +/- CAM	NA + JNJ-3989 (siRNA) + NA ± JNJ-6379 (CAM)	117	48	HBsAg decline 2.1 log IU/mL in double *vs* 1.8 log IU/mL in triple combination	No major AE
NAP + NA + Peg-IFN	REP2139 or REP 2165 + NA + Peg-IFN	40	48	HBsAg loss in 35% and HBsAg < 100 IU/mL in 75%	Related to Peg-IFN
SiRNA + NA +/- Peg-IFN	VIR 2218 (siRNA) + NA +/- Peg-IFN	80	24	HBsAg decline 2.03 log IU/mL in dual arm *vs* 2.55 log IU/mL in triple arm (HBsAg < 100 IU/mL in 95% and HBsAg < 10 IU/mL in 55%)	Related to Peg-IFN

CAM: Nucleocapsid assembly modulator; HBV: Hepatitis B virus; SiRNA: Small interfering RNA; NTCP: Sodium taurocholate co-transporting polypeptide; ASO: Antisense oligonucleotides; NAP: Nucleic acid polymers; TLRs: Toll-like receptors; RIG-I: Retinoic acid-inducible gene-1; PD-1: Programmed death receptor 1; PD-L1: Programmed cell death ligand 1; HBsAg: Hepatitis B virus surface antigen; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; LoQ: Limit of quantification; EoT: End of therapy; AE: Adverse events.

Toll-like receptor and retinoic acid-inducible gene-1 agonists

HBV can be recognized by receptors such as toll-like receptors (TLRs)[154] and retinoic acid-inducible gene-1 (RIG-1)[155] TLRs are receptors that initiated intracellular pathways and induce antiviral molecules such as interferons, and cytokines. It has been reported that the activation of TLR-mediated pathways results in the suppression of HBV replication. An oral TLR 7 (TLR7) agonist, GS9620, has shown a decrease in serum HBV-DNA and HBsAg in chimpanzees[134]. However, a phase IIb trial in humans, showed a minimal decrease in HBsAg levels, despite the increase in cytokines and NK cell activity[135,136]. A more recent trial has shown that the combination of selgantolimod, a TLR8 agonist, with a NA resulted in a minimal reduction of HBsAg levels[137]. RIG-I constitutes an intracytoplasmic receptor that interacts with RNA viruses. Once activated, it leads to signal transduction through protein kinase complexes and activation of transcription factors that migrate to the nucleus and activate interferon-stimulable genes leading to the production of IFN[138]. Inarigivir activates the RIG-I pathway. Although early studies reported a reduction in HBV-DNA levels, there were cases of severe hepatotoxicity, with multiple cases of acute liver failure and one death, that lead to its discontinuation [139].

Checkpoint inhibitors

The immune system of HBV-infected patients shows high levels of programmed death receptor 1 (PD-1)-expressing CD8 T cells and high levels of programmed cell death ligand 1 (PD-L1) expression. This suggests that PD-L1 blockade could be a suitable strategy to treat chronic HBV infection. Furthermore, anti-PD-L1 blockade increases the number of IFN-γ-producing T-cells and the amount of IFN-γ produced per cell[156]. Checkpoint inhibitors against PD-1 and PD-L1 have been shown to be effective in several malignancies by reversing T-cell exhaustion and restoring immunity. However, the efficacy to achieve HBsAg clearance has been disappointing. In the CheckMate 040 trial, nivolumab increased

HBV-DNA 1 Log from baseline in 10% of HBsAg-positive patients[140]. PD-1 blockade showed limited antiviral activity, and no patient exhibited HBsAg seroconversion[141].

Monoclonal antibodies

HBV entry can be interrupted by small compounds such as neutralizing monoclonal antibodies (NMAb). In a phase 2 study, it has been evaluated the combination of NMAb VIR-3434 with small interfering RNA (SiRNA) VIR-2218 for up to 20 wk. Combination treatment was generally well tolerated with no serious adverse events. The majority of patients achieved low levels of HBsAg (< 10 IU/mL) but any patient lost the HBsAg during the study[125].

Therapeutic vaccines

These immunogenic molecules are developed to stimulate the host immune response generating CD4 and CD8 HBV-specific T cells to suppress viral replication and HBsAg loss. Early studies in humans showed a small decline in HBsAg[142]. However, several new therapeutic vaccines are in development probably to be used in combination with other drugs such as SiRNA[143].

Other immunomodulatory approaches

In recent years, a better understanding of the immune response to HBV has emerged with new therapeutic possibilities. T cell receptor (TCR)- redirected T cell and chimeric antigen receptor (CAR) T cell involve genetic engineering to confer specificity in front of HBV. CAR-T cells are transduced with an antibody-like receptor to recognize HBsAg on the surface of infected hepatocytes whereas TCR-redirected T cells respond to HBV peptides[157]. However, the investigation in this field is still under development and is being tested in Phase I studies evaluating HBV-infected patients with HCC[158, 159].

Combinations of drugs in development

None of the new previously described molecules can achieve significant sustained HBsAg loss if used alone. Therefore, the most advisable strategy seems to be the combination of molecules with different mechanisms of action[160]. Table 3 summarizes the efficacy of the evolving combinations to achieve sustained HBsAg loss.

CONCLUSION

Long-term treatment for CHB has been used for decades, showing a good safety profile and high efficacy in controlling viral replication, improving histology, and decreasing the incidence of HCC, clinical decompensation, and mortality. However, the persistence of cccDNA and the low probability of HBsAg seroclearance with NA therapy made necessary indefinite treatment in a vast majority of patients. With the new insights into the role of the immune system in HBV infection persistence and the knowledge of the different viral cycle phases, there has been an increase in new therapeutic approaches in recent years. Moreover, several clinical trials evaluating new drugs with different mechanisms of action are ongoing with promising results. It is expected that in the coming years, there will be a paradigm shift in the treatment of CHB, as we have already seen in chronic hepatitis C, and functional cure in an important number of patients seems closer than ever. Meanwhile, an effort to improve diagnostic rates, and to assure access to treatment for all patients who need it must be urgently done.

FOOTNOTES

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