Review of Current and Potential Treatments for Chronic Hepatitis B Virus Infection

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Abstract: Chronic hepatitis B virus (HBV) infection remains a major global health burden. Millions of people are at risk for complications of chronic HBV infection, despite the widespread availability of an effective prophylactic vaccine. The current available treatments for HBV infection—interferon and nucleos(t)ide analogues—are effective at suppressing viral replication and decreasing the risk of cirrhosis. However, these treatments have a number of limitations, creating the need for alternative therapeutic agents. Recent advances in drug therapy have heralded a new horizon of novel therapeutic approaches for chronic HBV infection, with several promising antiviral and immunomodulatory agents currently in preclinical or clinical testing. This article reviews the current landscape of HBV treatments and highlights the most recent therapeutic strategies designed to directly target HBV or to improve immune response during chronic infection.

Hepatitis B virus (HBV) infection is a leading cause of chronic liver disease, affecting more than 290 million people worldwide.[1] Annually, 750,000 people die from complications of chronic HBV infection.[2] Elimination or suppression of HBV reduces the risk of developing chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). Current treatments are associated with improved liver-related outcomes but relatively low rates of sustained hepatitis B surface antigen (HBsAg) seroconversion. Novel and potentially promising therapeutic strategies are in development and may result in more durable and complete responses. This article reviews the current landscape of HBV treatments and highlights the most recent therapeutic strategies designed to directly target HBV or to improve immune response during chronic infection.

Phases of Chronic Hepatitis B Virus Infection

The natural history of chronic HBV infection is a dynamic interaction between viral replication and the host's immune response. Patients with chronic HBV infection can transition through 4 clinical phases, defined by the following clinical parameters: HBV DNA level, alanine

Keywords
Hepatitis B virus, chronic hepatitis B virus, capsid inhibitors, siRNA, immunotherapy

Table 1. Phases of Chronic HBV Infection

	HBeAg-Positive Chronic HBV (Immune Tolerant)	HBeAg-Positive Chronic HBV (Immune Active)	HBeAg-Negative Chronic HBV (Inactive Chronic HBV)	HBeAg-Negative Chronic HBV
HBV DNA Level	High	High	Undetectable/low	Moderate/high
ALT	Normal	Elevated	Normal	Fluctuating/elevated
Liver Histology	Minimal/no necroinflammation or fibrosis	Moderate to severe necroinflammation and accelerated fibrosis	Minimal necroinflammation and variable fibrosis	Necroinflammation and fibrosis

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

aminotransferase (ALT) level, hepatitis B e antigen (HBeAg) status, and liver histology (Table 1).[3] Active HBV replication, defined as the presence of HBeAg or HBV DNA, is associated with disease progression and increased risk of HCC.[4]

The first phase of chronic HBV infection is the immune-tolerant phase, which is associated with high levels of viremia and HBeAg but normal ALT levels. During the second phase, the HBeAg-positive chronic HBV immune-active phase, ALT elevates. After HBeAg loss, most patients enter the third phase, inactive chronic HBV, in which they are HBeAg-negative, have low or undetectable HBV DNA, and have normal ALT. In the fourth phase, patients are HBeAg-negative and have

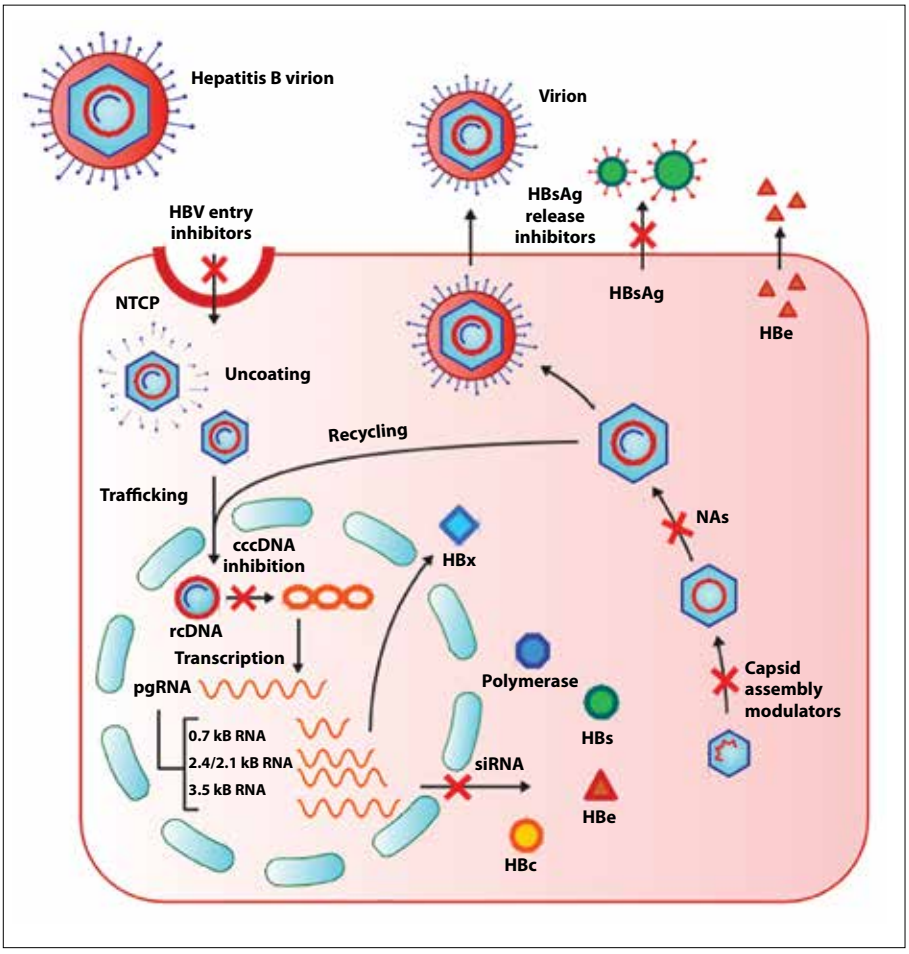

Figure. Schematic of HBV replication cycle in hepatocytes and current and future drug targets. Schematic by Sean Hendrickson in collaboration with Lisa Pedicone, PhD.

cccDNA, covalently closed circular DNA; HBc, hepatitis B core protein; HBe, hepatitis B e protein; HBs, hepatitis B surface antigen protein; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, hepatitis B x protein; NAs, nucleos(t)ide analogues; NTCP, sodium taurocholate cotransporting polypeptide; pgRNA, pregenomic RNA; rcDNA, relaxed circular DNA; siRNA, small interfering RNA.

Table 2. FDA-Approved Treatments for Chronic HBV Infection in Adults

	Drug	Dose	Potential Adverse Events	Drug Resistance	Notes
Preferred Therapies	PEG-IFN α2α	180 mcg weekly	Flu-like symptoms, fatigue, mood disturbances, thrombocytopenia, leukopenia	None	Not well tolerated; high risk of morbidity and mortality
	Entecavir[a]	0.5 mg daily	Lactic acidosis (may occur with decompensated cirrhosis)	Low	Effective against lamivudine-resistant HBV
	Tenofovir disoproxil fumarate	300 mg daily	Nephrotoxicity, osteomalacia	None	Effective against adefovir- or entecavir-resistant HBV
	Tenofovir alafenamide fumarate	25 mg daily	Lactic acidosis	None	Effective against adefovir- or entecavir-resistant HBV
Nonpreferred Therapies	Lamivudine	100 mg daily	Pancreatitis, lactic acidosis	High	None
	Adefovir	10 mg daily	Nephrotoxicity	High	None
	Telbivudine	600 mg daily	Creatinine kinase elevation, myopathy, peripheral neuropathy	High	Discontinued in the United States in 2016

FDA, US Food and Drug Administration; HBV, hepatitis B virus; PEG-IFN, pegylated interferon.
[a]Entecavir dose is 1 mg daily if the patient is lamivudine-experienced or has decompensated cirrhosis.

moderate to high HBV DNA levels and elevated ALT. The duration of each phase varies from months to decades. Transitions to a later phase and regression back to an earlier phase can occur.[5] Complete suppression of HBV with antiviral therapy greatly reduces the risk of adverse clinical outcomes.[6]

Life Cycle and Replication of Hepatitis B Virus Infection

Advances in understanding the molecular biology and replication cycle of HBV have allowed for the development of new therapeutic drug targets. A member of the *Hepadnaviridae* family, HBV is a small, enveloped, hepatotropic DNA virus that replicates and persists in the nucleus of infected hepatocytes (Figure).[7] The HBV virion is composed of an envelope and a nucleocapsid that contains a partially double-stranded, relaxed circular DNA (rcDNA). The virion enters the hepatocyte via the sodium taurocholate cotransporting polypeptide (NTCP) receptor, the viral envelope is shed, and the nucleocapsid is transported through the nuclear pore complex.[8] Capsid dissociation in the nucleus leads to the release of rcDNA, which is then converted to covalently closed circular DNA (cccDNA).[9] The cccDNA integrates with the host DNA and is transcribed into pregenomic RNA (pgRNA), which is then transcribed into viral messenger RNAs and reverse-transcribed into HBV DNA. The viral messenger RNAs are translated into 4 major proteins: HBsAg, HBeAg/core protein (Cp), polymerase, and x protein, whose function remains unclear.[7,9] The nucleocapsid with the partially double-stranded HBV DNA is re-enveloped, and the virion is secreted back into the cytoplasm; however, the virion also can be recycled from the cytoplasm back into the nucleus. In this way, cccDNA can replenish and persist without the need for entry of new virions. Each step of the HBV life cycle is a potential therapeutic target (Figure).

Current Treatments

To date, there are 2 classes of drugs approved by the US Food and Drug Administration (FDA) for the treatment of HBV: interferon (IFN) and nucleos(t)ide analogues (NAs) (Table 2).

Interferon

Standard IFN α was approved as the first agent for the treatment of HBV infection 40 years ago.[10] IFNs are cytokines with potent antiviral, antiproliferative, and immunomodulatory properties. Although the exact mechanism(s) remain elusive, IFNs ultimately induce

IFN-stimulated genes, resulting in the degradation of viral mRNA, inhibition of viral protein synthesis and HBV replication, and prevention of viral infection of cells.[11] IFNs also may augment cell-mediated immunity, thus promoting clearance of HBV-infected cells.[12]

In 2005, pegylated (PEG)-IFN α largely replaced standard IFN α as first-line treatment for chronic HBV infection owing to its improved pharmacokinetics and prolonged half-life.[13] Treatment of HBeAg-positive chronic HBV infection with PEG-IFN α2α for 1 year was associated with HBeAg seroconversion in 32% of patients vs 19% with lamivudine monotherapy (*P*<.001) at 6 months following therapy.[14] Sustained HBeAg seroconversion was confirmed in a small cohort of patients with HBeAg-positive chronic HBV infection, with the rate of seroconversion rising progressively from 37% at the end of treatment to 60% at 5 years.[15] Safety of PEG-IFN α2b was evaluated in patients with advanced fibrosis and compensated cirrhosis. Although use of PEG-IFN α2b did not precipitate immunologic flares, fatigue, anorexia, and thrombocytopenia occurred more often in patients with advanced fibrosis when compared with those without (*P*<.01).[16]

Preferred Nucleos(t)ide Analogues

Developed in the 1980s, NAs have similar structures to natural nucleos(t)ides and competitively inhibit HBV polymerase activity, thereby preventing synthesis of viral DNA. Long-term treatment with NAs has demonstrated improved survival rates and decreased rates of HCC.[17] NAs have an overall favorable safety profile but are associated with adverse events (AEs) such as abdominal pain/discomfort, upper respiratory tract infections, fatigue, and headache.[18] There are currently 5 FDA-approved NAs for the treatment of chronic HBV infection, although major professional societies researching liver disease recommend only entecavir (ETV) and tenofovir disoproxil fumarate (TDF) as monotherapies.[3,19]

The FDA approved ETV, a cyclopentyl guanosine analogue and potent selective inhibitor of HBV replication, in 2005.[20] In a phase 3, double-blind trial, ETV administered for 48 weeks in patients with HBeAg-positive chronic HBV yielded significantly greater histologic improvements and undetectable HBV DNA levels when compared with lamivudine (72% vs 62%; *P*=.009 and 67% vs 36%; *P*<.001, respectively).[21] Extended treatment through 96 weeks showed continued benefits with suppression of HBV DNA to less than 300 copies/mL in ETV-treated vs lamivudine-treated patients (80% vs 39%; *P*<.0001).[22] Treatment with ETV up to 5 years was associated with viral suppression in 94% of patients with chronic HBV infection.[23] In a study of 1315 patients who received ETV for 4 years, results demonstrated a 60% risk reduction of HCC and significant risk reduction of cirrhosis-related events, including variceal bleeding (hazard ratio [HR], 0.38; 95% CI, 0.20-0.74), spontaneous bacterial peritonitis (HR, 0.06; 95% CI, 0.01-0.32), and hepatic encephalopathy (HR, 0.78; 95% CI, 0.28-2.14), and liver-related mortality (HR, 0.14; 95% CI, 0.07-0.13) in patients with chronic HBV–related cirrhosis.[24] ETV has a similar safety profile to lamivudine, but without the drug resistance that limits lamivudine's efficacy.[21] Unlike older NAs, ETV is effective against lamivudine-resistant HBV.[25]

TDF is recommended as a first-line agent for chronic HBV infection. The FDA approved TDF, a prodrug of tenofovir, for chronic HBV infection in 2008. The safety and efficacy of TDF for the treatment of chronic HBV infection were evaluated in patients with HBeAg-positive and -negative chronic HBV infection, with results demonstrating higher rates of viral suppression after 48 weeks of treatment with TDF when compared with adefovir (ADV; 93% vs 63%; *P*<.001).[26] Virologic suppression occurred in patients with HBeAg-positive and -negative chronic HBV infection who received extended treatment with TDF for 5 years (84.5% and 87.9%, respectively) and for 7 years (99.3% and 80%, respectively).[27,28] Moreover, in a 10-year study of 641 HBeAg-positive and -negative patients, more than 98% of patients achieved HBV viral suppression with no evidence of drug resistance.[29] In a real-world study of 92 patients with chronic HBV infection treated with TDF for 3 years, there was no difference in achieving complete virologic response between treatment-naive and -experienced patients (*P*=.6207).[30] TDF monotherapy for the treatment of patients with chronic HBV infection and resistance to ETV or ADV was still associated with significant virologic suppression and was not significantly different between groups (84.4% vs 73.5%, respectively; *P*=.07).[31] In a 5-year study of patients with HBeAg-positive and -negative chronic HBV infection treated with TDF, 51% of patients had regression of fibrosis (*P*<.0001) and 71% of patients had regression of cirrhosis (*P*<.0001).[32] Genotypic resistance to TDF has not been detected.[27,33,34] Reductions in bone mineral density and increases in renal toxicity from long-term use of TDF have been reported in patients with HIV infection; however, similar AEs have not been reported in patients with chronic HBV infection.[29]

Tenofovir alafenamide fumarate (TAF) is a tenofovir prodrug with more efficient delivery of active metabolite to hepatocytes than TDF, leading to higher intrahepatic concentrations of active drug.[35] Owing to lower systemic exposure, TAF offers the potential for an improved safety profile. Administration of TAF at a dose of 25 mg daily was associated with a decrease in serum HBV DNA

comparable to that of the standard TDF dose of 300 mg daily.[36] In a large randomized trial of TAF vs TDF in 873 patients with HBeAg-positive chronic HBV infection, both treatment groups had similar results in achieving HBV DNA of less than 29 IU/mL at 48 weeks (64% vs 67%; *P*=.25).[37] TAF also was compared with TDF in 426 patients with HBeAg-negative chronic HBV, and, again, both treatment groups had similar results in achieving HBV DNA of less than 29 IU/mL at 48 weeks (94% vs 93%; *P*=.47).[38] In HBeAg-positive patients, the viral suppression rate in TAF-treated vs TDF-treated patients was 73% vs 75% (*P*=.47) and in HBeAg-negative patients, the viral suppression rate in TAF-treated vs TDF-treated patients was 90% vs 91% (*P*=.83), respectively.[39] Treatment with TAF had significantly smaller decreases in bone mineral density of the hip (mean % change –0.33% vs –2.51%; *P*<.001) and lumbar spine (mean % change –0.75% vs –2.57%; *P*<.001), as well as a significantly smaller median change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method (–1.2 vs –4.8 mg/dL; *P*<.001) when compared with patients who received TDF.[39] In 2017, TAF was added to the list of first-line treatments for chronic HBV infection. TAF and TDF are both well tolerated, but changes in renal parameters, specifically eGFR, favor use of TAF over TDF.[40]

The current recommended first-line agents for immune-active chronic HBV infection are PEG-IFN α, ETV, or tenofovir (TDF or TAF). ETV should not be used in patients with lamivudine or telbivudine resistance because of the high risk of ETV resistance. TDF has been shown to be effective in patients with lamivudine-, ADV-, or ETV-resistant HBV and is preferred to ETV in these patients.[41,42]

Nonpreferred Nucleos(t)ide Analogues

Lamivudine, the oldest oral NA approved for the treatment of chronic HBV infection, is a cytidine analogue that competes with cytosine in viral DNA synthesis.[43] In a 1-year double-blind trial of 358 patients with chronic HBV infection, lamivudine 100 mg daily significantly improved hepatic necroinflammation when compared with placebo (56% vs 25%; *P*=.001).[44] Lamivudine is a relatively inexpensive drug with favorable efficacy and safety profiles; thus, it was previously widely used as the first-line treatment for chronic HBV infection. However, prolonged lamivudine monotherapy is associated with a high rate of resistance owing to frequent mutations in the viral polymerase gene. Therefore, lamivudine is no longer used as a first-line agent for chronic HBV infection.[45]

ADV, an adenosine NA, was the second NA approved for the treatment of chronic HBV infection. ADV 10 mg daily administered for 48 weeks in patients with HBeAg-positive and -negative chronic HBV infection effectively reduced serum HBV DNA levels (*P*<.001 vs placebo for both groups) and improved liver histology by 53% and 64% (*P*<.001 vs placebo for both groups).[46,47] Treatment at 30 mg daily is more effective at reducing serum HBV DNA levels; however, this approach has an increased risk of nephrotoxicity.[48] Drug resistance mutations have been identified with a reported cumulative probability of mutations with virologic resistance of 20% in patients with chronic HBV infection within 240 weeks of treatment.[49,50] Higher rates of nephrotoxicity and drug resistance limit the utility of ADV as a monotherapy for patients with chronic HBV infection.

Telbivudine, a thymidine NA, was compared with lamivudine for efficacy and safety in the GLOBE trial and demonstrated significantly greater therapeutic response in HBeAg-positive (63% vs 48%; *P*<.001) and HBeAg-negative (78% vs 66%; *P*=.007) patients treated for 2 years with significantly less resistance (10.8% vs 25.9%; *P*<.001).[51] However, in a comparative study of 179 patients with chronic HBV infection receiving telbivudine vs ETV, results demonstrated high rates of viral mutations (9.1% vs 1.1%) and elevations in creatinine kinase levels (8.0% vs 0%).[52] In 2016, production of telbivudine was discontinued in the United States.[53]

Other Nucleos(t)ide Analogues

Emtricitabine is a cytidine analogue that inhibits HBV polymerase. It is currently not approved for the treatment of chronic HBV infection. In a randomized controlled trial comparing emtricitabine 200 mg daily with placebo once daily for 48 weeks, results demonstrated a reduction of HBV DNA to less than 400 copies/mL in 54% and 2% of patients, respectively (*P*<.001).[54] However, 13% to 18% of patients on emtricitabine developed resistance mutations, thus limiting its use as a monotherapy.[54,55]

Clevudine, a pyrimidine NA, inhibits the synthesis of positive-strand DNA, which may have additional effects on cccDNA.[56] In a randomized trial comparing clevudine 30 mg daily with placebo for 24 weeks in patients with HBeAg-positive and -negative chronic HBV infection, results demonstrated sustained viral suppression (92.1% vs 0%; *P*<.0001) and normalization of ALT (74.6% vs 33.3%; *P*=.0006).[57] Although there have been no safety or drug resistance issues detected with short-term treatment, extended durations of therapy are associated with increased rates of myopathy and drug resistance.[57] Currently, clevudine is approved for the treatment of chronic HBV infection only in South Korea.

Combination Therapy

Theoretically, combination therapy with PEG-IFN α and NAs is an attractive approach that may potentially increase efficacy owing to differing mechanisms of action.

However, strategies to combine these therapies have been met with varying levels of success.

In a randomized trial of HBeAg-positive and -negative patients, 48-week treatment with simultaneous (de novo) combination therapy of TDF and PEG-IFN α resulted in significantly more HBsAg loss after 0.5 years of treatment (9.1%, 2.8%, and 0%; *P*<.05 in combination, PEG-IFN α monotherapy, and TDF monotherapy, respectively).[58] In a large randomized trial of HBeAg-negative patients with HBV DNA loads of less than 20,000 IU/mL, simultaneous combination therapy of 48 weeks of TDF and PEG-IFN α did not improve the rate of HBsAg loss compared with the no-treatment group after 0.5 years of therapy (4% vs 0%; *P*=.38).[59]

Sequential (switch to) combination therapy, in which treatment with NAs (ETV or TDF) is followed by switching to PEG-IFN α, has been evaluated.[60] In the New Switch trial, HBeAg-positive patients achieved HBeAg loss and HBV DNA loads to less than 200 IU/mL 1 year after treatment with sequential NA therapy for 1 to 3 years, followed by 48-week or 96-week treatment with PEG-IFN α (9.8% vs 15.3%; *P*=.17).[61]

Add-on combination therapy for chronic HBV infection, in which PEG-IFN α is added to ongoing NA therapy (ETV or TDF), has shown declines in HBsAg levels but low rates of HBsAg seroclearance in the short term. PEGON, a randomized trial of patients with HBeAg-positive chronic HBV infection on ETV or TDF for greater than 1 year along with an additional 48 weeks of PEG-IFN α, demonstrated a decline in HBsAg levels but not HBsAg loss after 0.5 years posttreatment, compared with NA monotherapy (0.4 vs 0.2 $\log_{10}$ IU/mL; *P*=.01).[62]

Currently, practice guidelines do not support the use of combination therapy for the treatment of chronic HBV infection owing to the lack of robust evidence demonstrating superiority over monotherapy. However, these conflicting results demonstrate the need for further studies to assess the safety and efficacy of combination therapy to increase rates of HBsAg seroclearance.

Advantages and Limitations of Current Treatments

Advantages of chronic HBV treatment with PEG-IFN α include finite treatment duration and the absence of drug resistance.[63] Patients who respond to PEG-IFN α have a greater chance of HBeAg and HBsAg seroconversion and immune-mediated clearance after treatment.[64] However, treatment with PEG-IFN α has severe limitations, including frequent AEs such as thrombocytopenia and leukopenia, which require dose adjustment or even medication discontinuation.[65] PEG-IFN α is contraindicated in pregnancy and in patients with decompensated cirrhosis.[66] Additional contraindications include patients with a history of suicidal tendency or active psychiatric illness.

Patients generally have better adherence to oral NAs compared with subcutaneously injected PEG-IFN α. Newer NAs are preferred over PEG-IFN α because of their potent antiviral activity, high barrier to antiviral resistance, and more favorable safety profile.[67] However, the main disadvantages of NAs are lower rates of HBeAg and HBsAg seroconversion and the need for long-term therapy in the vast majority of patients.[68] In addition, NAs do not provide a direct effect on the level and activity of cccDNA, which can persist in the infected liver despite successful antiviral treatment. Therefore, the durability of response to NAs is generally low, usually requiring indefinite therapy.

Potential Treatment Options

The availability of a simple, safe, and highly effective cure for hepatitis C virus infection has reignited the search for a cure for HBV infection. The limited efficacy of currently approved treatments for chronic HBV infection underscores the urgent need for more effective agents that not only suppress viral replication, but also completely eradicate HBV infection. Several novel approaches are currently in preclinical or early clinical development.

Nucleos(t)ide Analogues

Besifovir dipivoxil maleate (Besivo, Ildong Pharmaceutical) is a guanine monophosphate that has shown potent suppression of HBV DNA. Treatment with besifovir dipivoxil maleate for 48 weeks was noninferior to TDF in achieving virologic response (80.9% vs 84.9%; *P*=.46).[69] In a 144-week, open-label, phase 3 study evaluating long-term use of besifovir dipivoxil maleate, results demonstrated good virologic response when compared with TDF (87.7% vs 92.1%; *P*=.36).[70] No drug-resistant mutations were found, and besifovir dipivoxil maleate had a better safety profile than TDF.[69,70]

Pradefovir mesylate (Metabasis Therapeutics), a prodrug of ADV, has been evaluated for its efficacy and safety for chronic HBV infection. In a phase 2 study of 51 patients with chronic HBV infection, short-term treatment with pradefovir mesylate was associated with a decline in serum HBV DNA levels with a similar safety profile to TDF.[71] A phase 3 clinical trial comparing pradefovir mesylate to TDF is currently in the enrollment stage (NCT04543565).

Entry Inhibitors

Bulevirtide (formerly Myrcludex-B; Hepcludex, Gilead) is a synthetic N-acetylated lipopeptide that binds to NTCP surface receptors and interferes with de novo HBV infection by decreasing viremia, HBsAg, and cccDNA levels.[72] Most studies of bulevirtide have focused

on chronic hepatitis δ virus infection or its coinfection with HBV. Bulevirtide 2 mg once daily subcutaneous injection was compared with bulevirtide combined with IFN α2α and IFN α2α alone in a phase 2 study. Results showed an HBV DNA decline greater than or equal to 1 log in the bulevirtide cohort, which was not significant (*P*=.2); however, there was a significant HBV DNA decline greater than or equal to 1 log in the bulevirtide–IFN α2α cohort (*P*=.04).[73] Bulevirtide is currently approved in the European Union for chronic hepatitis δ virus infection.

RNA Interference

RNA interference is a potent and specific posttranscriptional gene silencing mechanism that can inhibit translation of viral proteins needed for cccDNA formation, thus effectively reducing cccDNA.[74] Small interfering RNAs are large double-stranded RNAs processed to shorter nucleotide duplexes that enable gene silencing.[75] In an ongoing phase 2 study, JNJ-3989 (Janssen and Arrowhead) administered subcutaneously at doses up to 400 mg concomitantly with ETV or TDF for 24 weeks reduced HBsAg to less than 100 IU/mL in 88% of patients.[76] ARC-520 (Arrowhead) 2 mg/kg administered monthly along with a NA to HBeAg-positive and -negative patients with chronic HBV demonstrated a HBsAg mean reduction of 0.38 and 0.54 IU/mL, respectively. Treatment was generally well tolerated, with pyrexia as the only observed AE.[77] VIR-2218 (Vir Biotechnology) in patients with chronic HBV infection demonstrated marked reductions in HBsAg.[78] In HBeAg-negative patients, HBsAg load through 48 weeks dropped average maximums of 1.03 $\log_{10}$ IU/mL with 20 mg of VIR-2218 and 1.65 $\log_{10}$ with 200 mg, whereas in HBeAg-positive patients, average maximum drops in HBsAg measured 1.16 $\log_{10}$ IU/mL with 20 mg of VIR-2218 and 1.57 $\log_{10}$ with 200 mg.[79]

Antisense oligonucleotides are small, single-stranded nucleic acid sequences that selectively bind to their target RNAs to trigger degradation. Phase 2 data suggest that treatment with GSK3228836 (formerly IONIS-HBVR_X; Ionis and GlaxoSmithKline) for 4 weeks is associated with a reduction in HBsAg when compared with placebo in patients with chronic HBV infection on NA therapy (mean HBsAg $\log_{10}$ IU/mL ± standard error change from baseline, –2.514 ± 0.783 vs –0.008, respectively).[80] In NA-naive patients, HBsAg mean change was –1.556 ± 0.398 (*P*=.001 vs placebo) and HBV DNA mean change was –1.655 ± 0.427 (*P*<.001 vs placebo).[80]

Capsid Assembly Modulators

The HBV Cp is a multifunctional protein critical for the HBV life cycle. Capsid assembly modulators are small molecules that bind HBV Cps and interfere with the encapsidation of pgRNA and formation of viral nucleocapsids.[81] ABI-H0731 (Assembly Biosciences) is a potent and selective first-generation capsid assembly modulator that inhibits HBV replication and cccDNA formation in in-vitro research.[82] Treatment with ABI-H0731 for 28 days in patients with HBsAg-positive and -negative chronic HBV was safe and demonstrated potent antiviral activity with mean maximum HBV DNA reductions from baseline of 1.7, 2.1, and 2.8 $\log_{10}$ IU/mL in the 100-, 200-, and 300-mg dose cohorts, respectively.[83] Reductions in pgRNA correlated with reductions in HBV DNA. A number of additional capsid assembly modulators are under clinical development.

Hepatitis B Surface Antigen Release Inhibitors

HBsAg is the most abundant circulating viral antigen and has direct immunoinhibitory activity against both innate and adaptive immune responses.[84] Nucleic acid polymers are emerging antiviral therapies that block assembly of subviral particles, which effectively reduces both circulating and intracellular HBsAg.[85] In phase 2 research, the addition of nucleic acid polymers to TDF and PEG-IFN α2α did not alter tolerability and significantly increased rates of HBsAg loss (*P*<.001 vs control) and HBsAg seroconversion (*P*=.046 vs control).[86]

Immunotherapy

Toll-like receptors are the initial sensors of viral infection because they initiate intracellular signaling pathways that induce antiviral mediators such as cytokines.[87] Vesatolimod (Gilead) and selgantolimod (Gilead and Vir Biotechnology) are toll-like receptor agonists under clinical study for chronic HBV infection. Although vesatolimod was well tolerated, an initial study did not demonstrate a significant decline in HBsAg. At week 48, 6%, 16%, and 15% of patients on vesatolimod 1, 2, and 4 mg, respectively, achieved median HBsAg declines of at least 0.5 $\log_{10}$ IU/mL compared with placebo (18%).[88] Early phase 2 data on selgantolimod were promising and demonstrated a small number of patients achieving HBsAg loss.[89]

In chronic HBV infection, antiviral B- and T-cell responses are defective. The so-called exhaustion state is characterized by poor cytotoxic activity, impaired cytokine production, and sustained expression of multiple inhibitory receptors and pathways.[90] These receptors and pathways, which include programmed death 1 and cytotoxic T-lymphocyte–associated antigen 4, are thought to play a role in immune dysfunction, making them attractive therapeutic targets.[91] However, a major concern of immunotherapy is uncontrolled immune activation, which can lead to fatal hepatitis flares or extrahepatic organ damage.

Covalently Closed Circular DNA Inhibitors

One of the key mechanisms for the persistence of the HBV genome is the presence of cccDNA in the nucleus of infected hepatocytes, allowing for continued viral transcription. Specifically targeting cccDNA may be an effective curative option for chronic HBV. A cleaving sequence-specific DNA using transcription activator-like effector nucleases or genome editing using clustered regularly interspaced short palindromic repeats could potentially block the formation of cccDNA and silence its transcription. These direct effects on cccDNA may offer a cure not feasible with IFN α or a NA. Potential cccDNA inhibitors are currently in very early development.[92,93]

Vaccines

The aim of therapeutic vaccines for chronic HBV infection is to achieve a functional cure. The first HBV vaccine therapy was studied in 1995 and was only able to achieve undetectable HBV DNA levels in 37.5% of study participants.[94] Since then, therapeutic vaccines have been studied widely but have been largely unsuccessful owing to challenges including HBV genetic variability, persistence, and immune evasion.[95] In a phase 2 study of patients with chronic HBV infection, the combination of GS-4774 (GlobeImmune and Gilead) with TDF demonstrated increased immune response but no significant reduction in HBsAg levels at week 24 when compared with the TDF-only group. The mean HBsAg declines for the 2-, 10-, and 40-YU GS-4774 arms were –0.096, –0.016, and –0.135 $\log_{10}$ IU/mL, respectively, which did not statistically differ from the placebo arm (–0.079 $\log_{10}$ IU/mL).[96] Several DNA vaccines are under development, including heterologous prime-boost approaches, vaccines against multiple HBV proteins, and combination vaccine and/or antiviral drugs and immune modulators. However, these studies are in preclinical or phase 1 stages and therefore are not reliable treatment options for the immediate future.

Conclusion

A strong need to develop new and effective treatments for chronic HBV infection persists. The mechanisms and novel drug targets under current exploration are multifaceted. Attaining the goal of a clinical cure for chronic HBV infection likely will require combinations of immunomodulatory and antiviral therapies that target multiple steps in the HBV life cycle, including the elimination of cccDNA. Recent advances in technology provide a reasonable hope of a cure in our lifetime.

Disclosures

The author has no relevant conflicts of interest to disclose.

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