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HEPATITIS B (J LIM, SECTION EDITOR)

Future Therapies for Functional Cure of Chronic HBV: Review of Investigational Drugs in Phase 1 and 2 Development

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Abstract

Purpose of Review Treating patients with chronic hepatitis B (CHB) infection with long-term oral antiviral therapy or pegylated interferon is the current standard of care (SOC). However, functional cure, defined as sustained hepatitis B surface antigen (HBsAg) seroclearance that is associated with favorable clinical outcomes, is a rarely achieved treatment endpoint with the SOC.

Recent Findings Remarkable advances in CHB therapy have been made in the recent years. This review was aimed to describe the different new treatment agents that are in the clinical phase of development. These include two main groups of agents that either target the viral replication cycle or enhance host immune control on the hepatitis B virus (HBV). The former group includes viral entry inhibitor, RNA gene silencers, core protein inhibitors, nucleic acid polymer, and monoclonal antibodies. The latter group includes toll-like receptor agonists, RIG-1/NOD2 agonist, therapeutic vaccines, and apoptosis inducer.

Summary While some agents show promise in reduction of HBsAg levels and even HBsAg seroclearance, others are relatively modest in term of additional virological control effected by their different modes of action against HBV. These agents are in general well tolerated. Many upcoming new drugs against HBV are expected to enter phase II clinical trials. New challenge ahead would be the choice and duration of combination therapy to achieve a satisfactory rate of HBsAg seroclearance.

Keywords Chronic hepatitis B virus · Antiviral therapy · Functional cure · Hepatitis B surface antigen

Introduction

Chronic hepatitis B (CHB) infection affects 292 million individuals (3.9% of the global population) as of year 2016 [1]. The prevalence of CHB is highest in the Asia-Pacific region, but many other countries also have high CHB prevalence ranging from 3.3 to 6.1% such as the Eastern Mediterranean region and the African regions [2]. As of year 2015, 0.88 million deaths were related to CHB-related decompensation or hepatocellular carcinoma (HCC), which is comparable to those due to malaria (0.44 million deaths) and human immunodeficiency virus infection (1.06 million deaths). In June 2016, the World Hepatitis Assembly adopted the Global Health Sector Strategy on viral hepatitis and formulated a global action plan to decrease the incidence of viral hepatitis infection by 90% (equivalent to 0.1% prevalence of HBsAg among children), and to reduce annual hepatitis-related mortality by 65% in year 2030 [3]. There are 5 areas to be worked on in order to achieve these goals: primary prevention strategies including hepatitis B vaccination, prevention of mother-to-child transmission (MTCT), injection, blood and surgical safety, harm reduction for people who inject drugs, and treatment for patients with chronic viral hepatitis. With newborn vaccination and hepatitis B immunoglobulin, the incidence of MTCT of hepatitis B virus (HBV) has dramatically reduced, leading to a drastic drop in the prevalence of CHB in children younger than 5 years old from 4.7% in the pre-vaccination era to 1.3% [2]. The bulk of CHB-infected population therefore comes from individuals who acquired the infection before the era of immunization, or who were not immunized due to lack of access to healthcare facilities or lack of awareness in this issue.

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To reduce the risk of complications from CHB, long-term oral nucleos(t)ide analogues (NAs) or a fixed duration of pegylated interferon alpha injection (PEG-IFNa) can be used in CHB patients who have significant viremia and either elevated alanine aminotransferase (ALT) or significant fibrosis [4, 5]. Short-term treatment goals including hepatitis B virus DNA suppression and ALT normalization can be achieved in a majority of patients by NA. Histological improvement of liver fibrosis and reduction in risk of decompensated cirrhosis and HCC are also established treatment benefits [6–8]. While treatment-induced hepatitis B e antigen (HBeAg) seroconversion is relatively not rare (around 15% per year by NA), hepatitis B surface antigen (HBsAg) seroclearance is hard to be achieved with the available therapies [9]. Sustained HBsAg seroclearance, with or without anti-HBs seroconversion, is defined as "functional cure" in the current era [10]. It is a desirable treatment endpoint because functional cure is associated with a low risk of advanced fibrosis or cirrhosis, and even fibrosis regression [11•], and this effect is clinically translated into the benefit of significantly lower risk of HCC, especially if HBsAg seroclearance occurred before the age of 50 [12••, 13]. This forms the basis for international guidelines' recommendations that long-term NA can be stopped 1 year after HBsAg seroclearance in the absence of cirrhosis [4, 5]. In view of the extremely low rate of HBsAg seroclearance using the current therapies, innumerable novel agents are being developed with the hope to enhance the rate of achieving functional cure with a finite duration of therapy. These can be broadly classified as virus-directing agents or immune-modulating agents. In the following sections, different drug classes will be discussed with emphasis placed on those agents that are currently in the clinical phase of development.

Virus-Directing Agents

Oral NAs inhibit viral replication by targeting the DNA polymerase. This is only one of the many steps involved in the viral replication cycle. New virus-directing agents target alternative steps, including viral entry, mRNA translation, encapsidation, and protein secretion [Fig. 1].

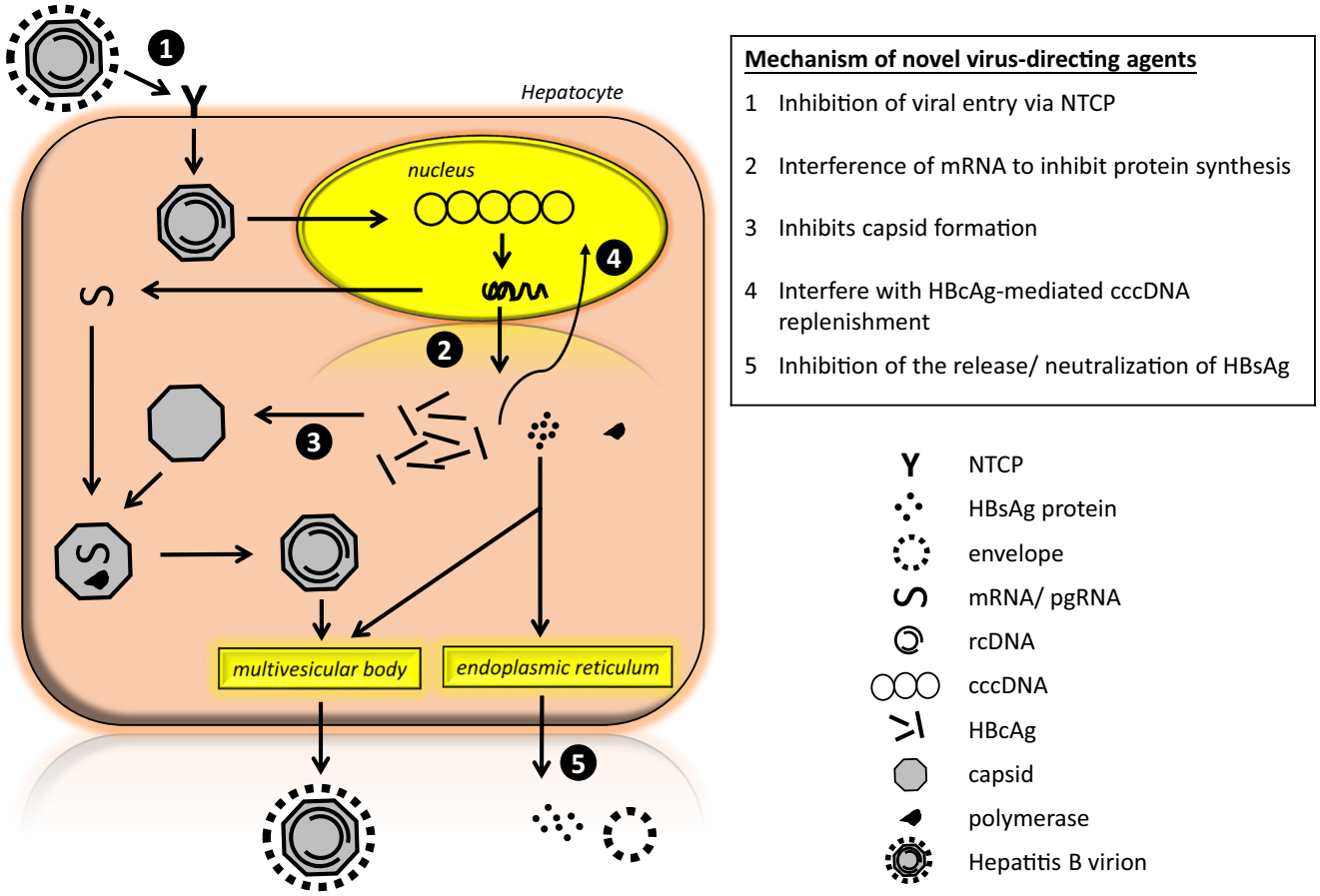
Entry Inhibitor

Hepatitis B virus (HBV) enters hepatocytes via binding to sodium taurocholate cotransporting polypeptide (NTCP) on hepatocytes, which is the major receptor specific for HBV and has high affinity for the large HBsAg protein [14, 15•]. The first-in-class entry inhibitor is Myrcludex-B, which is a HBV pre-S1–derived synthetic lipopeptide that competes with HBV for NTCP receptor and hence prevents viral entry. This compound was well tolerated at intravenous 20 mg or subcutaneous 10 mg in healthy volunteers [16]. In a phase II study which involved 40 CHB [(co-infected with hepatitis delta virus (HDV)] patients, > 1 $\log_{10}$ reduction of HBV DNA at week 12 was observed in 6 out of 8 patients receiving daily subcutaneous injection of 10 mg Myrcludex-B in combination with PEG-IFNa for 24 weeks [17]. ALT normalization was observed in 22/40 (55%) patients, but there were no significant changes in the HBsAg levels. In another phase II study in patients with co-infection of HBV and HDV, combining daily subcutaneous Myrcludex-B 2 mg with weekly subcutaneous 180 μg PEG-IFNa for 48 weeks led to undetectable HBsAg in 4/15 (27%) patients at week 72, and 75% of them experienced anti-HBs seroconversion [18]. Myrcludex-B was well tolerated although drug-related adverse events were reported, one of which include increased total bile salts. There are no trials yet studying combination of Myrcludex-B and PEG-IFNa in CHB monoinfected patients.

Ribonucleic Acid (RNA) Interfering (RNAi) Gene Silencer

Following viral entry, the viral DNA will enter the host nucleus and convert into covalently closed-circular DNA (cccDNA). Transcription of cccDNA leads to formation of messenger RNA (mRNA), which are transported outside of the nucleus as the template for translation in the cytoplasm. Intrinsically, foreign viral mRNAs will bind to naturally occurring siRNAs and are destroyed by RNA-induced silencing complex (RISC), which indirectly inhibits protein synthesis. RNA interfering gene silencers (RNAi) are synthetic short interfering (si) RNAs which are complementary to the viral mRNAs and utilize the RISC mechanism to prevent translation of mRNA and downstream protein synthesis [19]. RNA interference can also be mediated by another class of drug, i.e., anti-sense oligonucleotides (ASO) which utilize the degradation process involving RNase H. These compounds are also under early phase clinical trials.

There are already several RNAis in the clinical phase of development. Host immune reconstitution is also potentiated via reduction in the immune-inhibitory viral proteins especially HBsAg and HBeAg. ARC-520 was the first RNAi that entered clinical phase of trial. In a phase II study involving CHB patients treated with ARC-520 and entecavir, serum HBsAg levels were markedly reduced and the treatment effect lasted for at least 80 days before returning to the baseline levels after a single dose of ARC-520 [20]. Despite achieving encouraging results, the trial was prematurely terminated due to death of the non-human primates attributed to toxicity caused by ARC-520 excipient (not the siRNA itself). A number of other RNAi are in the clinical phase of trial, including ARB-1467, ARO-HBV (JNJ-3989), VIR-2218, DCR-HBVs, and RO7062931. The impressive reduction in HBsAg levels appears to be a class effect for all RNAi. For instance, in the phase II trial involving CHB patients treated with combination



cccDNA: covalently closed circular DNA, CTD: C-terminal domain, HBcAg: HBV core antigen, HBcrAg: HBV core-related antigen, HBeAg: HBV e antigen, HBsAg: HBV surface antigen, mRNA: messenger RNA, NTCP: sodium taurocholate co-transporting polypeptide, p22cr: truncated 22kDa precore protein, pgRNA: pre-genomic RNA, rcDNA: relaxed circular DNA

Fig. 1 Target sites for new virus-directing agents in CHB

NA and ARB-1467, HBsAg reduction was observed in all subjects. Biweekly intravenous ARB-1467 led to HBsAg ≤ 1000 IU/mL with ≥ 1 $\log_{10}$ decline from baseline during the first 10 weeks of therapy in 7 out of 11 (64%) HBeAg-negative patients; moreover, 5/7 (71%) subjects reached HBsAg values < 50 IU/mL at week 6 of therapy [21]. This compound is generally well tolerated. Another example is ARO-HBV, which was given subcutaneously with oral antiviral agent in the phase 2 trial. All 24 CHB patients who received monthly doses of ARO-HBV for 3 injections showed > 1 log HBsAg reduction from baseline, and the nadir was reached around 4 months post initiation of therapy. The pharmacologic effect persisted for > 4 months after the last dosing. Most patients (88%) achieved HBsAg ≤ 100 IU/mL after 3 injections of ARO-HBV. ARO-HBV was reported to be the well-tolerated apart from mild injection site reactions in 10% of patients [22]. These two compounds, together with VIR-2218, have entered phase II clinical trials, while the other few are at phase I (Table 1).

The agents mentioned above target mainly the S gene. Preclinical studies have explored whether knocking down X gene by RNAi is a favorable approach [23]. RNAi conjugates termed "GAIXC" targeting either the S gene, X gene, or both were injected subcutaneously to mice that expressed the HBV genome. Cohorts treated with GAIXC that knocked down the X gene (with or without S gene knockdown) enhanced nuclear localization of hepatitis B core antigen from about 10% to up to 90%, which is considered unfavorable for treatment response [24]. This apparent beneficial effect of not knocking down X gene (and hence reducing core antigen concentration in hepatocytes' nucleus) should be more extensively examined especially in the context of the deleterious hepatocarcinogenic effect of X protein.

Core Protein Allosteric Modulator

Hepatitis B core protein (HBcAg) is synthesized from transcription and translation of the HBV core gene. This protein is essential for capsid formation, encapsidation, and reverse transcription of pre-genomic RNA (pgRNA), virion formation and secretion, cccDNA amplification, and restoration of host immune response [25]. Among the many functions of

Table 1 Currently registered drug trials in chronic hepatitis B infection

	Class/mechanism of action	Name	Sponsor	Stage of development	Reference
Virus-directing agent	Entry inhibitor/blocks NTCP-mediated virus entry	Myrcludex-B	Hepatera, Russia with MYR GmbH	Phase II	NCT02881008
	RNA interfering gene silencer/RNA interference	ARC-520	Arrowhead Pharma	Terminated at phase II	NCT02452528
		ARO-HBV (JNJ-3989)	Arrowhead Pharma	Phase II	NCT03365947
		ARB-1467	Arbutus Biopharma	Phase II	NCT02631096
		ALN-HBV	Alnylam Pharmaceuticals	Terminated at phase I	NCT02826018
		VIR-2218	Alnylam Parmaceuticals	Phase II	NCT03672188
		DCR-HBVS	Dicerna Pharmaceuticals	Phase I	NCT03772249
		RO7062931	Roche	Phase I	NCT03038113
	CpAM/HBcAg inhibition	GLS4 (Morphothiadin)	HEC Pharma	Phase II	NCT03638076
		NVR 3-778	Novira Therapeutics, Inc.	Phase I	NCT02112799 (single center) and NCT02401737 (multicenter)
		JNJ-6379	Janssen Sciences Ireland UC	Phase II	NCT03361956
		ABI-H0731	Assembly BioSciences	Phase II	NCT03576066 NCT03780543
		ABI-H2158	Assembly BioSciences	Phase I	NCT03714152
		RO7049389	Roche	Phase I	NCT02952924
		AB-506	Arbutus Biopharma Corporation	Phase I	ACTRN12618000987268 (Australia New Zealand Clinical Trials Registry)
		QL-007	Qilu Pharmaceuticals Co., Ltd.	Phase I	NCT03244085
	Nucleic acid polymers/inhibition of HBsAg release	REP 2139	Replicor	Phase II	NCT02726789
		REP 2165	Replicor	Phase II	NCT02565719
	Monoclonal antibody/neutralization of HBsAg	GC1102	Green Cross	Phase II	NCT02304315
Immune stimulation	Toll-like receptor agonist	GS 9620	Gilead Sciences	Phase II	NCT02166047
		RG 7795 (RO6864018)	Roche	Phase II	NCT02391805
		GS 9688	Gilead Sciences	Phase II	NCT03491553
		RG 7854 (RO7020531)	Roche	Phase I	NCT02956850
		AL-034 (JNJ-64794964)	Alios Biopharma Inc.	Phase I	NCT03285620
	RIG-I and NOD2 agonist	SB-9200 (Inarigivir soproxil)	Spring Bank Pharmaceuticals	Phase II	NCT02751996 NCT03932513
	Therapeutic vaccine	INO-1800	Inovio Pharmaceuticals	Phase I	NCT02431312
		HB-110	Genexine, Inc.	Phase I	NCT01641536
		TG-1050	Transgene	Phase I	NCT02428400
		HepTcell (FP-02.2)	Altimmune	Phase I	NCT02496897
	Apoptosis inducer	APG1387	Ascentage Pharma Group Inc.	Phase I	NCT03585322
Others	FXR agonist	EYP001	Enyo Pharma	Phase I	NCT03272009

CpAM core protein allosteric modulator, *FXR* farnesoid X receptor, *HBcAg* hepatitis B virus core antigen, *HBsAg* hepatitis B virus surface antigen, *NTCP* sodium taurocholate cotransporting polypeptide, *NOD2* nucleotide-binding oligomerization domain, *RIG-I* retinoic acid-inducible gene-I

HBcAg, capsid formation is the most well known. HBcAg join together to become dimers and further arranged to form icosahedral lattice (each containing 240 HBcAg) [26]. This lattice, also known as the capsid, is vital for encapsidation of pgRNA which acts as the template for reverse transcription to form viral DNA. Core protein allosteric modulators (CpAMs) are novel agents that target capsid formation (primary mode of action of CpAMs). Class 1 CpAMs cause formation of aberrant capsids (abnormal shape), while class 2 CpAMs cause formation of empty capsids (normal shape) which cannot encapsidate pgRNA [27]. CpAMs can also inhibit replenishment of intranuclear cccDNA (secondary mode of action of CpAMs) over time, which may contribute to immunomodulatory properties [28•]. According to an in vitro study, the EC50 was approximately 7 times more for CpAMs to exert their secondary mode of action compared with that for primary mode of action [29].

NVR 3-778 is the first orally bioavailable class 2 CpAM. In the phase I trial involving CHB patients who received different doses of oral NVR 3-778 ± PEG-IFNa, serum HBV DNA and RNA reductions were remarkable in the scale of 1–2 log IU/mL at day 28. However, serum HBsAg levels were not significantly reduced during the treatment period [30]. Similar results were observed in other CpAMs. In the phase 2 trial of JNJ-6379, when given at 75 mg daily for 28 days led to serum HBV DNA and HBV RNA decline of 2.89 $\log_{10}$ IU/mL and 1.85 $\log_{10}$ copies/mL, respectively; there were no significant changes in the HBsAg levels [31]. For the phase 2 trial of ABI-H0731, interim analysis at week 24 after completing 24 weeks of treatment showed that the decline in HBV DNA and RNA was 2 logs greater in patients who received ABI-H0731 plus entecavir compared with patients treated with entecavir alone. In contrast, there were no patients who had HBsAg decline by ≥ 0.5 logs after treatment for 24 weeks [32]. These subjects are having ongoing long-term follow-up beyond week 24 (up to 36-month post-treatment) for assessment of late response (NCT03780543), especially for the serum HBsAg reduction. RO7049389 given at various doses for 28 days led to serum HBV DNA and HBV RNA decline of around 3 and 2.5 $\log_{10}$ IU/mL, respectively; serum HBsAg levels were not reported in this phase I trial [33]. These agents are generally safe. Other CpAMs in clinical trials of development are shown in Table 1. It is eagerly awaited to observe viral protein reduction after longer treatment of duration by CpAMs which might be able decrease the cccDNA content in the hepatocytes. At present, CpAMs may not be the first and quick choice to achieve early functional cure.

Nucleic Acid Polymer

Nucleic acid polymers (NAPs) block the secretion of HBsAg from infected hepatocytes by interfering with the release of subviral particles that constitute more than 99% of circulating HBsAg [34]. By lowering circulating HBsAg, the dampened immune response can potentially be restored.

REP-2139 or REP-2165 (Rep-2139 variant with improved tissue clearance) are first-in-class NAPs [35]. They were given intravenously to CHB patients in combination with tenofovir disoproxil fumarate and PEG-IFNa in a phase II trial. Within the first 24 weeks of therapy, 90% had > 1 $\log_{10}$ HBsAg reduction. After treatment for 48 weeks, 28/40 patients had serum HBsAg < 1 IU/mL, and 24 of these patients had HBsAg seroclearance [36]. NAPs were well tolerated in CHB patients.

Monoclonal Antibodies

Neutralizing antibodies that target HBsAg is another potential mechanism to reduce the HBsAg load. GC 1102 is a recombinant monoclonal hepatitis B immunoglobulin with high affinity to HBsAg. In the phase I clinical trial which recruited 53 CHB patients whose serum HBsAg titer were ≤ 1000 IU/mL, HBsAg seroclearance occurred in 1/8 (12.5%) and 2/9 (22.2%) patients receiving 4 times per week of GC 1102 at 80,000 IU and 240,000 IU, respectively, after 7 weeks of treatment. Few adverse events including flushing, nausea, and dizziness were observed in the 240,000 IU group and were mild and transient [37]. It is currently in phase II clinical trial and has completed recruitment.

Immune-Modulating Agents

In CHB, there is failure to mount an effective and coordinated adaptive immune response to the virus, leading to viral persistence. One of the mechanisms for immune exhaustion is that the virus continuously produces lots of viral proteins, especially HBsAg, which is at least 1000 times higher than the virion itself. Excessive HBsAg may act as a decoy for HBV-specific humoral immunity, which promotes a state of HBV-specific T cell anergy and deletion [15•]. A number of agents have been developed trying to restore the host immunity.

Toll-Like Receptor Agonist

Toll-like receptor 7 (TLR7) agonists stimulate directly the peripheral dendritic cells and B cells, and indirectly the myeloid cells, natural killer cells, and T cells. TLR7 agonists that are currently in clinical phase of trial include GS 9620, RG 7795, RG 7854, and AL-034 (JNJ-64794964) (Table 1). In the phase I trial of a single oral dose of AL-034 in 34 healthy adults, all single doses were safe and well tolerated without grade 3 or above adverse events. The reported adverse events include fever with flu-like symptoms in 5 and transient asymptomatic lymphopenia in 4 subjects. Interferon-stimulated gene expression and cytokine levels were increased and peaked within 12–24 h of dosing in patients who received

higher doses of AL-034 [38]. In the phase II trial of GS-9620 which was combined with tenofovir disoproxil fumarate (TDF), inflammatory cytokines and interferon-stimulated gene mRNA transcripts were induced. The effect of serum HBsAg, on the other hand, was insignificant [39]. GS 9688, instead, is a toll-like receptor 8 agonist. It is another example of immune stimulator which was shown to induce cellular immune mediators and antiviral cytokines in healthy subjects and CHB patients [40]. It appears that the TLR agonists being developed are mostly administered orally and has modest boosting effect on the cytokines, but the efficacy on viral protein suppression is yet to be proven.

RIG-1/NOD2 Agonist

SB9200 (inarigivir soproxil) is an oral dual agonist of retinoic acid-inducible gene-I (RIG-1) and nucleotide-binding oligomerization domain (NOD2), which are host pattern recognition receptors that induce IFN-mediated antiviral immune response. In addition, RIG-1 activation also suppresses pgRNA encapsidation. In the phase 2 dose escalation study of SB9200 (ACHIEVE trial) where 80 CHB patients were randomized to receive SB9200 at 25, 50, 100, and 200 mg daily or placebo in a 4:1 ratio for 12 weeks followed by switching to TDF, 16 (26%) patients who received SB9200 achieved the predefined response of HBsAg reduction equal or greater than 0.5 log from baseline at week 12 or 24. HBsAg decline ≥ 0.5 $\log_{10}$ was observed at all doses of SB9200. This response was more commonly seen in genotype B patients compared with genotype C patients. In term of safety, sustained ALT flare > 200 IU/mL was seen in 4 (6%) patients, which occurred within the first 2–4 weeks and was associated with decrease in HBV DNA and HBsAg. The dose of SB9200 was reduced in 3 out of 4 patients while discontinuation of SB9200 was undertaken in 1 patient. There were no changes in bilirubin, coagulation profile, or albumin, and no systemic interferon-like adverse events were reported [41•].

Therapeutic Vaccine

In contrast to preventive vaccines, the efficacy of therapeutic vaccines is modest. In the phase II trial of GS-4774 in virally suppressed CHB patients, no significant reductions of HBsAg were observed and none of the patients achieved HBsAg seroclearance [42]. Other therapeutic vaccines that are in the clinical phase of development are shown in Table 1.

Apoptosis Inducer

APG-1387 is a novel bivalent small molecule inhibitor of apoptosis protein antagonist which was designed to restore apoptosis mediated by the programmed cell death (PD)

Table 2 Summary of the efficacies on serum HBsAg for selected novel antiviral therapies

Novel agent	Effect on serum HBsAg	Remarks	Reference
Entry inhibitor	27%: undetectable HBsAg at week 72	Myrcludex-B combined with PEG-IFNa for HBV/HDV co-infected patients	[18]
RNAi	100% HBeAg-positive and 20% HBeAg-negative patients had HBsAg decline; mean HBsAg reduction was 3 and 1 $\log_{10}$ for HBeAg-positive and HBeAg-negative patients, respectively	ARC-520 combined with NAs	[20]
	64%: HBsAg $\leq$ 1000 IU/mL + $\geq$ 1 $\log_{10}$ decline from baseline at week 10	ARB-1467 combined with NAs for HBeAg-negative patients	[21]
CpAM	No significant reduction	NVR3-778 combined with PEG-IFNa; or JNJ-6379; or ABI-H0731	[28•, 29, 30]
NAP	90%: > 1 $\log_{10}$ HBsAg reduction 60%: HBsAg seroclearance	REP-2139 or REP-2165 combined with TDF and PEG-IFNa	[33]
Monoclonal antibodies	12.5%: HBsAg seroclearance at week 7	GC 1102 given to patients with low baseline HBsAg	[34]
TLR agonist	No significant reduction	GS-9620 + TDF	[37]
RIG-1/NOD2 agonist	26%: > 0.5 log IU/mL reduction week 12 or 24	SB9200	[39]
Therapeutic vaccine	No significant reduction	GS-4774	[40]
Apoptosis inducer	14%: > 0.5 $\log_{10}$ reduction at week 24	nivolumab in TDF-treated HBeAg-negative patients ± GS-4774	[41•]

CpAM core protein allosteric modulator, *HBeAg* hepatitis B e antigen, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *HDV* hepatitis D virus, *NA* nucleos(t)ide analogues, *NAP* nucleic acid polymer, *PEG-IFN* pegylated interferon alpha, *RIG-1/NOD2* retinoic acid-inducible gene-I/ nucleotide-binding oligomerization domain, *RNAi* RNA interfering gene silencer, *TDF* tenofovir disoproxil fumarate, *TLR* toll-like receptor

pathway, in turn restoring HBV-specific $CD8^+$ T cells response which was dampened by HBV. Another apoptosis inducer, nivolumab, is also being evaluated to treat patients with CHB. Both molecules were initially developed to treat cancer patients. In the phase I study of nivolumab, NA-treated CHB patients without cancer were given nivolumab with or without GS-4774. A modest reduction of HBsAg was observed with mean 0.47 $\log_{10}$ decline at week 24 for those given 0.3 mg/kg nivolumab. A total of 14% patients had > 0.5 $\log_{10}$ reduction in HBsAg at week 24.The treatment was in general well tolerated and no patients had autoimmune manifestations including pneumonitis, colitis, rash, or endocrinopathies [43•]. The potential risk of hepatotoxicity associated with these "immune-checkpoint inhibitors" should be emphasized. This cannot be overlooked since the target population is not suffering from malignancy, and the use of these agents over safer first-line NAs need to be justified.

Others

FXR Agonist

EYP001 is an orally bioavailable small molecule which is a non-steroidal, non-bile acid farnesoid X receptor agonist. It was shown to inhibit HBV in in vitro studies and was well tolerated in healthy subjects [44]. However, in the phase I study of EYP001 in CHB patients, no significant changes of HBV markers were observed after 4 single 300 mg oral doses [45]. The molecule is being tested in a phase 1b study with 4-week treatment.

Relevant molecules discussed above are shown in Table 1.

Conclusion

Functional cure for CHB is a desired treatment endpoint which is associated with fibrosis regression and favorable clinical outcomes including lower risk of liver decompensation and HCC. Current first-line therapies for CHB are safe and effective in suppressing HBV DNA, but are inadequate in achieving early functional cure and oral NAs need to be taken indefinitely. Numerous novel agents have entered clinical trials and some are expected to enter phase III soon. A few classes of agents show impressive results in reduction in HBsAg titer and even early HBsAg seroclearance after a finite and short duration of therapy, including entry inhibitor, RNAi, nucleic acid polymer, monoclonal antibodies, and RIG-I/NOD2 agonist (Table 2). Only those agents with good safety profile should be further developed before they enter clinics as treatment options for patients with CHB. Theoretically, combining two novel agents with different mechanisms of action should be more effective in suppression of viral replication. Few studies, however, have investigated this approach. The study using GS-4774 with nivolumab showed modest reduction in serum HBsAg, but no control arm (nivolumab alone) was available for comparison. One could not conclude that combining a therapeutic vaccine with an apoptosis inducer is better than using apoptosis inducer alone. Although the best combination regimen is still being actively sought, any cocktail of therapies would likely require NA as a backbone because of its proven antiviral efficacy and safety. A combination of various agents will likely be needed to produce synergistic effects in virological control and potentially achieve early functional cure in CHB.

Compliance with Ethical Standards

Conflict of Interest Lung-Yi Mak declares no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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