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REVIEW

Hepatitis B virus therapy: What's the future holding for us?

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Abstract

Hepatitis B is one of the leading causes of liver cancer worldwide and unfortunately the number of people affected with hepatitis B virus (HBV) infection is still on the rise. Although the HBV has been known to cause fatal illness since decades but the population effected by this lethal virus have still only a few options for its management. The major treatment strategies include interferons and nucleos(t)ide analogues. These agents have so far produced unsatisfactory results in terms of complete virus eradication. Interferons cannot be used for long term therapy because of their potential side effects. Prolong treatment with nucleos(t)ide analogues has also been reported to cause serious side effects besides the increasing resistance by the virus. The need for new innovative solutions for treatment of HBV has been realized by global research institutes and pharmaceutical industry. Present review focuses in detail on the new ideas that are being transformed into therapeutic tools for use as future therapies in HBV infection. Modern drug designing and screening methods have made the drug discovery process shorter and more reliable. HBV therapeutics will take a new turn in coming years owing to these intelligent drug designing and screening methods. Future therapy of HBV is aiming to include the use of vaccines (both prophylactic and therapeutic), immunomodulators such as antibodies, non-nucleoside antivirals such as RNAi and inhibitors of viral life cycle.

Key words: Hepatitis B virus treatment; Hepatitis B virus vaccines; Immunomodulators; Non-nucleoside antivirals; Nucleoside analogues

Core tip: The need to develop new therapeutic agents for hepatitis B virus treatment is the motivation factor for many research groups and pharmaceutical industries worldwide. The therapies in development from immunomodulation agents to non-nucleoside viral inhibitors hope to replace the current treatments with the promise of increased efficacy, minimum side effects and shorter duration of cure.

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INTRODUCTION

Chronic hepatitis B virus infection (CHB) lies among chief public health threats globally and is basically a main reason for the development of liver cirrhosis and hepatocellular carcinoma with substantial disease burden; therefore representing the high unmet medical requirement[1]. Almost more than five hundred million people are projected to be persistently infected with the hepatitis B and C virus and they are at high risk of developing chronic liver disease (CLD), cirrhosis and hepatocellular carcinoma (HCC) ultimately. Hepatitis B virus (HBV) is 3.2 kb, partially double-stranded DNA enveloped virus capable of infecting hepatocytes. It belongs to the family *Hepadnaviridae*[2]. Currently there are eight HBV genotypes ranging from A-H[3,4]. Its virion particle consists of a core particle encapsulating the viral genome, polymerase, nucleocapsid protein, besides a lipoprotein envelope containing viral antigens. There are four major open reading frame sin viral DNA genome that include: (1) The pre-core/core gene, that codes for nucleocapsid protein and for the non-structural, secreted, pre-core protein, and hepatitis B e antigen (HBeAg); (2) polymerase gene that codes for enzyme, RNase H reverse transcriptase, and terminal protein domains; (3) PreS2/M-, PreS1/L-, Surface/S-gene that code for the 3 envelope proteins; besides (4) *X* gene, that codes for regulatory X-protein[5,6]. Molecular virology of HBV dictates that it is not directly cytopathic[7] and upon infection, it remains in latent state within the hepatocytes[8].

Increasing evidence showed that distinct geographic distributions of HBV genotypes may influence disease severity and response to treatment. It has been observed that HBV genome integration witint host chromosome is not vital for life cycle of HBV. The disease progression by HBV depends upon the clinical spectrum that is wide, ranging from a subclinical inactive carrier state, to advanced chronic hepatitis, cirrhosis that leads to decompensation, and ultimately culminating in hepatocellular carcinoma. The lifecycle of HBV within a cell is shown in Figure 1[6].

The dynamic natural history of CHB infection involves a complex interaction between the host immune system and the virus. During the course of chronic exposure to HBV, persistent inflammation process accompanies liver damage and cell death. These elements lead to chronic liver disease[7]. Carriers of HBV are susceptible to the development of[2] cirrhosis and decompensation within liver along with 100-fold high risk of development of hepatocellular carcinoma (HCC)[1,9-11]. Viral proteins play their roles through altering gene expression. These proteins augment oncogenesis, metastases and resistance to apoptosis and growth inhibition. HBV genome contains a gene coding for the HBx protein that has been studied to potentially contribute in inducing hepatocytes malignancy and transformation. However there are immense number of unanswered questions within the process of developing and progression of carcinogenesis by the virus as well as the perturbed signaling pathways within the liver. Virologists are following the trend of research that is focused on life cycle of the virus as well the cell signaling pathways that are disturbed during pathogenesis leading to the development of cancer. The most obvious and prominent reason for poor management of HBV infection is delayed detection/diagnosis or detection at the stage where the liver has reached to end stage liver disease. Therefore, timely diagnosis and CHB treatment is vital for the reduction of mortality and morbidity[1]. There are many key factors that impede adequate treatment like: apprehensions to initiate, end, financial cost and resistance of therapy[12]. However, obstacles HBV-related chronic liver disease may be compact by viral suppression. There are following goals of the therapy: to improve quality of life and promote survival by prevention of advancement to cirrhosis and decompensated cirrhosis, HCC and death through continuous inhibition of HBV replication.

Broadly, depending upon the treatment duration there are two different treatment options for patients with CHB infection: (1) Therapies that are of fixed duration including immunomodulators like standard/conventional or PEGylated interferon-α (IFN-α); and (2) Long-term treatment with nucleos(t)ide analogues lamivudine, adefovirdipivoxil, entecavir, tenofovir or telbivudine.

Current therapies aims at persistent suppression of viral replication that typically results in biochemical remission and reduced histological activity of chronic hepatitis. Consequently, the risk of progression to next stage *i.e.,* cirrhosis, also decreases. Therefore, reducing incidence of HCC in non-cirrhotic and some extent in cirrhotic patients[6,13,14]. However, many patients that undergo the currently available therapies do not show long-lasting control after the withdrawal of treatment. Specially, rates of hepatitis B surface

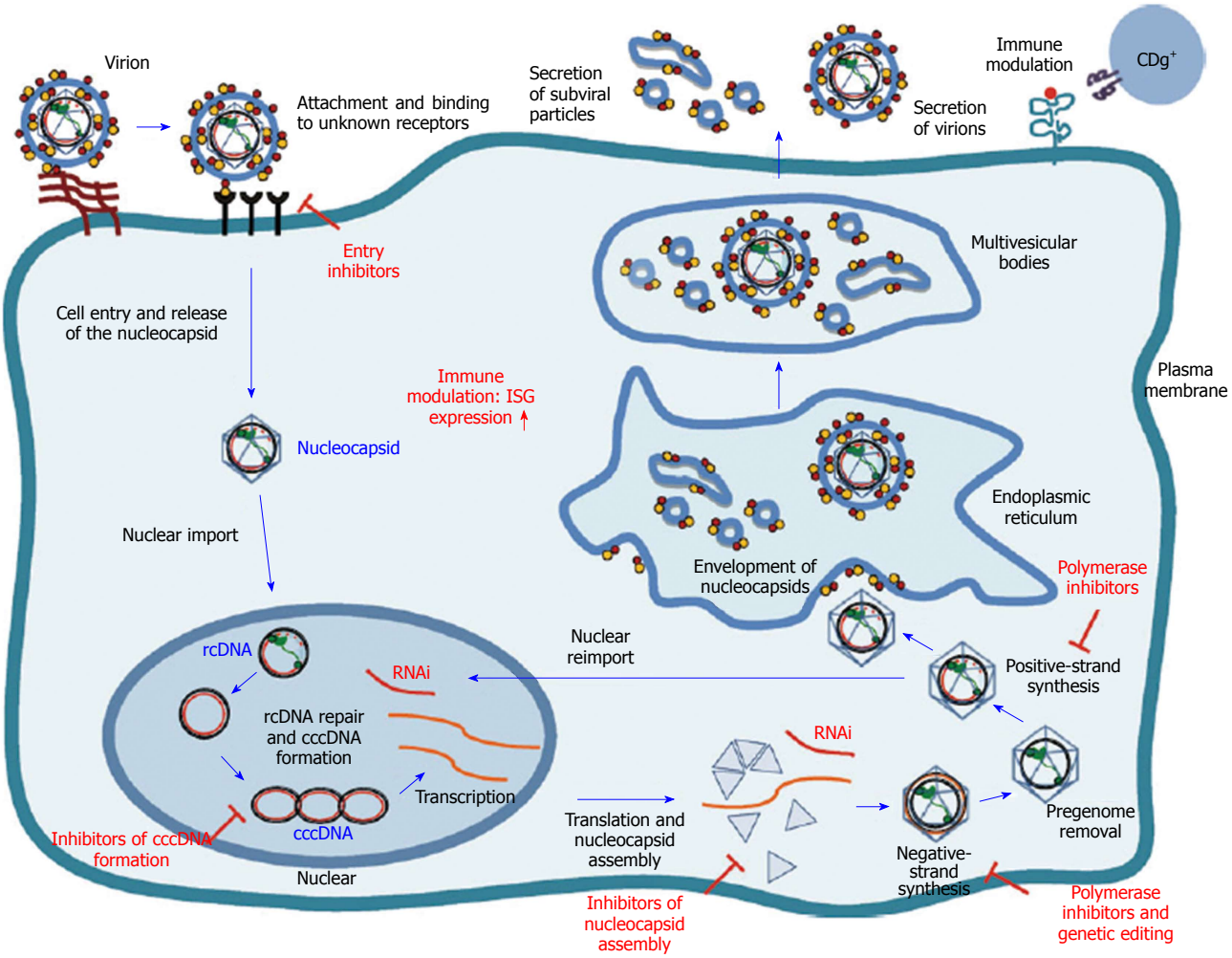

Figure 1 Hepatitis B virus life cycle along with inhibitors targeting the various stages of the hepatitis B virus lifecycle (Adapted from Grimm *et al*[6] 2011). Following attachment of virus to the receptors, cell entry and release of nucleocapsid, nuclear import of virus to nucleus, transcription and translation leads to the synthesis of covalently closed circular DNA (cccDNA), envelopment of nucleocapsid within endoplasmic reticulum, formation of multivesicular bodies and finally secretion of subviral and virion particles. Moreover red bar lines shows the inhibitors targeting various stages of the virus life cycle such as: entry inhibitors, inhibition of cccDNA formation, and inhibition of assembly, polymerase inhibition and genetic editing and immunomodulation targeting the cell surface receptors. ISG: Immune serum globulin.

antigen (HBsAg) loss and seroconversion to hepatitis B surface antibody (HBsAb) are very low[15,16].

The objective of this current review is to provide an update on the recent advances in HBV therapeutics addressing all the drugs available in the market and those in clinical trials to provide an update to those who are either working on HBV or in health care sector.

CURRENT THERAPIES FOR HBV

Currently, there are sevendrugs approved by Food and Drugs Administration (FDA) for the treatment of chronic hepatitis B infection. These drugs are intron A (IFN-α), Pegasys (Pegylated Interferon), Epivir HBV (Lamivudine), Hepsera (Adefovir), Baraclude (Entecavir), Tyzeka (Telbivudine), and Viread (Tenofovir). These seven drugs have been licensed by FDA but not a single drug provides a complete cure; but they do stop/slow down the progressive liver damage. There are limitations of each drug; Interferon therapy offers fix treatment duration but mostly associated with serious side effects that lead to the cessation of therapy. Oral nucleoside or nucleotides inhibitors induce drug resistance by prolong use. The treatment response rate of currently used drugs against HBV infection two years post-treatment is summarized in Table 1[17]. The treatment response rate is defined in terms of undetectable HBeAg, HBeAg seroconversion (absence of hepatitis B e antigen in serum and the presence of antibodies against it) and HBV DNA less than 300/400 copies/mL in HBeAg negative patients.

Pegasys (Pegylated Interferon)

IFN-α-2a/b was the first approved treatment option for CHB infection in most of the countries. However later on, the improved pharmacokinetics properties, efficacy and convenient dosing of Pegylated Interferon have caused the replacement of standard IFN-α-2b. Pegasys is given as a shot once a week as compare to

Table 1 A list of hepatitis B virus vaccines in development

Treatment	Undetectable HBV DNA in HBeAg positive patients	Anti-HBeAg serconversion in HBeAg positive patients	HBV DNA < 300/400 copies/mL in HBeAg negative patients
Pegylated interferon	25	30	63
Lamivudine	39	22	72
Adefovir	21	12	51
Entecavir	67	22	90
Telbivudine	60	26	88
Tenofovir disoproxil fumarate	74	21	91

HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

standard interferon that is given as a shot three times a week[18-20]. The half-life of interferon is increased by pegylation. The treatment success rate of Pegasys is 24% as compared to 12% of standard interferon[21]. Pegasys is a better treatment option than lamivudine in terms of HBV DNA suppression and seroconversion of HBsAg[1]. The treatment success rate of Pegasys and lamivudine was 32% and 19% respectively[22,23]. Pegasys is not recommended for those CHB who are victims of autoimmune hepatitis, liver cirrohosis, show serious side effects or having age below one year. Interferon blocks DNA synthesis of HBV. Pegasys treatment is the most favorable for those CHB patients possessing strong immune system with high level of liver enzymes, infected after childhood and the virus is replicating.

Epivir-HBV (Lamivudine)

Lamivudine is a cytidine nucleoside analogue that inhibits the reverse transcriptase enzyme of HBV. Lamivudine is an orally administered and well tolerated at a daily dosage of 100 mg for one year[24]. It profoundly suppresses serum HBV DNA and showed bio-availability for more than 80%[25]. The rate of HBeAg seroconversion (absence of hepatitis B e antigen in serum and the presence of antibodies against it) in CHB patients by Epivir-HBV or Lamivudine for the treatment duration of one year is 32%[26,27] and increases up to 65% by five years treatment[28]. Additionally the treatment response is not dependent on ethnicity[20]. Lamivudine therapy can be stopped after the seroconversion and sustained viroloigcal response is maintained in approximately 80% of cases. The treatment is associated with the development of viral resistance that occurs by mutations in the YMDD motif of HBV polymerase. The incidence of lamivudine resistant HBV mutants increases upto 70% by five years treatment. The viral breakthrough occurs at 6-9 mo of therapy and detectable HBV DNA at six month of therapy is linked with the emergence of higher resistance rate. Combinational therapy of lamivudine with other therapies such as PEG-IFN or adefovirhave no significant effect on the treatment response, however the rate of emergence of viral resistance is reduced[29,30].

Hepsera (Adefovir)

Hepsera is the tradename foradefovirdipivoxil. Adefovir is a nucleotide analogue which has shown activity against HBV. Hepsera is daily administered as 10 mg oral tablets. The most common serious side effects associated with hepsera are rash, swelling of throat, lips, tongue and face, difficulty in breathing and proximal kidney tubular dysfunction[31]. A recent clinical trial of seventy treatment naive HBV patients demonstrated that the treatment efficacy in terms of HBV reactivation was almost comparable for lamivudin and adefovir *i.e.,* 37.1% and 28.6% respectively. 61.5% patients on lamivudine developed drug resistance; however none of the patients on adefovir developed drug resistance. Thus, adefovir has the advantage over lamivudine in terms of developing lower drug resistance profile[32].

Baraclude (Entecavir)

Baraclude or entecavir is a potent inhibitor of HBV' s DNA polymerase enzyme[33]. Phase 3 clinical study of baraclude demonstrated significantly higher treatment efficacy than lamivudine in term of histologic, biochemical and virologic improvements[34]. Resistance to baraclude is not common; however it occurs in half number of patients who have used lamivudine. Baraclude is daily orally taken at a dosage of 0.5 mg for patients who are treatment naive for HBV treatment and at dosage of 1 mg for patients who demonstrated resistance for lamivudine[34].

Tyzeka (Telbivudine)

Tyzeka is orally taken at a daily dosage of 600 mg. It is more potent than lamivudine and adefovir. Like lamivudine and adefovir, it is commonly associated with the emergence of resistance. However, a recent meta-analysis study of telbivudine and lamivudine showed that telbivudine is a better treatment choice for HBV infection due to its lower rate of resistance[35].

Viread (Tenofovir disoproxil fumarate)

Tenofovir disoproxil fumarate is a nucleotide analogue that is also a potent inhibitor of HIV and HBV polymerase. It is orally taken at the dosage of 300 mg per day. It is more effective than lamivudine and adefovir. It is

Table 2 A Lists of hepatitis B virus vaccines in development

Name of vaccine	Type	Developed by	Phase
Sci-B-Vac	Prophylactic 3rd generation vaccine	SciVac Ltd, Israel	Approved in Israel, Asia and Africa
HEPLISAV-B	Prophylactic vaccine	Dynvax Technologies Corporation, United States	Phase Ⅲ
GS-4774	Therapeutic vaccine	Gilead Sciences, United States	Phase Ⅱ
Hepsyn-B	Therapeutic vaccine	Immune Targeting Systems Ltd, United Kingdom	Pre-clinical
VAXINE's HBV Vaccine	Therapeutic	Vaxine Pty, Ltd, Australia	Phase Ⅰ
VAXINE's HBV Vaccine	Prophylactic	Vaxine Pty, Ltd, Australia	Phase Ⅱ
HBV^+ DRibbles vaccine	Prophylactic and therapeutic	Southeast University, Nanjing, Jiangsu, China	Pre-clinical
ABX 203	Therapeutic	ABIVAX, France	Multicenter Phase Ⅱ/Ⅲ Trials
INO-1800	Therapeuti	Inovio Pharmaceuticals, United States and Roche	Phase Ⅰ (expected to start in 2015)
DV-601	Therapeutic	Dynvax Technologies Corporation, United States	Phase Ⅰb
Altravax Therapeutic Vaccine	Therapeutic	Altravax, Inc, United States	Pre-Clinical

HBV: Hepatitis B virus.

effective to telbivudine, lamivudine and entecavir resistant patients. However, it is less effective in adefovir resistant patients[36].

FUTURE THERAPIES FOR HBV

Vaccines

Currently used HBV Vaccine was developed initially in 1984[37]. The same vaccine that was developed from baker's yeast with a little modification is used to date. It was introduced in 1986 in United States. The HBsAg vaccine is 80%-100% efficacious in prevention of infection or hepatitis in those who receive the prescribed course of vaccine. However, the immunogenicity of vaccine is found to decline with age. After the age of 40 years, almost 90% of recipients respond positively to a three-dose series, and at the age of 60 years, merely 75% of vaccines are able to develop antibody titers that give protection[38]. Alum is the most widely used adjuvant in humans. It has an exceptional safety record and shows a strong bias toward Th2 type antibody responses while, a marginal Th1 cell-mediated response is observed *in vivo* and often requires multiple booster immunizations[39,40]. The need to develop a new vaccine that is able to ensure 100% efficacy with long lasting immune response *i.e.,* without booster doses has always been there. Another approach designated as therapeutic vaccination aims at designing immunotherapies that produce either specific or non-specific immune responses against HBV that could help to achieve sustained viral control by limited treatment[41,42]. The therapeutic vaccines are not only under trial for monotherapy but have also been evaluated as a combination therapy with existing anti-HBV. Chongqing Jiachen Biotechnology Ltd. Conducted a phase Ⅱ clinical trial of Synthesized Peptide εPA-44 with Entecavir in 2012[43]. Phase Ⅲ clinical trial of lamivudine and recombinant hepatitis B surface antigen was conducted by French National Agency for Research on AIDS and Viral Hepatitis in Dakar, Senegal in 2008[44]. Therapeutic vaccination has shown promising results in animal models by inducing T cell immune responses therefore, limiting viral infection[45]. Some of the vaccine products in development are discussed here. Table 2 summarizes various HBV vaccines currently in development.

Sci-B-Vac

Sci-B-Vac is a brainchild of two physicians from Israel at the Weizmann Institute of Science and is a product of Israel's SciGen. Sci-B-Vac is designated as the first commercially available third-generation vaccine effective against HBV and is already approved in Philippines, Hong Kong,Vietnam,India,Central Africaand Georgia. Sci-B-Vacsi not a single protein. It is a hollow "envelope" that contains three purified recombinant proteins which have been derived from a line of hamster cells - these cells are much closer to human cells instead of yeast. The vaccine has completed its clinical trial and the data shows that the SCI-B-VAC vaccine that contains the S-protein component of the HBV surface together with the PreS1 and Pre-S2, is considerably more immunogenic than a second- generation recombinant HBV vaccine[46,47]. The vaccine is equally efficient in all types of study populations including infants, adults and patients with end stage renal disease, non-responders to the already available HBV vaccines including obese and elderly[47-50]. It has also been shown that fewer number of doses *i.e.,* two are sufficient to provide adequate rapid seroprotection[51]. Recent studies have asserted that Sci-B-Vac is more efficient than Engerix-B (the most popular brand in market) due to its rapid and higher response[52]. It can be therefore said once FDA grants the approval Sci-B-Vac, it will capture the major share in market for HBV immunization.

GS-4744

GS-4774 is as a therapeutic vaccine that has been engineered to generate T cell immune responses against cells that contain HBV antigens along with the antiviral therapy with the aim of improving response rate in patients with CHB infection. GS-4774 is a heat-killed, recombinant, yeast-based immunotherapy designed to express antigens that are specific for HBV[53]. The GS-4774 Tarmogen expresses a fusion

protein utilizing sequences of the HBV contained in the four major HBV genotypes worldwide, in order to ensure applicability for this product across multiple markets[54]. Gilead initiated a phase 2 clinical trial in July 2014 investigating GS-4774 in individuals with chronic HBV infection who are not currently receiving any treatment[55]. According to latest data GS-4774 was found to be safe and well-tolerated in healthy subjects. The weekly and monthly regimens of GS-4774 both provided HBV-specific immune responses at all evaluated doses[56]. GS-4774 can therefore be regarded as a promising member of HBV Therapy Regimen providing physicians with a very reliable option for HBV treatment.

Heplisav-B or 1018 ISS adjuvant

Heplisav is a vaccine under development by Dynavax technologies and is currently in Phase-Ⅲ of clinical trials. It contains ISS *i.e.,* immunostimulatory sequences (1018 ISS) and HBsAg[57]. Phase Ⅲ clinical trials have that Heplisav-B a Toll-like receptor-9 (TLR-9) agonist produces a rapid and high titer leading to sustained seroprotection in healthy individuals as well as hyporesponders with lesser number of immunizations[57-59].

Heplisav is different from the vaccines already present in the market as it contains synthetic adjuvant called immunostimulatory sequences (ISS) instead of alum. ISS are cytosine phosphoguanosine (CpG) motifs that originate from bacterial DNA and are potent activators of immune system[60]. It has been shown that these CpG motifs use TLR-9 to stimulate the innate arm of immune system leading to the activation of a chain of immune responses intermediated by IL-18, IL-12 and IFN-γ derived from macrophages and natural killer (NK) cells. This chain of events promotes Th1 responses for both protein and vaccines derived from DNA[60]. Antibody production and B-cell proliferation are also significantly enhanced the presence of these CpG motifs[60,61].

Heplisav is clearly a vaccine of the future with an ability of producingseroprotection against HBV with lesser number of immunizations and in a rapid succession, especially amongst immunologically week populations and is therefore, ideal candidate to decrease the number of morbidities and mortalities of chronic HBV infections effectually.

Hepsyn-B

Hepsyn-B is a lead product of immune targeting systems (ITS). ITS has commenced lead optimization of Hepsyn B and has received a grant from the UK Biomedical Catalyst funding scheme for FP 02 development in Hepatitis B infection. Hepsyn-B is a fluoropeptide vaccine (Hepsyn-B), based on ITS's proprietary Depovaccine and Densigen technologies, to induce immune control over the disease, increase likelihood of clearance of infected liver cells and reducing the need for prolonged costly drug therapy[62,63]. Hepsyn-B™ is a DepoVaccine product that contains eight Densigens which are derived from highly conserved regions of the Hepatitis B virus. The product is intended to provide therapeutic benefit to patients who are chronically infected with Hepatitis B of any of the four major sub-types (A-D)"[63].

The vaccine is currently in pre-clinical development stages. The goal of current standard of care treatment is to reduce viral load and permit seroconversion so subjects progress to an inactive state where liver disease progression is halted. Antiviral T-cell immunity is a key driver of this outcome. It has been suggested that therapeutic vaccination with Hepsyn-B and other similar products will improve treatment outcomes and reduce reactivation rates by "actively reconstituting disease protective T-cell immune responses"[64].

Vaxine's HBV vaccine

The Australia based biotechnological company is in process of developing a HBV prophylactic as well as an HBV therapeutic vaccine. The prophylactic vaccine is based on combining the Advax™ adjuvant with a unique hepatitis B vaccine antigen. Vaxine's prophylactic HBV vaccine was ranked as one of the top 5 global products that entered the phase Ⅱ clinical testing in 2007 by Thomson Scientific. The company has received an approval to conduct the vaccine trial for HBV immunization of subjects with impaired immune systems because of diabetes, older age or kidney failure[65].

Vaxine's therapeutic HBV vaccine is actually a nasal vaccine that utilizes the ability of hepatitis B core antigen of stimulating a strong Th1 type response against hepatitis B surface antigen[65]. The vaccine is currently in phase 1 trial[66].

HBV$^+$ DRibbles vaccine

HBV$^+$ DRibbles vaccine is an autophagosome-based HBV vaccine from HBV-expressing hepatoma cells. This vaccine is a brainchild of scientists from Department of Microbiology and Immunology, Medical School of Southeast University and Cancer Research and Biotherapy Center, the Second Affiliated Hospital of Southeast University, Nanjing, Jiangsu, China and Laboratory of Cancer Immunobiology, Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR, United States. The vaccine has shown positive results by inducing polyvalent anti-HBV T-cell responses and therapeutic efficacy in mouse models that mimic acute and chronic HBV infection in human. The HBV$^+$ DRibbles produced from a HBV expressing cell line were effective as a prophylactic vaccine or a therapeutic vaccine to treat mice with established HBV replication. The study demonstrated that HBV$^+$ DRibbles mixed with α-Al_2O_3 nanoparticles could elicit an endogenous T-cell response that swiftly eliminatesan established "HBV infection".

The results suggested that HBV^+ DRibbles vaccine together with a potent adjuvant was capable to elicit therapeutic immune response and overcome HBV tolerance in the mouse model[67]. The efficiency of HBV^+ DRibbles vaccine can be attributed because to α-Al_2O_3 nanoparticles, in contrast to traditional Alum adjuvant, which are capable to deliver antigen for very efficient priming of cytotoxic lymphocytes and capable of boosting the anti-tumor efficacy of tumor-derived autophagosomes[68]. All these features make HBV^+ DRibbles vaccine a promising candidate as a future HBV therapeutic vaccine.

ABX 203

ABX 203 is the first collaborative result of ABIVAX France with CIGB Cuba. In order to shorten the current treatment period of HBV ABX 203 has been developed as a therapeutic vaccine candidate that is capable of delivering long-lasting control of the viral load. It is composed of both the surface and core antigens of the hepatitis B (HBs and Hbc antigens) and thus a mix of 2 viral proteins.

The Clinical trials of ABX203 have shown encouraging data that shows the efficacy of this vaccine in trial in healthy volunteers as well as in phase Ⅰ study and phase Ⅱ studies in patients with chronic HBV infection[69]. The vaccine has entered a multicenter phase Ⅱ/Ⅲ clinical trial that is estimated to be completed in 2017[70].

INO-1800

INO-1800 is a multi-antigen SynCon® DNA immuno-therapeutic vaccine that targets hepatitis B virus clades A and C surface antigens and HBV core antigens. Inovio pharmaceuticals has entered into agreement for collaboration with Roche to develop IN0-1800[71]. Preclinical trial data successfully reported generation of strong immune responses that include T cell and antibody activation by INO-1800 that leading to the elimination of targeted liver cells within mice. These results show the true potential of this DNA vaccine in treatment of HBV infection and prevention of progression into liver cancer. The company has planned to initiate a phase Ⅰ clinical trial of INO-1800 in 2015[72].

DV-601

DV-601 is a protein based therapeutic vaccine that was able to induce both cellular and humoral immune responses and was able to drive multi-functional and multi-specific T cell immune responses in the liver of chronically HBV infected mice. The vaccine employs the use of a novel protein based vaccine formulation that comprises HBsAg and hepatitis B core antigen along with ISCOMATRIX adjuvant. This particular formulation was able to successfully break the tolerance in this chronic viral disease[73]. In 2011 the drug successfully underwent Phase 1b clinical trials that showed all doses were generally well tolerated and safe in cohorts at all doses[74].

Altravax's therapeutic vaccine

Altravax is a privately held United States based bio-pharmaceutical company that bagged SBIR grant from NIH in January 2013[75,76]. Altravax has developed a therapeutic DNA vaccine product delivered by electroporation and expressing a mixture of HBsAg variants. A number of immunogenic HBsAg variants containing xenogeneic sequences with novel T epitopes have been identified using a directed molecular evolution approach. Mixing several variants has increased the immunotherapeutic potential of the combined vaccine by including many different xenogeneic epitopes. Beginning with seven individual variants, all possible 3-variant combinations are being screened using a tiered strategy to identify the most immunogenic mixtures in normal and HBsAg-transgenic mice[77]. Altravax's preclinical studies in animals indicated the effectiveness of the vaccine for therapeuticpurpose in chronic HBV patients. The product has now formally entered the preclinical development phase that will include manufacturing and safety studies that are prerequisite for submitting an investigational new drug (IND) application to FDA[77].

IMMUNOMODULATORS

There are many immunomodulators currently in development for HBV infection. A few of them are discussed here. These include recombinant interleukins, antibodies and agonists of pattern recognition receptors. Table 3 gives summary of immunomodulators currently in various stages of development for HBV infection.

CYT-107

Recombinant human interleukin-7 (CYT107) is an immune-modulator for immune T-cell retrieval and augmentation. IL-7 is produced as growth factor and cytokine by thymic or bone marrow stromal cells and other epithelia. IL-7 critically and non-redundantly stimulates the development of T lymphocyte by thymopoiesis and from the thymus downstream, on expansion of peripheral T-cells[78,79]. The repeated dose trials of first-generation of rhIL-7 were shown in pre-clinical and phase Ⅰ studies in oncology and HIV-infected patients that were well tolerated in recurrent dose trials, with long-term increases in both CD4 and CD8 T cells. The second-generation rhIL-7 is CYT107, a product made by Cytheris, a biopharmaceutical company in clinical stage. Trials conducted in clinical settings that recruited over 120 patients within Europe, Taiwan and North America have confirmed the ability of IL-7 to develop and protect CD4+ and CD8+ T-cells[79,80]. After initial safety evaluation CYT107 has now been successfully evaluated in phase Ⅰ/Ⅱa clinical

Table 3 Immunomodulators in pipeline for hepatitis B virus treatment

Immune enhancer	Function	Developer	Phase
CYT-107	Recombinant IL-7	Cytheris SA, France	Phase Ⅱ
TG-1050	Adenovirus based targeted immunotherapy	Transgene SA, France	Pre-clinical
GS-9620	TLR-7 agonist	Gilead Sciences, United States	Phase Ⅱ
GC1102	Monoclonal antibody Recombinant HBIg	Green Cross Corporation, Japan	Phase Ⅱ
CYT-003	TLR-9 agonist	Tekmira Pharmaceuticals Corporation, Canada	Pre-clinical (Phase Ⅱ for Asthma)
SB 9200	RIG-I and NOD2 activator	Spring Bank Pharmaceuticals, United States	Phase Ⅱ

HBV: Hepatitis B virus; HBIg: Hepatitis B Immunoglobulin; TLR: Toll-like receptor; RIG-I: Retinoic acid-inducible gene I; NOD2: Nucleotide-binding oligomerization domain containing 2; IL-7: Interleukin-7.

trial evaluating recombinant human Interleukin-7 (CYT107) in combination with the standardized antiviral treatment and vaccination in HBeAg-negative chronically infected HBV patients[81,82].

TG-1050

TG-1050 is a targeted immunotherapy candidate based on adenovirus-based for the treating chronic hepatitis B. The pre-clinical package for TG-1050 is capable of supporting TG-1050 to induce a vigorous, extensive, long-lasting T cells with features similar to those found in effected individuals who resolve infection along with antiviral activity. Significantly, TG-1050-educated T cells have the ability to recognize immune factors derived from all circulating strains of HBV viral genotypes, including genotypes B and C[64,83]. Additionally, a combined study conducted by Ruijin Hospital in Shanghai and Transgene Biopharmaceutical Technology (Shanghai) Co., Ltd. and Transgene SA, displayed that amount of antibodies produce against adenovirus are similar to those produced in chronically infected HBV patients and healthy individuals. The company plans to starta first-in-humans clinical evaluation in the next few months[84].

GS-9620

GS-9620 is an oral agonist of TLR-7. It is currently in phase Ⅱ clinical trial for treating individuals with CHB[85]. In previously conducted preclinical phase of the study, GS-9620 was able to induce a prolonged suppression of HBV antigens and serum levels of viral DNA within animal models of HBV induced hepatitis[86,87]. It has been established that the antiviral response mediated by GS-9620 in preclinical models of CHB is probably facilitated in part by the cytolytic activity of CD8+ T cells. Strong intrahepatic B cell response when initiated might have played a vital role in seroconversion of HBsAg antigen[88].

GC 1102

GC 1102 is a new recombinant hepatitis B immunoglobulin (HBIg) from Chinese Hamster Ovary (CHO) cells. It is a monoclonal antibody and has high affinity and avidity to hepatitis B surface antigen and several advantages compared to HBIg derived from blood plasma of human donors[89]. The antibody is currently in Phase Ⅱ Clinical Trials at Seoul Asan Medical Center Kore and is sponsored by Green Cross Corporation[90].

CYT-003

Tekmira's lead TLR-9 program, CYT-003, was in-licensed from Cytos Biotechnology Ltd., where it was evaluated clinically in allergic asthma and successfully completed Phase Ⅱ Clinical Trials for Asthma. The company is currently evaluating the utility of CYT-003 in HBV. TLR-9 agonists are a novel approach to the reactivation of immune system in patients chronically infected with HBV. Stimulation of cellular TLRs is expected to provoke a response mediated by innate arm of the immune system leading to the production of cellular proteins capable of targeting viral infections such as HBV[91].

SB 9200

SB 9200 a product of Spring Bank Pharmaceuticals that works by activation of pattern recognition receptors including retinoic acid-inducible gene Ⅰ and nucleotide-binding oligomerization domain containing 2, involved in the detection of viral RNA within cells. It up-regulates the host immune response selectively to viral infection by blocking replication of the virus and at the same time by produces endogenous interferon. It is potentially less likely to produce resistance because it targets the host proteins that are involved in the immune response in contrast to directly acting on the virus. The drug was found to cause a significant decline in preclinical animal models in viral load of HBV. The company is currently planning to proceed towards Phase Ⅱ clinical development of SB 9200 for HBV infected patients[92].

NON NUCLEOSIDE ANTIVIRALS

Non-nuceoside anti-virals (NNAVs) are the cornerstone of future therapies for HBV. These include phenyl-propenamides, hetero-aryl-di-hydro-pyrimidines, RNAis and Novel Protein Inhibitors. These approaches are being analyzed with great success in clinical trials

Table 4 Non-nucleoside anti-viral drugs in development for hepatitis B virus

Name	Mechanism	Developed By	Phase
CpAMs	Allosteric Modulation of HBCp	Assembly Biosciences, United States	Pre-clinical
AT61 and AT130	Assembly Activation (Inhibit Capsid Assembly)	Victorian Infectious Diseases Reference Laboratory, Australia	Pre-clinical
BAY41-4109	Assembly Activation (Inhibit Capsid Assembly)	AiCuris, Germany	Phase Ⅰ
NVR 3-778	HBV Cp Inhibition (cccDNA suppression)	NoviraTheraputics, United States	Phase Ⅰb
NVP018	Cyclophilin inhibition	Tekmira Pharmaceuticals Corporation, Canada	Phase Ⅰ
TKM-HBV$_{4G}$ and TKM-HBV$_{3G}$	RNAi	Tekmira Pharmaceuticals Corporation, Canada	Phase Ⅰ
STING agonists	PRR Activation	Tekmira Pharmaceuticals Corporation, Canada	Pre-clinical
ARC-520	RNAi	Arrowhead Research Corporation, United States	Phase Ⅱ
ALN-HBV	RNAi	Alnylam Pharmaceuticals, Inc. United States	Pre-clinical
GLS4	Assembly Activation (Inhibit Capsid Assembly)	HEC Pharm Group, China	Phase Ⅱ (China)
BSBI-25	cccDNA Inhibition	Baruch S. Blumberg Institute, United States	Pre- clinical
Birinapant	SMAC	TetraLogic Pharmaceuticals, United States	Phase I
CPI-431-32	Inhibition of cyclophilin A	Ciclofilin Pharmaceuticals, United States	Pre-clinical
Myrcludex B	HBV entry inhibition	Hepatera Ltd, Russia and MYR GmbH, Germany	Phase Ⅱ
Simvastatin	HMG CoA reductase inhibitor	University of Oklahoma and United States Veterans Administration	Phase I

RNAi: RNA inhibition; HBV Cp: Hepatitis B virus core protein; PRR: Pattern recognition receptors; SMAC: Synthetic small molecule and peptidomimetic of second mitochondrial-derived activator of caspases.

and most of them hold great promise in the future. The NNAVs in development for HBV are enlisted in Table 4.

Core protein allosteric modulators

Core protein allosteric modulators (CpAMs) belong to the category of anti-viral small molecules which are responsible for targeting the function of a virus DNA that is hidden in the infected livers of individuals suffering from hepatitis B. CpAMs have the ability to alter the activity of hepatitis B core protein that is vital for the virus's survival. Purified hepatitis B core protein can impulsively assemble, within seconds, to form complexes that are soccer-ball shaped and are identical to capsids in the infectious virus[93]. By careful examination of the mechanism of assembly, investigators at Indiana University in association with Assembly Biosciences have steered the discovery of a variety of families of small molecule CpAMs that are capable of reducing viral load and key antigens of virus selectively and effectively, which is considered to be the paramount marker of a functional cure[94]. In hepatitis B, CpAMs fight the virus by disturbing multiple aspects of the viral lifecycle, that include altering the function of a special viral DNA known as covalently closed circular DNA (cccDNA), that acts as the viral reservoir and hides in the infected liver cells nuclei. This cccDNA functions as a template for the assembly of viral proteins and extra copies of the viral genome, backing the persistence of the infection. Currently available HBV therapies do not affect cccDNA, because of which only 3 to 5 percent of hepatitis B patients become disease free, which requires most infected individuals to take these antivirals for the rest of their lives. HBV inhibition in this case has been achieved by causing mutations in capsid proteins that as a result affects the self-assembly, reverse transcription and packaging of HBV molecule[95,96]. The firm is currently working for selection of a first generation lead molecule[93].

Phenylpropenamides (AT-61 and AT-130)

AT-61 and AT-130 are phenylpropenamides that belong to non-nucleoside assembly activators (anti-capsid activity) for HBV treatment[97]. AT-130 acts by binding a hydrophobic pocket that is also capable of accommodating the previously characterized Hetero-aryl-di-hydro-pyrimidines or HAP compounds, but favors a distinctive quasi-equivalent site on the capsid surface. Therefore, this pocket acts as an uninhibited drug binding site and a potential target for different assembly effectors with a wide range of mechanisms of action[98,99]. Although both of these compounds have shown significant anti-viral activity against resistant strains of HBV but AT-130 has also shown greatest activity in cell culture[98,100]. AT-61 demonstrated antiviral specific activity in cell culture with minimal adverse effects[101]. It has been recently revealed that AT-130 enhances the rate of core protein (Cp) assembly and stabilizes favorably non-capsid polymers of Cp. Therefore, further strengthening the case of AT-130 as future non-nucleoside anti-HBV drug[101].

BAY 41-4109

BAY41-4109 belongs to HAPs or Hetero-aryl-di-hydropyrimidines which are non-nucleoside assembly activators that include potent anti virals such as HAP1, HAP12, BAY41-4109 acting as allosteric effectors that prompt an assembly-active state and, at high concentration, preferentially stabilize non-capsid polymers of Cp[102,103]. BAY 41-4109 has been shown to be used a valuable addition to current therapies for HBV in murine models, and it can also be tested as a therapeutic tool during the spread of resistant HBV strains that occurs during treatment with nucleoside

analogues[104]. These anti-capsid compounds show (CpAMs) significant impact on Cp nuclear functions at multiple levels: blocking of new cccDNA formation/ accumulation, reduction of an established cccDNA pool and inhibition of HBc occupancy and histone acetylation on the cccDNA that translate into a reduced pre-genomic RNA (pgRNA) transcription[101]. BAY 41-4109 is currently in Phase1 Clinical trial being developed by AiCuris, Germany[105]. Together these compounds represent an interesting avenue for HBV treatment that can provide great promise in the future.

NVR 3-778

Novira's lead core inhibitor candidate, NVR 3-778, disrupts the HBV lifecycle by inducing the assembly of defective capsids and is an effective drug inhibitor of HBV replication both *in vitro* cell culture models and a humanized liver mouse model of CHB. An excellent preclinical safety profile has been established for NVR 3-778 and a Phase 1 clinical trial is underway in New Zealand[106]. Phase Ia has been successfully completed and has revealed that the drug is safe and well tolerated in healthy volunteers[107]. Phase Ib of the Clinical Trials has been started and is expected to be completed in December 2015[106]. This novel mechanism of action promises to change the paradigm for CHB treatment. It can be administered and with the standard treatment for HBV *i.e.,* (nucleosides and interferon), Novira's core inhibitors are expected to provide greater and faster suppression of cccDNA and new virus production. Directly or indirectly, core inhibitors may also reduce HBsAg levels and release the block on immune response pathways to further reduce the time to cure. Higher and faster cure rates promoted by core inhibitors will in turn enable finite therapy so that many CHB patients will no longer require lifelong treatment[107].

NVP018 or OCB-030

NVP018 also known as OCB-030 is available in oral form and is a second-generation cyclophilin inhibitor based on sangamide with a well-differentiated preclinical profile in comparison with other cyclophilin inhibitors. Cyclophilins are a group of proteins that have been occupied in controlling innate immune responses subsequent to viral infection. Blocking of the of cyclophilins interaction with interferon signaling pathways is one of the mechanisms *via* which viruses take control of host innate immune response[108]. Data demonstrated at the International Liver Congress ™ (2014), the periodic meeting of the European Association for the Study of the Liver, showed that OCB-030 may also inhibit the HBV replication by two mechanisms *in vitro*. First, OCB-030 may directly inhibit several phases of viral replication in liver cells and second, it may indirectly act by augmenting the host immune response *via* Interefron regulators factors, including strong inhibition of an interaction that take splace between cyclophilin A and IRF9 (a key component of the JAK/STAT pathway). Results also showed that the possibility of developing resistance, a substantial clinical problem with current therapies for hepatitis B is very low with OCB-030[108,109]. Tekmira is planning to file an IND with the FDA, or and an equivalent agency in another country to launch the Phase Ⅰ clinical trials of the drug OCB-030 in 2015[110].

TKM-HBV

Tekmira's TKM-HBV database comprises two wet-lipid nanoparticle (LNP) interpretations TKM-HBV$_{4G}$ (4th generation LNP) and TKM-HBV$_{3G}$ (3rd generation LNP) interpretations. Both interpretations comprise a combination of three UsiRNA RNAi triggers that target highly conserved regions on the 4 HBV pgRNAs[111]. TKM-HBV also has shown diminution in HBsAg and cccDNA in the urokinase plasminogen activator-severe combined immunodeficiency (uPA/SCID) chimeric mouse model. Collectively data showed that TKM-HBV$_{3G}$ may facilitate at least a 1log$_{10}$ reduction in HBsAg in the treatment center, at safe therapeutic doses[112]. Preclinical trials of TKM-HBV$_{3G}$ data showed cccDNA reduction as a downstream result of inhibiting the assembly of all HBV proteins *via* the RNAi that includes preventing cccDNA episomal conservation and ultimate establishment by inhibiting the production of all HBV proteins. TKM-HBV's RNAi mechanism of action results in downstream inhibition of new HBV subviral particle and its formation. By vigorously inhibiting HBsAg and subviral particle construction, TKM-HBV may also ease the reactivation of immune system against HBV and cccDNA by activating humoral and T-cell facilitated immune mechanisms[112].

Second TKM-HBV formulation 4th gen LNP and preparation was publicized in November 2014 by Tekimira Pharmaceutical Corporation. TKM-HBV$_{4G}$ is basically times more effective than TKM-HBV$_{3G}$[113,114]. The study should evaluate the pharmacokinetics, acceptability and safety of the drug TKM-HBV$_{4G}$ and TKM-HBV$_{3G}$ in healthy subjects. TKM-HBV$_{3G/4G}$ has the potential to be a keystone drug in successfully treating CHB infection because of its ability to counter various elements of the HBV lifecycle[113].

Stimulators of interferon genes agonist

Stimulators of interferon genes (STING) agonists are activators of pattern recognition receptors (PRRs) activators present in the cytosol of immune cells. By stimulating genes responsible for interferon activation within body it may lead to the induction of the supplementary IFN-α and β, which exhibit the antiviral properties[114]. Tekmira in collaboration with Blumberg Institute and is attempting to investigate and identify a small orally active potent molecule that are the human STING agonists. The molecules shall possess the desired attributes which shall progress it to the human

clinical studies[115].

ARC-520

Arrowhead's ARC-520 is a product of RNAi (interference) technology, using short interfering RNA (siRNA) particles. These particles are injected in dynamic polyconjugate (DPC) nano particles bound to target ligands, which transport them to their target sites where viral infection has taken place. The DPCs are coated with a highly resistant polymer made of both polar and non-polar elements, which make them resistant to auto-immunity components in the bloodstream. On reaching the target sites, DPCs are taken up by endosomes containing the virus particles. The polymers coating the DPCs lyse the endosomes and the siRNAs interfere with the genetic machinery of the virus particles, knocking out virulence genes, hampering DNA replication, disturbing transcription and hence inhibiting protein synthesis. These mechanisms collectively prevent spread of virus particles further in the host[116]. ARC-520 aims to deliver a functional cure for the HBV infection and restore the adaptive immune system with the help of its RNAi mechanism. It has been tested successfully in mice and chimpanzee models, where it has shown to reduce the amount of viral DNA, HbsAg and HbeAg by as much as 90%-95%, lasting up to one month or more[117]. ARC-520 successfully completed its Phase Ⅰ Clinical Trials showing excellent safety and tolerability results in healthy volunteers[118,119]. The company is at present investigating the single dose Phase Ⅱa study in chronic HBV patients which so far have shown significant reduction in HBsAg in chronic HBV patients[120,121]. The company received an IND for Phase Ⅱ study of ARC-520 in January 2015[122].

ALN-HBV

ALN-HBV RNAi is a potent drug with an excellent therapeutic potential and its potent mechanism of action blocks all steps of the HBV life cycle including assembly, secretion of virus, Replication, and secretion of sub-viral antigens. The development of a candidate program targets to work with the Alnylam Pharmaceuticals Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology. The technology enables the subcutaneous dose administration with upgraded potency, safety, durability and wide therapeutic index of the drug. ESC-GalNAc conjugate can be developed into an excellent approach in the class of RNA therapeutics targeting HBV[123].

The pre-clinical studies with drug indicate substantial, multi-log reductions in HBV viral titers and surface antigen (HBsAg). The drug proved to support the evidence for an immune-mediated therapeutic effect in chronically infected chimpanzees. The results investigated another striking feature in achieving functional cure for HBV cure by the use of the RNAi therapeutics against the conserved regions of the HBV genome[124]. Alnylam Pharmaceuticals is expected launch the product name for its ALN-HBV Development Candidate by of 2015 and file an IND or IND equivalent around the end of 2015[125].

Morphothiadine or GLS4

Morphothiadine Mesilate (GLS4) is another HAP (heteroaryl-di-hydro-pyrimidines) compound. GLS4 is a pipeline product of HEC Pharm that can combine with the HBV core protein dimer, and interfere the assembly process and functions of HBV nucleocapsid, and thus it can effectively inhibit HBV replication through two active ways of inhibiting viral structure assembly and gene replication.

Compared to the traditional existing nucleoside analogues, MorphothiadineMesilate shows higher inhibitory activity in the HBV inhibition tests[125,126]. According to the company's website the Phase Ⅰ Clinical Trial application of GLS4 was submitted to China Food and Drug Administration (CFDA) in 2010, and received the approval letter in November 2011. The phase Ⅰ study was initiated early of 2012 and finished in Dec, 2012. Data in phase Ⅰ show that GLS4 has favorable safety and efficacy signals, and no confirmed drug-related adverse events are observed. It also shows favorable pharmacokinetic profile as a potential clinical candidate. Phase Ⅱa trial was initiated in early May. 2013 and results came out in February 2014. Filing for Phase Ⅱb trial has submitted to CFDA and the pharmaceutical is planning to launch it in China by 2016[127,128].

BSBI-25

BSBI-25 is a cccDNA inhibitor under development by Baruch S. Blumberg Institute. The compound is still in preclinical stage of development. The drug aims to work on the removal of cccDNA protecting hepatocytes and to prevent the replase of HBV due to rapid recover in serum HBV-DNA after termination of antiviral treatment. Encouraging evidence of cccDNA degradation in the absence of hepatotoxicity has been reported in which lymphotoxin-β and IFN-α receptor stimulation up-regulated the levels of the host factors APOBEC3A and APOBEC3B cytidine deaminases, respectively, the action of which mediated by the core protein in HBV-infected cells. The human liver needle biopsies and primary hepatocytes led to the cccDNA degradation and cytidine deamination, apurinic/apyrimidinic site formation that prohibited HBV recurrence[129,130].

Birinapant

Birinapant (TL32711) is a potent, bivalent SMAC (synthetic small molecule and peptidomimetic of second mitochondrial-derived activator of caspases) mimetic that binds with differential affinity to multiple members of the inhibitor of apoptosis proteins (IAP) family including cIAP1, cIAP2, XIAP, and ML-IAP[131,132]. Initially developed by Tetralogic Pharmaceuticals as

Table 5 Nucleoside analogs in development for hepatitis B virus

Name	MOA	Developed by	Phase
Clevudine	DNA polymerase inhibition	Bukwang Pharmaceutical, South Korea	Approved in South Korea and Philippines
Besifovir	DNA polymerase inhibition (pro-drug)	Ildong Pharmaceuticals and LG Life Sciences	Phase Ⅲ
Tenofoviralafenamide	DNA polymerase inhibition (pro-drug)	Gilead Sciences, United States	Phase Ⅲ
CMX157	DNA polymerase inhibition (pro-drug)	ContraVir Pharmaceuticals, United States	Phase Ⅲ
AGX-1009	DNA polymerase inhibition (pro-drug)	Agenix, Australia	Phase Ⅰ

HBV: Hepatitis B virus; MOA: Mechanism of action.

anticancer agent, this drug has proven its efficacy in infectious diseases as well. The use of the mouse model of HBV, birinapant showed excellent results it was well tolerated and exhibited activity in the clearance of cells infected with HBV. The drug is currently in Phase Ⅰ Clinical Trials undergoing safety and tolerability studies in CHB[132].

CPI-431-32

CPI-431-32, a novel agent developed by Ciclofilin Pharmaceuticals, targets and inhibits a host cellular enzyme known as cyclophilin A (CyPA). CyPA is responsible for activation of viral proteins critical for the life cycles of HCV, human immunodeficiency virus type 1 (HIV-1) and HBV. By understanding how cyclophilins mediate viral replication, the company has developed a host-targeting antiviral, CPI-431-32 which is used for the treatment of HCV, HBV, HIV-1, and infection with more than one of these viruses simultaneously (co-infection)[133,134].

Myrcludex B

Myrcludex B is a HBV entery inhibitor currently in Phase Ⅱ Clinical Trials. A joint venture of Hepatera Ltd and its development partner MYR GmbH, Myrcludex B. After positive preclinical and Phase 1 studies the drug has successfully completed phase Ⅱa of the clinical trials showing evidence that the inhibition of intrahepatic spread of HBV may become part of future curative regimes[135-137].

Simvastatin

Simvastatin is FDA approved 3-hydroxyl-3-methylglutaryl coenzyme A (HMG CoA reductase inhibitors that are used to treat hypercholesterolemia. Besides exhibiting strong anti-HBV activity in cell culture models. Simvastatin has shown synergestic anti-HBV activity with nucleos(t)ide analogues including adefovir, entecavir, tenofovir and lamivudine[138]. The University of Oklahoma and the United States Veterans Administration successfully conducted a phase Ⅰ proof-of-concept study for the drug Simvastatin against the CHB patients that was completed in 2012[139].

NUCLEOSIDE/NUCLEOTIDE ANALOGS

Nucleoside analogs (NUCs) have so far served as the main weapon in the armory against hepatitis B along with the Interferons. However the development of resistance, biochemical irregularities, along with poor durability are the limitations of the NUCs[132]. The drug companies are therefore focusing on altering the approach of utilizing the NUCs as discussed under. Table 5 shows the nucleoside/nucleotide analogs development in for HBV.

Clevudine

Clevudine is a nucleoside analogue already approved in Phillipines and South Korea with incomplete licensing in Indonesia, Thailand, India, and Malaysia for the treatment of Hepatitis B. It has been found to inhibit HBV infection at the multiple steps of its replication cycle. The drug has an extended half-life which causes the significant reduction of cccDNA in animal models[140].

But despite of these potent antiviral activity Clevudine has shown to induce myopathy that is characterized by depletion of mitochondrial DNA on long term therapy[141,142]. This potent anti-viral needs to be administered with proper considerations of its ability to cause serious long-term side effects[143,144].

Besifovir/LB80380/ANA-380

LB80380 is an oral nucleotide pro-drug that incorporates into the viral DNA and prevents its replication. Phase Ⅱ Clinical Trials after Safety and Tolerance studies of the drug showed effective antiviral activity against viruses strains *i.e.,* wild-type and drug-resistant mutations[145,146]. Ildong Pharmaceuticals and LG Life Sciences are currently conducting Phase Ⅲ Clinical Trials of the drug to prove that besifovir is non-inferior to a control drug that are expected to be completed in July 2015 along with Phase Ⅰ Bioequivalence studies[147].

Tenofoviralafenamide

Tenofovir is the primary treatment for lamivudine-resistant HBV in the United States and Western Europe. There has been no Resistance to tenofovir characterized for three years after the drugs approvalfor HBV treatment[18]. Gilead Sciences is currently conducting Phase Ⅲ safety and efficacy studies of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate for Treatment of HBeAg-positive hepatitis B that is expected to be completed in November 2015[36,148]. Other than Tenofoviralafenamide

two more pro drugs of tenofovir namelyCMX157 (ContraVir Pharmaceuticals) and AGX-1009 (Agenix, Australia) are in Phase Ⅱ and Ⅰ of the clinical trials respectively[143].

In conclusion, HBV is a progressive liver disease and current therapies require continuous monitoring for serious side effects along with the development of resistance and therefore shorter durability. The increasing rates of resistance to antiviral therapy necessitates consideration of combination therapy and impels to look for novel treatment options. There is a deficiency of risk calculators including those similar to the Framingham risk score that evaluates the risk of coronary heart disease having a limited treatment of chronic HBV infection. The future therapies mentioned in this article are primarily focused on the designing of such therapies that require shorter duration of treatment, are more efficacious and have fewer side effects without the development of resistance. The idea to use therapeutic vaccines as monotherapy and along with the nucleoside/NUCs may prove to be of great success in designing future regimens for HBV therapy. The fact that pharmaceutical companies by realizing the increased demand of replacing the depleting army of NUCs are now focusing on Non-nucleoside antivirals including RNAi's and other novel protein inhibitors is a testimony that future therapy of HBV infection is non-NUCS.

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