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New and Emerging Therapeutic Approaches for Chronic Hepatitis B

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In this Issue...

Chronic hepatitis B affects approximately 400 million people worldwide and is the leading cause of hepatocellular carcinoma and cirrhosis. While current treatments can significantly reduce HBV replication and lower HBV DNA to undetectable levels, these treatments most often require lifelong use — they do not *cure* HBV.

Is a cure possible? In this issue, Dr. Chloe L. Thio from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine reviews recent publications describing the state of our current knowledge about the HBV life cycle, the early stage research into new drugs aimed at helping to achieve HBV cure, and the new drug tenofovir alafenamide (TAF) for HBV treatment.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the life cycle of hepatitis B and why developing a cure for hepatitis B is difficult.
- Discuss the available data on tenofovir alafenamide (TAF).
- Summarize emerging therapies for potential HBV cure.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

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Guest Faculty Disclosure

Dr. Thio has indicated that she has received grant support from Gilead Sciences, Inc.

Unlabeled/Unapproved uses

Dr. Thio has indicated that there will be references to unlabeled and currently unapproved use of TAF for hepatitis B.

IN THIS ISSUE

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COMMENTARY

Chronic hepatitis B is the leading cause worldwide of hepatocellular carcinoma and end-stage liver disease. While liver disease progression can be slowed with current hepatitis B treatments, a cure remains elusive. For people with active chronic hepatitis B, treatment is usually lifelong, since hepatitis B surface antigen (HBsAg) seroconversion with treatment is uncommon.[1] People who have chronic hepatitis B that does not meet treatment guidelines, or who have recovered from a past infection, remain at risk for reactivation with immunosuppressive therapy. This will be a growing concern as immunosuppressive therapies become the treatment of choice for a variety of medical conditions. For all these reasons, it is imperative to develop a hepatitis B cure.

Two types of cure could be achieved: a functional cure and an eradication cure. A functional cure would mimic natural recovery after discontinuation of therapy, which would mean loss of HBsAg and development of antibody to HBsAg (anti-HBs). In a functional cure, there would still be a risk for reactivation of disease due to the covalently closed circular (ccc)DNA in the hepatocyte nucleus. On the other hand, with an eradication cure, the cccDNA is eliminated, so HBV is no longer present. Eradication cure is clearly more difficult to achieve, since this is not usually accomplished with natural recovery. Treatments are in development to achieve either a functional or eradication cure, and a number of these strategies are reviewed in this issue.

Hayes et al (reviewed herein) describe the current state of knowledge regarding the HBV life cycle that leads to formation of cccDNA. Since the cccDNA serves as the template for HBV transcription, understanding its development is essential towards developing a cure. This article puts into perspective some of the virological approaches that are currently under investigation to achieve HBV cure and allows the reader to envision other possible steps for antiviral development. Although only a few virological approaches are discussed in this eViralHepatitis Review issue, other antivirals in development are described in a recent review by Liang et al.[2]

Although tenofovir alafenamide (TAF) as a single agent will not cure hepatitis B, it is currently under FDA review for approval for hepatitis B treatment. This agent has recently been approved in various combination pills for the treatment of HIV and has equivalent efficacy to the commonly prescribed tenofovir disoproxil fumarate (TDF).[3] The advantage of TAF over TDF is that it enters the cells before being metabolized to the active form, tenofovir, which has been shown to be associated with renal and bone toxicities. Because of this mechanism, much lower doses of TAF can be given than TDF. In patients with chronic hepatitis B, Buti et al and Chan et al (reviewed in this issue) demonstrate equal efficacy of TAF and TDF for treating chronic hepatitis B with less bone and renal toxicity. Thus, until we have a cure for hepatitis B, TAF (once approved) will be effective for hepatitis B treatment without the long-term toxicity concerns of TDF.

Approaches for curing hepatitis B are either virological or immunological. Virological approaches are aimed at stopping the HBV life cycle. As one example, the reviewed article by Urban et al demonstrated that blocking the receptor for HBV entry (NTCP) can lead to a decline in HBV DNA most consistently in those receiving 10 mg dose. Another virological approach is to silence the RNA transcripts produced from the cccDNA. The reviewed paper Yuen et al reports on a study in which a combination of siRNAs have been developed to achieve this effect with some reduction in viral proteins. However, many of the patients were on entecavir prior to receiving the siRNA or received entecavir with the siRNA, so how much the siRNA contributes to HBV DNA decline or decline in viral proteins is not known.

The immunological approach is based on the idea that HBV-specific immune responses during chronic hepatitis B are defective, so restoration of the immune response may contribute to curing hepatitis B. The restoration can occur via stimulation of the general immune response or of the HBV-specific immune response. The papers by Gane et al and by Liu et al (both reviewed herein) focus on restoring the general immune response, but take different approaches. Gane et al focus on a compound that stimulates TLR7, which activates the innate and adaptive immune responses. This is an early-phase study, so it is not surprising that HBV markers are not affected by one or two doses of this compound. It is encouraging that the investigators see stimulation of the immune system at the higher doses, as measured by higher amounts of ISG15. However, whether more doses of this compound will actually lead to restoration of an immune response to hepatitis B remains to be studied.

Liu et al take a different approach by blocking a known immune checkpoint—the PD-1 axis—in a woodchuck hepatitis model. The immune checkpoints are upregulated on chronically stimulated T-cells and thereby render exhausted T cells, which have diminished proliferative capacity and poor cytokine production. Blocking these immune checkpoints can partially reverse T-cell exhaustion, as has been shown effective against a variety of tumors.[4] Liu et al demonstrate that in the woodchuck model, blocking the PD-1 axis along with both an antiviral and HBV vaccine can partially restore the woodchuck hepatitis virus immune response. The other encouraging aspect of this study is that the investigators did not demonstrate fulminant hepatic failure in the woodchucks, which is a concern when there is a lot of antigen in the liver and the immune system is activated.

The articles reviewed in this issue summarize the current state of knowledge regarding the HBV life cycle and some of the emerging therapies for HBV cure. However, these HBV cure therapies are still in early-phase trials, so a focus on long-term treatment with little toxicity is the current state of care.

References:

1. Terrault NA, Bzowej NH, Chang KM, et al; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016 Jan;63(1):261-83

2. Liang TJ, Block TM, McMahon BJ, et al. Present and future therapies of hepatitis B: From discovery to cure. *Hepatology*. 2015 Dec;62(6):1893-908

3. Wohl D, Oka S, Clumeck N, et al; GS-US-2,92-01040111 and Study Team. Brief Report: A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results. *J Acquir Immune Defic Syndr*. 2016 May 1;72(1):**58**-64.

4. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 2015 Apr 13;27(4):450-61

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Initial Steps in HBV Infection

Hayes CN, Zhang Y, Makokha GN, Hasan MZ, Omokoko MD, Chayama K. Early events in hepatitis B virus infection: From the cell surface to the nucleus. *J Gastroenterol Hepatol*. 2016 Feb;31(2):302-309.

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Developing a cure for hepatitis B requires understanding the HBV life cycle, including how the covalently closed circular (ccc)DNA is established in the hepatocyte nucleus. The cccDNA is the stable episomal form of HBV that is essential for HBV replication, as it provides the template for transcription of viral mRNAs. This review article provides an excellent summary of the early events in HBV infection that lead to the establishment of cccDNA.

Two highly conserved, positively charged residues in the antigenic loop of the hepatitis B surface antigen (HBsAg) interact with heparin sulfate proteoglycans on the surface of the hepatocyte, which facilitates binding of the pre-S1 region of hepatitis B to its primary receptor, sodium-taurocholate cotransporting polypeptide (NTCP). This receptor is also responsible for sodium-dependent import of bile salts. After NTCP binding, HBV uses endocytosis to enter the cell, although the precise mechanisms of endocytosis have not been elucidated. With endosomal maturation, the release of the HBV nucleocapsid (which contains the HBV DNA) into the cytoplasm may be facilitated by a cell-permeable peptide translocation motif. These naked core particles are then actively transported along the microtubule network to the nucleus, likely via the motor protein dynein. The maturation of the nucleocapsid dissociates at the nuclear pore complex, which allows HBV DNA, core proteins, and the covalently bound HBV polymerase to enter the nucleus. Final entry of HBV DNA is likely aided by a nuclear localization signal in the terminal protein domain of the HBV polymerase. This transport process through the cytoplasm into the nucleus occurs within 15 minutes.

Once in the nucleus, the partially double-stranded relaxed circular HBV DNA is converted to cccDNA in a series of steps. Initially, the covalently bound polymerase and RNA primer are removed. Then, host enzymes are used to complete the partial double strand and then ligated to form a closed DNA. This is then bound to histones and nonhistone proteins, including HBV core protein, to form a stable minichromosome or cccDNA. This cccDNA is the template for transcription for the mRNAs, which are then exported to the cytoplasm for translation into HBV proteins and for HBV replication. These latter steps are not discussed in this review article. It is important to understand that replication in the cytoplasm results in newly synthesized capsids that can also enter the nucleus and establish more cccDNA, so each infected hepatocyte has more than one copy of cccDNA. The cccDNA can persist for decades; therefore, strategies that decrease cccDNA production or maintenance are needed to cure hepatitis B.

As the article points out, there has been much progress in understanding the HBV life cycle, but many questions remain. Therefore, further work on more details of the life cycle is important for developing a cure.

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Tenofovir Alafenamide and Hepatitis B Treatment

Buti M, Gane E, Seto WK. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-negative chronic hepatitis B: week 48 efficacy and safety results. EASL 2016. Abstract GS06

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HL Chan, S Fund, WK Seto et al. A phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-positive chronic hepatitis B: week 48 efficacy and safety results. EASL 2016. Abstract GS12

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Abstracts presented at EASL 2016 included two randomized, double-blinded studies investigating tenofovir alafenamide (TAF) for treating HBeAg-positive and HBeAg-negative chronic hepatitis B. In the first, Buti and colleagues randomized 425 HBeAg negative patients (2:1) to receive 25 mg TAF (n = 285) or 300 mg tenofovir disoproxil fumarate (TDF; n = 140). The cohort was 61% men and 70% Asian, with a mean age of 45 years. About 20% had received HBV treatment previously and the main genotypes were B (21%), C (40%), and D (32%). Mean HBV DNA was 5.7 log IU/ml and median ALT of 67 U/L. After 48 weeks

of treatment, HBV DNA < 29 IU/ml was achieved in 94% of the TAF group and 93% of the TDF group. Only 2% in the TAF arm and 3% in the TDF arm had virological failure (remaining nonresponders were due to missing data). ALT normalization was significantly more common in the TAF than in the TDF arm (50% vs 32%).

In the HBeAg+ study, Chan et al randomized 873 patients 2:1 to receive 25 mg TAF (n = 581) or 300 mg TDF (n = 292). The majority (64%) were male, 80% were Asian, and the mean age was 38 years. About 25% were treatment experienced. The most common genotypes were also B (17%), C (52%), and D (23%). The mean HBV DNA was 7.6 log IU/ml and was > 8 log IU/ml in about 50%. The mean ALT was 85 U/L. After 48 weeks, 64% in the TAF group and 67% in the TDF group achieved HBV DNA < 29 IU/ml. ALT normalization was more common in the TAF group (45% vs 36%), but the difference did not reach statistical significance. HBeAg seroconversion was similar between groups at 10% in the TAF group and 8% in the TDF group.

Discontinuations due to adverse events was low in both treatment groups (0.7% in both arms in the HBeAg negative study and 1% in both arms in the HBeAg+ study). In addition, in both studies, patients receiving TAF had a significantly smaller mean percentage decrease from baseline in hip and spine bone mineral density at week 48 ($P < .001$) compared to the TDF group. The median change in estimated GFR from baseline to week 48 was lower in the TAF group than in the TDF group in both studies ($P < .01$). As in other TAF studies, more people had elevated LDL cholesterol in the TAF arms (4%-5%) than in the TDF arm (< 1%).

In summary, both studies demonstrate that TAF was noninferior to TDF in treatment-naïve and treatment-experienced patients with either HBeAg negative or positive chronic hepatitis B.

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Myrcludex B: Phase 2a Trial Data

S. Urban, P Bogomolov, N Voronkova, L et al. A phase 2a proof of concept clinical trial with HBV/HDV entry inhibitor Myrcludex B. AASLD 2014, LB-20

View Journal Abstract

The sodium taurocholate cotransporting polypeptide (NTCP) has been identified as a primary receptor for hepatitis B that binds to the pre-S1 region of HBV.[1] Myrcludex B is an HBV entry inhibitor that consists of chemically synthesized lipopeptides from this pre-S1 region, which binds to the NTCP receptor. This phase 2a study was designed to assess safety, tolerability, and antiviral activity of Myrcludex B for HBV (the study also included a hepatitis D cohort, which is not discussed here). The study participants all had HBeAg negative chronic hepatitis B with HBV DNA > 2000 IU/ml (median 4.27 log IU/ml) and did not have cirrhosis. The participants were given either 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg subcutaneously (8 participants/group) of Myrcludex B once daily for 12 weeks. The 10 mg group also received an additional 12 weeks of treatment.

Response was best in the 10 mg group, with 6/8 achieving > 1 log HBV DNA decline at week 12, while only 7/32 (21%) in the other groups achieved this outcome. ALT normalization occurred in 22/40 (55%) of the participants. No changes in HBsAg levels occurred. Tolerability was excellent, except for injection site dermatitis in three participants who all received the 10 mg dose. Further studies are needed to determine if this drug will be useful as a component of therapies that could potentially cure hepatitis B.

References:

1. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *Elife*. 2012 Nov 13;1:e00049.

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ARC-520 Phase II Study

M Yuen, S Liu, C Lai, et al. ARC-520 produces deep and durable knockdown of viral antigens and DNA in a phase II study in patients with chronic hepatitis B. AASLD 2015 Abstract LB-9

View Journal Abstract

ARC-520 is a siRNA designed to silence HBV mRNAs in the cytoplasm, with the goal of reducing RNAs that are used for synthesizing HBV proteins and for producing HBV DNA. Without these RNA products, replication of HBV would stop and HBsAg would also be reduced, which may result in recovery of the T cell response (since HBsAg may be a component of immune tolerance). The siRNAs in ARC-520 are conjugated to cholesterol and hepatocyte-targeted ligands to allow it to enter the hepatocyte, be taken up by endosomes, and then released into the cytoplasm after endosomal membrane lysis.

This study enrolled 58 participants, of whom 10 received placebo. Thirty-eight participants were HBeAg-negative and received one dose of ARC-520, ranging from 1 mg/kg-4 mg/kg intravenously. The 20 HBeAg-positive participants all received 4 mg/kg intravenously. At study entry, the mean age was 41 years and 32/38 HBeAg negative participants and 14/20 HBeAg positive participants were on entecavir with undetectable HBV DNA. All participants received entecavir throughout the study. Viral parameters were measured over 85 days.

The study primary study outcome was change in quantitative HBsAg (qHBsAg). The only group that showed at least a 1 log decline in qHBsAg was the HBeAg-positive group not taking entecavir at study entry. In this group, the qHBsAg declined a mean of - 1.1 log IU/ml, with the maximum reduction of - 1.9 log IU/ml. In contrast, for HBeAg-positive patients on entecavir at study entry, the mean qHBsAg decline was only - 0.3 log IU/ml. In the HBeAg-negative patients, regardless of being on entecavir at study entry, qHBsAg decline ranged from a mean of - 0.2 log IU/ml to - 0.4 log IU/ml, with a maximum of - 0.7 log IU/ml. The duration of HBsAg decline continued for approximately eight weeks before rebounding to pre-ARC-520 levels. In the HBeAg-positive participants, the quantitative HBeAg declined a mean of - 1.2 log IU/ml. No serious adverse events occurred, with 23% reporting mild or moderate adverse events. Further studies are required to determine if multiple doses would lead to a better response.

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TLR7 Agonist GS-9620 and Chronic Hepatitis B

Gane EJ, Lim YM, Gordon SC, et al. The oral toll-like-receptor agonist GS-9620 in patients with chronic hepatitis B infection. *J Hepatol* 2015 63(2):320-8.

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In chronic hepatitis B, the hepatitis B-specific immune response is defective, with impaired T cell effector function and induction of immune inhibitory pathways. Thus, another approach to curing hepatitis B is to develop immunotherapy that stimulates the immune response against hepatitis B (as a complement to antiviral therapy). One direction currently being studied in hepatitis B is stimulating toll-like-receptor 7 (TLR7) — a pattern-recognition receptor that increases adaptive and innate immune response upon stimulation. The investigative agent GS-9620 has been designed to stimulate TLR7; in a woodchuck hepatitis model, GS-9620 led to HBsAg loss.[1]

This study by Gane et al included 100 subjects, of whom 84 received GS-9620. Of those 84, 41 were treatment naïve with a mean HBV DNA of 3.95 log IU/ml, and 43 were on treatment and had undetectable HBV DNA. Seventy-five percent were HBeAg positive and 75% were male. All participants had qHBsAg > 250 IU/ml. Participants received escalating doses of GS-9620 of 0.3 mg, 1 mg, 2 mg, or 4 mg. They received either one or two doses, with the second dose seven days after the first. They were followed for seven days after each dose.

One or two doses of GS-9620 did not result in HBV DNA or HBsAg reduction. However, the investigators detected an increase in ISG-15 mRNA in participants receiving the 2 mg (~ 16-fold increase) and 4 mg (~ 32-fold increase) doses, but no significant increase in those receiving lower doses. ISG-15 is a cytokine induced by type 1 interferons. No serious

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adverse events occurred.

This dose-dependent ISG-15 induction suggests that there is immune stimulation at the higher doses of GS-9620.

References:

1. Menne S, Tumas DB, Liu KH, et al. Sustained efficacy and seroconversion with the Toll-like receptor 7 agonist GS-9620 in the Woodchuck model of chronic hepatitis B. *J Hepatol*. 2015; 62: 1237–1245.

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Anti-PD-L1 Plus Therapeutic Vaccine for Chronic Woodchuck Hepatitis

Liu J, Zhang E, Ma Z, et al. Enhancing virus-specific immunity in vivo by combining therapeutic vaccination and PD-L1 blockade in a chronic hepadnaviral infection. *PLoS Pathogens* 2014:10(1): e1003856

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Another approach to stimulating the general immune response is to block the inhibitory pathways or immune checkpoint markers that are upregulated in chronic hepatitis B. The goal with blockade of these markers is to reverse exhaustion and restore a T-cell's immune response. One example that has been studied in the woodchuck model is blockade of PD-L1, the ligand for PD-1.

In this study, Liu et al used the woodchuck hepatitis virus (WHV) model, which is similar to human HBV. In the first part of the study, they demonstrated that PD-1 expression during acute WHV infection correlated with WHV DNA levels, with levels increasing just after the peak of WHV DNA and decreasing as the DNA decreased. They next found that woodchucks with chronic WHV infection had higher PD-1 levels in PBMCs (peripheral blood mononuclear cells) and CD8+ T-cells compared to uninfected woodchucks, as well as to woodchucks that recovered from a WHV infection. Giving six weeks of entecavir reduced the WHV DNA and in parallel reduced the PD-1 levels on CD8+ T-cells and on PBMCs.
In the last part of the study, the investigators had four groups of woodchucks with three woodchucks in each group. Group 1 was the control group that did not receive any drug; group 2 received entecavir; group 3 received entecavir along with a HBV DNA vaccine; and group four received entecavir, HBV DNA vaccine, and anti-PD-L1. Entecavir was given for 24 weeks in groups 2 through 4. Starting in week 12, woodchucks in groups 3 and 4 received the vaccine injected weekly. The vaccine was a plasmid containing woodchuck hepatitis core and surface antigens. In group 4, the anti-PDL1 agent was given three times in week 24. WHV-specific T cell responses were not detectable in groups 1 or group 2. The vaccine plus entecavir group (group 3) resulted in a slight expansion of the WHV-specific T cells; however, blocking PD-L1 (group 4) significantly increased the T-cell response to 14% (compared to 0% in the controls) in the week immediately following anti-PD-L1. This increase in T-cell responses persisted through the end of the study (week 38). Furthermore, the woodchucks that received the anti-PD-L1 (group 4) had better viral control than the other groups.

Viral load in all groups that received the entecavir became undetectable while on the drug, but rebound occurred after cessation of entecavir except in the group that also received anti-PD-L1 (group 4). Similarly, WHsAg declined in all groups while on entecavir, but the levels rebounded after stopping entecavir in all groups except the anti-PD-L1 (group 4). Analysis of liver specimens revealed lower DNA replication in the liver of the woodchucks that received the anti-PDL1 than in the other groups. This finding was also true for cccDNA levels.

There is concern that blocking the immune checkpoint markers will lead to fulminant liver disease due to a robust immune response; however, only one of the woodchucks that received anti-PD-L1 had a flare that was thought to be due to development of liver cancer. Liver enzyme increases were seen in all groups with reduction of WHV DNA with entecavir and was similar in the anti-PD-L1 group. However, much more research is needed before such a strategy can be used in patients.

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KEY TAKEAWAYS

- Tenofovir alefenamide (TAF) is effective for treating hepatitis B and is safer than tenofovir disoproxil fumarate (TDF).
- Eradication of cccDNA is needed to achieve a complete cure of hepatitis B.
- Several drugs to cure hepatitis B are in development, but none will be available in the near future.

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