EDITORIAL

Future of Chronic Hepatitis B Infection Therapies

Current treatments for chronic hepatitis B (CHB) infection rarely achieve functional cure, and unfortunately, complete cure and sterilizing cure are many years away. Functional cure has been rarely achieved (0%–10%) with conventional oral therapies.[1,2] As of today, there are 2 types of approved drugs for CHB treatment: conventional and pegylated interferon formulations and nucleos(t)ide analogs (NAs). NAs do not eradicate hepatitis B virus (HBV) and rarely result in a functional cure. Pegylated interferon is effective for less than 20% of patients with CHB, and the functional cure rate is only about 7% to 8%.[3] This challenge has led to planned development of new therapies that target HBV entry, replication cycle, covalently closed circular DNA, integrated virus, and HBV virions release or therapies that enhance human immune response.

One of these new therapies is a core protein allosteric modulator (CpAM). CpAMs interfere with hepatits B core antigen dimers and capsid assembly, creating aberrant capsids or empty capsids.[4] This process inhibits formation and release of new viruses, spread of the virus to uninfected cells, and covalently closed circular DNA replenishment in infected cells.[5] Despite its potential, several CpAMs have been discontinued due to liver toxicity (AB-506, AB-836, and ABI-H2173). For example, AB-506 production was terminated in October 2019 after it was shown to cause grade 4 alanine aminotransferase (ALT) flares in 4 patients with CHB of East Asian descent in a phase I trial.[4] Fortunately, the ALT elevations rapidly resolved after discontinuation of the drug.[6] Because of this study and other CpAMs that have been discontinued due to hepatotoxicity, it is important to carefully assess the safety and tolerability of new CpAMs, especially liver toxicity.

Canocapavir (ZH-H1505R) is a CpAM with a novel pyrazole structure and may be different from previous Class I and Class II CpAMs. Impressively, it is stated to be active against all HBV genotypes and some HBV variants that are resistant to Class I and Class II CpAMs. This study in healthy human volunteers has shown that it was generally well tolerated, with the most common adverse event being a grade 1 increase in ALT levels. This was a small cohort study with only 1 participant who is Asian (representing only 2.5% of the study population). Since a previous study[6] has shown ALT elevations primarily in Asians, it is imperative to further study the ALT elevations in a larger study with more balanced racial composition. More broadly, the cause(s) of ALT elevation within this class of drugs should be further studied. Interestingly, 1 patient withdrew due to grade 3 increase in amylase levels without clinical evidence of pancreatitis. This potential organ toxicity should also be further studied.[7]

The future of CHB treatment is headed toward the use of combination therapy, where different drugs target different modes of HBV infection and may require up to 4 viral targets. A CpAM known as ABI-H0731 has been studied in combination with a NA (entecavir). It has been shown to decrease HBV DNA to undetectable levels and reduce HBV RNA levels compared to entecavir alone. Additionally, prolonged combined therapy beyond 24 weeks have been shown to reduce hepatitis B surface antigen, hepatitis B e antigen, and hepatits B core antigen,[4] which was not seen with CpAMs alone. Interestingly, the CpAM being developed by Janssen actually showed less viral suppression when used with a small interfering RNA (siRNA).[8]

The siRNA is designed to target specific HBV DNA to induce its degradation. A recent study of siRNA (JNJ-3989) with or without CpAM (JNJ-6379) and NA found that it was generally well tolerated. The siRNA plus NA cohort displayed a significant reduction in HBsAg, HBV DNA, HBV RNA, HBeAg, and HBcrAg. Importantly, the HBsAg reduction persisted 336 days after siRNA was stopped. However, the antiviral activity for triple therapy (siRNA + CpAM + NA) was difficult to assess due to short treatment duration.[9] Similarly, a phase 2b study (REEF-1) looking at siRNA (JNJ-3989) with or without CpAM (JNJ-6379) and NA found that a combination therapy with siRNA plus NA had the greatest reduction in HBsAg at the end of 48 weeks.[8]

A combination therapy study of a siRNA and a monoclonal antibody targeting HBsAg (VIR-3434) found a significant reduction in HBsAg levels in all participants and HBsAg levels lower than 10 IU/mL in most participants. This study demonstrated that HBsAg levels were reduced more in combination therapy than either alone, affirming the complimentary effects[10] and pointing to combination therapy with up to 4 agents as the next phase in HBV drug development. CpAMs could be a cornerstone in this new therapy paradigm. Additionally, a study of a new antisense oligonucleotide (bepirovirsen) conjugated to N-acetyl galactosamine (GSK3389404) to enhance hepatocyte delivery was studied against a placebo. This study found a dose dependent HBsAg reduction regardless of baseline HBsAg with 9% of participants maintaining HBsAg and HBV DNA loss 24 weeks after the end of treatment.[11]

We believe these advancements in CHB treatment, such as with Canocapavir, points toward a future with combination therapy and allows us to be one step closer to functional cure of CHB.

KATERINA ROMA
Division of Internal Medicine
Kirk Kerkorian School of Medicine at University of Nevada
Las Vegas, Nevada

ROBERT G. GISH
Hepatitis B Foundation
Doylestown, Pennsylvania

References

1. Kim GA, Lim YS, An J, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014; 63(8):1325–1332.
2. Gish RG, Chang TT, Lai CL, et al. Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. J Viral Hepat 2010;17(1):16–22.
3. Kim V, Abreu RM, Nakagawa DM, et al. Pegylated interferon alfa for chronic hepatitis B: systematic review and meta-analysis. J Viral Hepat 2016;23(3):154–169.
4. Hui RW-H, Mak L-Y, Seto W-K, et al. Role of core/capsid inhibitors in functional cure strategies for chronic hepatitis B. Curr Hepatol Rep 2020; 19(3):293–301.
5. Zoulim F, Zlotnick A, Buchholz S, et al. Nomenclature of HBV core protein-targeting antivirals. Nat Rev Gastroenterol Hepatol 2022;19(12):748–750.
6. Yuen MF, Berliba E, Sukeepaisarnjaroen W, et al. Safety, pharmacokinetics, and antiviral activity of the capsid inhibitor AB-506 from Phase 1 studies in healthy subjects and those with hepatitis B. Hepatol Commun 2022; 6(12):3457–3472.
7. Jiang X, Hua B, Liu G, et al. Safety, tolerability, and pharmacokinetics of a novel HBV capsid assembly modulator Canocapavir: a randomized first-in-human study. Gastro Hep Advances 2023;2(4):524–531.
8. Yuen MF. Efficacy and safety of the siRNA JNJ-3989 and/or the capsid assembly modulator (CAM) JNJ-6379 for the treatment of chronic hepatitis B virus infection (CHB): results from the phase 2B REEF-1 study. 2021. https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-collaborator-presents-phase-2b-clinical-data-reef-1. Accessed February 7, 2023.
9. Yuen MF, Locarnini S, Lim TH, et al. Combination treatments including the small-interfering RNA JNJ-3989 induce rapid and sometimes prolonged viral responses in patients with CHB. J Hepatol 2022; 77(5):1287–1298.
10. Gane E, Jucov A, Dobryanska M, et al. Safety, tolerability, and antiviral activity of the siRNA VIR 2218 in combination with the investigational neutralizing monoclonal antibody VIR 3434 for the treatment of chronic hepatitis B virus infection: preliminary results from the phase 2 MARCH trial. American Association For The Study of Liver Diseases (AASLD). 2022. https://www.natap.org/2022/AASLD/AASLD_19.htm. Accessed February 7, 2023.
11. Yuen MF, Heo J, Kumada H, et al. Phase IIa, randomised, double-blind study of GSK3389404 in patients with chronic hepatitis B on stable nucleos(t)ide therapy. J Hepatol 2022;77(4):967–977.

Received February 14, 2023. Accepted February 14, 2023.

Correspondence:
Address correspondence to: Katerina Roma, DO, 1701 West Charleston Blvd., Ste 230, Las Vegas, Nevada 89102; e-mail: katerina.roma@unlv.edu. Robert G. Gish, MD, 6022 La Jolla Mesa Drive, San Diego, California 92037. e-mail: rgish@robertgish.com.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Most current article

2772-5723
https://doi.org/10.1016/j.gastha.2023.02.006