Core protein inhibitors: Opportunities and challenges at the forefront of hepatitis B cure

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Running Head: Core protein inhibitors for HBV infection

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Abbreviations:

ALT, alanine aminotransferase; CAM, capsid assembly modulators; CHB, chronic hepatitis B; cccDNA, covalently closed circular DNA; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NUCs, nucleos(t)ide analogues; pegIFN, pegylated interferon; pgRNA, pregenomic RNA; siRNA, small interfering RNA
The advent of potent Nucleos(t)ide analogues (NUCs) has significantly reduced the disease burden associated with chronic hepatitis B (CHB) infection. However, unresolved challenges persist due to the necessity for extended durations of NUCs therapy for the majority of patients and the rare occurrence of hepatitis B surface antigen (HBsAg) seroclearance, indicative of a functional cure for hepatitis B virus (HBV) infection. As a result, a diverse array of investigational drugs is presently in development and undergoing clinical trials, including direct-acting antivirals such as entry inhibitors, RNA interference agents (small interfering RNA [siRNA] or antisense oligonucleotides), HBsAg release inhibitors, capsid assembly modulators (CAMs) - also known as core protein inhibitors - and immune modulators. Among these agents, core protein inhibitors emerge as promising drugs due to the pivotal role of the core protein in HBV persistence across various stages of the viral cycle. There are two types of core protein inhibitors: Type 1, involved in aberrant capsid formation, and Type 2, responsible for generating an empty capsid.

In this issue, Yuen et al. conducted a randomized, double-blind, placebo-controlled Phase 1b study of oral EDP-514, a Type II core protein inhibitor. This study enrolled treatment-naive CHB patients with detectable viremia, including both hepatitis B e antigen (HBeAg)-positive (≥ 20,000 IU/mL) and HBeAg-negative (≥ 2,000 IU/mL) individuals. A total of 25 patients were randomized to receive EDP-514 at doses of 200 mg, 400 mg, or 800 mg, or placebo, administration once daily. EDP-514 exhibited a dose- and time-dependent reduction in HBV DNA levels, with a corresponding decrease in HBV RNA levels over time. Conversely, despite such a robust reduction in viral nucleic acid load, no significant changes were observed in HBsAg, HBeAg, or hepatitis B core-related antigen (HBcrAg). No instances of treatment discontinuation or severe adverse effects were reported.

This study is significant in demonstrating the profound effect of viral suppression over a short follow-up period and the safety profiles of the drugs. While NUCs typically do not elicit a rapid reduction in HBV RNA levels within a short period, EDP-514 exhibited notable efficacy, achieving a reduction in HBV RNA levels by more than 2 log10 IU/mL across all three dose cohorts. The remarkable antiviral effect can be attributed to the action of CAMs hindering the assembly of HBV RNA encapsidation, as serum HBV RNA primarily consists of encapsidated pregenomic RNA (pgRNA) released in the enveloped form of virus-like particles. However, the durability of the efficacy in suppressing viral replication was not identified in this study, as evidenced by the
rebound of HBV DNA and RNA levels following the discontinuation of the drugs. Such off-therapy relapses are almost anticipated, particularly considering the absence of alanine aminotransferase (ALT) flare after EDP-514 administration, given that ALT levels typically signify effective immune control of HBV. A recent Phase II study of the first-generation core protein inhibitor, Vebicovir, in combination with NUCs, demonstrated that even with extended treatment duration exceeding 52 weeks, durability also proved to be unattainable, with no patients experiencing ALT flare during the on-treatment phase, and all patients experiencing virologic relapse after drug discontinuation. This result suggests that EDP-514 may also require prolonged treatment duration to achieve sustained viral suppression.

No change in HBsAg levels observed in this study may be attributed not only to the short-term follow-up period, as stated by the authors, but also to the high proportion of HBeAg-negative patients within the study cohort (n = 21, 84%). In HBeAg-negative patients, the production of HBsAg is primarily derived from integrated HBV DNA, and it is noteworthy that EDP-514 does not directly affect integrated HBV DNA. Although potent antiviral agents significantly reduced the development of hepatocellular carcinoma (HCC), HBV DNA integration remains a persistent risk factor in HCC development. Even after HBsAg seroclearance, the biological function of integrated HBV DNA leading to oncogenesis is comparable to that of HBsAg-positive patients. As HBV integration occurs early in the course of HBV infection in hepatocytes, novel antiviral agents should aim to reduce the pool of HBV integration. A previous study showed that the prolonged use of NUCs can decrease HBV DNA integration, likely due to hepatocyte turnover after treatment, where infected cells are replaced with uninfected ones, consequently diluting the integration pool. Additionally, the potent antiviral activity of NUCs reduces intrahepatic HBV DNA, including double-stranded linear DNA, which serves as a source of HBV integration. Given that EDP-514 exhibits a profound effect in lowering HBV DNA levels, it is expected to exert an indirect reduction in integration as well.

Achieving a functional cure for HBV infection presents complex hurdles, involving the silencing of both covalently closed circular DNA (cccDNA) and integrated HBV DNA. A recent research has indicated that increased concentrations of the CAM II molecule can potentially reduce cccDNA levels in human primary hepatocytes by blocking the recycling of newly synthesized nucleocapsids. However, this assertion necessitates validation through rigorous studies and also in human trials. Notably, CAMs do not directly impact cccDNA decay or suppress
integrated HBV DNA based on their mode of action. Consequently, a combination of therapies that target different stages in the HBV life cycle and restore HBV-specific immunity is crucial for progressing towards a cure. Several combinations of therapies have been explored, including core protein inhibitors with toll-like receptor 7 agonists, siRNA, NUCs, or pegylated interferon (pegIFN). Studies have demonstrated that adding a core protein inhibitor to NUCs leads to a more potent reduction in viral activity compared to NUCs alone, and HBsAg seroclearance has been observed with the combination of a core protein inhibitor with siRNA and pegIFN-α. Considering that many current CHB patients are already undergoing NUCs treatment, the efficacy of sequential therapy, as one modality for combining different approaches, with the newer agents is also expected.

It is evident that while NUCs currently remain the frontline treatment for mitigating the devastating outcomes of CHB infection, newer drugs such as EDP-514 represent promising advancements. The study conducted by Yuen et al. presents compelling evidence for the potential of EDP-514 as a component of future therapeutic approaches. Anticipation surrounds the results of follow-up studies on EDP-514, particularly regarding the possibility of achieving HBsAg seroclearance and the durability of its efficacy with prolonged use. In light of achieving a functional cure of HBV infection, the study by Yuen et al. raises several important questions, seeking elucidation. Does the protracted administration of EDP-514 decreases the levels of circulating HBV antigens such as HBeAg, HBcAg, or even HBsAg? Would a combination of RNA-targeting agents, immunotherapy, or others with CAMs evoke an augmented virological response, robust and sustainable suppression of HBV replication in the context of dynamic alterations in the cccDNA pool, thereby leading to a sustained off-therapy response? What role would EDP-514 play in attenuating cccDNA levels by impeding the replenishment of cccDNA via the recycling of nucleocapsids? The elucidation of these queries will significantly advance our understanding of intrahepatic HBV regulation, potentially offering a roadmap for the refinement of treatment modalities for CHB patients.
References


