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Editorial

Linvencovir: Paving the way for functional cure in hepatitis B

Jiwon Yang and Jonggi Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Functional cure, defined as unquantifiable hepatitis B virus (HBV) DNA and sustained hepatitis B surface antigen (HBsAg) loss, is the ultimate goal of antiviral treatment for chronic hepatitis B (CHB).[1,2] With currently available antiviral treatments, such as nucleos(t)ide analogues (NUCs), functional cure is rarely achievable despite long-term treatment, necessitating innovative, finite new antiviral treatments.[3-5] Numerous compounds have been under development to achieve functional cure. Fortunately, some have been successful in proving their efficacy, although the efficacy remains unsatisfactory.[6,7] Hou et al. reported the efficacy, safety, and pharmacokinetics of Linvencovir, a novel small-molecule capsid assembly modulator (CAM), in Part 3 of the phase 1/2 study.[8] Previous reports demonstrated Linvencovir's favorable safety and pharmacokinetic profiles in healthy volunteers and viremic patients with CHB.[9,10] This study assessed the efficacy in three different cohorts; 32 Linvencovir-treated patients receiving NUCs, 10 Linvencovir-treated treatment-naïve patients in combination with NUCs, and 30 Linvencovir-treated treatment-naïve patients in combination with NUCs and peg-interferon for 48 weeks, followed by an additional 24 weeks of observation without Linvencovir but with NUCs.

Unfortunately, no patient achieved functional cure at week 24 post-study treatment, which was the primary endpoint of this study. HBV DNA was effectively suppressed in all three cohorts, as expected using NUCs. Notably, serum HBV RNA was also successfully suppressed in the majority of patients by Linvencovir, despite a rebound increase after withdrawal. However, HBsAg titer, another important marker to predict functional cure, was not sufficiently decreased despite the combination of NUC and Linvencovir.

In terms of safety, Linvencovir was tolerable without significant concern in its use alongside NUCs, which is satisfactory. Collectively, Linvencovir in this Part 3 phase 1/2 study showed limited efficacy, especially in achieving functional cure, unlike previous studies using newly developed compounds for functional cure.[9,10] Considering the mechanism of action in HBV natural history, treatment with CAM might not be sufficient to achieve functional cure effectively. Combination therapy with another class of drugs, such as siRNA or immunomodulators, could be an option to further increase the

Corresponding author : Jonggi Choi
Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-1328, Fax: +82-2-485-5782, E-mail: j.choi@amc.seoul.kr
https://orcid.org/0000-0002-7470-5850

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rate of functional cure, which has been partly evaluated in other studies. However, this small step is important in paving the way for functional cure.

Authors' contribution

J Yang and J Choi were responsible for drafting and finalization of the manuscript.

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Conflicts of Interest

J Choi has received a research grant from Gilead Sciences. J Yang has nothing to disclose.

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Abbreviations:

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; CHB, chronic hepatitis B; NUCs, nucleos(t)ide analogues; CAM, capsid assembly modulator