Letter to the Editor

Xalnesiran with or without an immunomodulator in chronic hepatitis B: still a challenge in functional cure

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Comment on: Hou J, Zhang W, Xie Q, *et al.* Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B. N Engl J Med 2024;391:2098-109.

Submitted Feb 08, 2025. Accepted for publication Mar 05, 2025. Published online Mar 25, 2025.
doi: 10.21037/hbsn-2025-92
View this article at: https://dx.doi.org/10.21037/hbsn-2025-92

Recently, Hou *et al.* found that xalnesiran in combination with pegylated interferon-alpha 2a resulted in 23% hepatitis B surface antigen (HBsAg) loss [24 weeks after the end of treatment (EOT)] in patients with chronic hepatitis B (CHB) who achieved virologic suppression on long-term nucleotide analogue (NA) therapy, and 47% HBsAg loss in patients with HBsAg below 1,000 IU per milliliter, which provides a new and safe therapeutic option for the functional cure of patients with CHB (1). However, there are several important issues that deserve further discussion.

First, the primary outcome of the study is HBsAg loss at 24 weeks after the EOT (1), which is inconsistent with standard definitions (stopping all medications, confirmed by 2 tests at least 24 weeks apart) due to the fact that patients only stopped xalnesiran and immunomodulators and most patients continued NA therapy (2). The optimal efficacy group was the xalnesiran combined with pegylated interferon-alpha 2a and NA therapy group, with 30% (9/30) of patients achieving HBsAg clearance at EOT, only 37.5% (3/8) achieving HBsAg loss during follow-up. The proportion of functional cure (HBsAg loss at 24 weeks after EOT), calculated according to the standard definition of functional cure, was only about 11.3%, and 22.5% among patients with HBsAg below 1,000 IU per milliliter, which is not a high rate compared to reported functional cure rate with interferon-based therapy. Therefore, we suggest that functional cure should be evaluated after stopping all medications.

Second, the criteria for stopping NA in this study were HBsAg below 100 IU per milliliter with more than 1 log decrease from baseline or HBsAg loss, it is unreasonable to confuse two different HBsAg statuses. HBsAg loss is a satisfactory endpoint in CHB treatment, patients with HBsAg below 100 IU per milliliter at EOT after NA therapy achieve HBsAg loss by sequential interferon-alpha therapy or stopping therapy. A recent meta-analysis showed that HBsAg loss was achieved in over 40% of patients with HBsAg below 100 IU per milliliter at EOT after stopping treatment (3). In this study, up to 93% (28/30) of patients achieved HBsAg less than 100 IU per milliliter and 30% (9/30) achieved HBsAg loss after xalnesiran combined with pegylated interferon-alpha 2a therapy. However, only 11 cases met the criteria for stopping therapy and only 38% (3/8) actually achieved HBsAg loss after stopping therapy. It is difficult to characterize the proportion of HBsAg loss after stopping therapy for patients with HBsAg below 100 IU per milliliter, and the durability of HBsAg loss after stopping therapy for those who achieve HBsAg loss at EOT.

Finally, current standard approach to achieving functional cure in CHB population with low level of HBsAg is pegylated interferon-based therapy (2,4), however, which was not used as a control in this study. New Switch Study suggests that patients with HBsAg below 1,500 IU per milliliter achieve over 30% HBsAg loss with NA combined or sequential pegylated interferon-alpha therapy (5). In this study, xalnesiran combined interferon-alpha 2a and NA

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therapy group achieve highest HBsAg loss rate of 60% in patients with HBsAg below 1,000 IU per milliliter (only 33% maintained HBsAg loss after EOT). A meta-analysis showed that patients who achieved HBsAg below 1,000 IU per milliliter after NA therapy achieved over 20% HBsAg loss rate after EOT (3), suggesting additional xalnesiran combined with pegylated interferon-alpha therapy may not significantly improve functional cure rate. The current main challenge is to reduce HBsAg levels and improve functional cure rate in patients with high HBsAg levels, a major population with CHB. The manner in which HBsAg is achieved below 1,000 or 100 IU per milliliter may be an important determinant of achieving HBsAg loss, and re-establishing HBV specific immunity in the host along with reducing HBsAg levels may be critical for functional cure.

In conclusion, xalnesiran with pegylated interferon and NA therapy in functional cure remains challenging. Re-establishing host's specific immunity to HBV along with reducing HBsAg levels may be critical for achieving functional cure. Combining medications may be a key approach to achieving functional cure, which medications, two or more, and whether sequential or simultaneous combinations can improve functional cure rate remain to be answered. HBsAg below 1,000 or even 100 IU per milliliter is a watershed for achieving functional cure, yet how to reach this watershed is a challenge for most CHB patients. Future research needs to explore the optimal treatment regimen for reaching this watershed and how to achieve functional cure once the watershed has been reached.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article did not undergo external peer review.

Funding: This work was funded in part by grants from the Chongqing Talents Project (No. cstc2021ycjh-bgzxm0150), Scientific and Technological Research Program of Chongqing Municipal Education Commission (No. KJZD-K202300404), the First Batch of Key Disciplines on Public Health in Chongqing of Health Commission of Chongqing, the Remarkable Innovation-Clinical Research Project of The Second Affiliated Hospital of Chongqing Medical University.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-92/coif). The authors report that this work was funded in part by grants from the Chongqing Talents Project (No. cstc2021ycjh-bgzxm0150), Scientific and Technological Research Program of Chongqing Municipal Education Commission (No. KJZD-K202300404), the First Batch of Key Disciplines on Public Health in Chongqing of Health Commission of Chongqing, the Remarkable Innovation-Clinical Research Project of The Second Affiliated Hospital of Chongqing Medical University. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Tang Q, Xue Y, Hu P. Xalnesiran with or without an immunomodulator in chronic hepatitis B: still a challenge in functional cure. HepatoBiliary Surg Nutr 2025;14(2):348-350. doi: 10.21037/hbsn-2025-92

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