Breakthroughs Beyond the Journal

JOURNAL OF HEPATOLOGY

Toward functional cure of hepatitis B: Is combination therapy the key?

Hou J, Zhang W, Xie Q, *et al.* Xalnesiran with or without an Immunomodulator in Chronic Hepatitis B. N Engl J Med. 2024 Dec 5;391(22):2098-2109. doi: 10.1056/NEJMoa2405485. PMID: 39774313.

Background and context

Chronic hepatitis B virus (HBV) infection is a major health burden and it is estimated that 3% of the world's population are chronically infected.[1] Infected individuals are at risk of developing chronic liver disease leading to cirrhosis, liver-related complications and development of hepatocellular carcinoma (HCC).[2] Antiviral treatment with nucleos(t)ide analogues (NA) effectively suppresses HBV DNA replication thereby reducing the risk of disease progression and HCC development in patients without cirrhosis.[3] However, NA treatment is usually on a long-term basis as HBsAg loss only rarely occurs.[3] Despite the overall good tolerability of NA therapy, the need for potentially lifelong treatment is suboptimal due to long-term side effects, increasing treatment costs and the potential stigma associated with medical treatment, making a finite duration treatment desirable. Functional cure, defined as sustained HBsAg loss with undetectable HBV DNA 24 weeks off-treatment, is the intended goal of finite antiviral treatment[4] and is associated with even lower risks of complications and importantly HCC.[5,6] Treatment strategies aiming for functional cure are currently being investigated in clinical trials that include compounds with different mechanisms of action. Direct-acting antivirals targeting viral entry, viral protein production and secretion, or capsid assembly are under investigation, as are immunomodulatory therapies to reinvigorate the immune response against HBV. Recently, combination therapies including both immunomodulators and direct-acting antivirals have shown promising results. Xalnesiran is a N-acetyl-D-galactosamine-conjugated synthetic double-stranded small-interfering RNA molecule that targets the S conserved region of the HBV genome,[7] silencing multiple transcripts, and is administered every 4 weeks. Ruzotolimod is a TLR7 (Toll-like receptor 7) agonist selectively activated in the liver.[8]

Objectives, methods and findings

In the phase II study published in the *New England Journal of Medicine*, 160 patients with chronic HBV infection and established effective NA treatment without clinically significant fibrosis or cirrhosis were randomly assigned to receive (A) xalnesiran 100 mg or (B) 200 mg, (C) xalnesiran 200 mg plus ruzotolimod 150 mg, (D) xalnesiran 200 mg plus pegylated interferon alfa (PEG-IFN), all in addition to continued NA treatment, or (E) NA alone.[9] The total treatment duration was 48 weeks in all treatment groups with xalnesiran administered subcutaneously every 4 weeks, ruzotolimod orally every other day from weeks 13 to 24 and 37 to 48, and PEG-IFN subcutaneously once weekly for 48 weeks, followed by 48 weeks of follow-up. The primary end point was defined as HBsAg loss at 24 weeks after the end of treatment (EOT). One patient was excluded from the study before receiving trial treatment, leading to 159 patients included in the final analysis.

Overall, treatment response rates were highest in the PEG-IFN combination arm compared to patients receiving xalnesiran plus NA, xalnesiran plus ruzotolimod and NA, or NA alone. The primary end point was achieved in 23% of patients in the xalnesiran plus PEG-IFN group, compared to 7%, 3%, 12%, and 0% in groups A, B, C and E, respectively. Comparable results were achieved for the secondary end point of HBsAg seroconversion at 24 weeks post-EOT, with xalnesiran plus PEG-IFN showing the highest percentage (20%). Rates of HBsAg loss were highest at EOT and declined with ongoing follow-up to 17% in the group of patients receiving xalnesiran and PEG-IFN at 48 weeks post-EOT. Importantly, HBsAg response was only present in patients with baseline HBsAg levels <1,000 IU/ml, regardless of the treatment received. Most adverse events leading to dose modifications, treatment interruption or trial withdrawal occurred in patients receiving PEG-IFN treatment.[9]

Significance of findings

This study demonstrated that combination treatment with a small-interfering RNA (xalnesiran) and an immune-modulatory agent (ruzotolimod or PEG-IFN) in addition to continued NA treatment led to HBsAg loss in a substantial proportion of patients. Interestingly, response rates were higher in patients receiving PEG-IFN compared to the TLR7 agonist ruzotolimod. The reasons for these differences are unclear but could be due to the broader immunomodulatory activity of IFN, which affects both the innate and adaptive immune response.[10] The beneficial combination of HBV RNA-silencing and immune-modulatory agents has recently been shown in another phase IIb study including the antisense oligonucleotide bepirovirsen, which itself has dual antiviral and immunological effects, and PEG-IFN.[11] In this open-label study, patients on stable NA therapy received bepirovirsen 300 mg for 12 or 24 weeks followed by PEG-IFN treatment for up to 24 weeks with a follow-up of up to 36 weeks.[11] In an indirect comparison to the bepirovirsen monotherapy study,[12] 24 weeks off-treatment rates of HBsAg loss were higher in patients receiving sequential PEG-IFN treatment (15%) compared to finite bepirovirsen treatment alone with or without NA (9-10%).[12] Again, the primary end point of HBsAg loss only occurred in patients with low HBsAg levels (<3,000 IU/ml) and was highest in patients

with HBsAg levels ≤1,000 IU/ml. This emphasizes the link between viral antigen burden and the possibility of HBV immune response reinvigoration. Since immune exhaustion is related to the excessive amount of circulating HBsAg, reducing the burden of viral antigens with HBV RNA-silencing agents is a reasonable approach to facilitate the effects of immunomodulatory therapy aimed at restoring HBV immune responses.[13] Although cross-study comparisons should be made with caution due to differences in baseline characteristics of the cohorts, including ethnicity and HBsAg levels, as well as differences in study design (combination or sequential therapy, duration of follow-up), the synergistic effect of an additional immunomodulatory agent has been demonstrated in published studies.[9,11,12] Still, several questions remain in the quest for finite HBV treatment and functional cure. First, more data on the durability of HBsAg loss are needed, as HBsAg reversion was shown with longer follow-up duration. Results on the rates of sustained HBsAg loss are needed to reliably distinguish a functional cure from prolonged RNA-interference due to the long half-life of these drugs. Second, the overall number of patients achieving functional cure in the clinical trials is low, and larger studies including longitudinal immunologic and intrahepatic assessments are warranted to better understand the relationship between treatment outcomes and underlying immuno-pathophysiological mechanisms. Finally, the side-effect profile of immunomodulators must also be considered. PEG-IFN is associated with significantly more side effects than NAs, leading not only to more intensive on-treatment monitoring but also to treatment contraindications. Newly developed immunomodulators should ideally overcome these limitations and provide a simpler and better tolerated treatment.

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Financial support

The authors did not receive any financial support to produce this manuscript.

Conflict of interest

The author of this study declares that they do not have any conflict of interest.
Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2025.03.024.

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