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Letter to the Editor

Functional cure of chronic hepatitis B encounters resmetirom

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Dear Editor,

On March 14, 2024, the US Food and Drug Administration (FDA) approved resmetirom for fast-track treatment of adult patients with metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis, making it the world's first approved drug. Chronic hepatitis B (CHB) and metabolic dysfunction-associated steatotic liver disease (MASLD) are the most prevalent chronic liver diseases worldwide,[1] and concurrent MASLD is common in patients with CHB, with a prevalence of 29.6–34.9%.[2] When using resmetirom to treat MASH patients with CHB, it is important to consider the potential impacts of hepatic steatosis on improving functional cure of CHB.

Hepatic steatosis is beneficial to functional cure of CHB by decreasing hepatitis B virus DNA levels and increasing HBsAg seroclearance

Both CHB and MASLD can lead to hepatic inflammation and liver fibrosis, increasing the risk of adverse liver outcomes.[3] However, CHB patients with concurrent steatosis tend to have lower HBV activity, including lower proportions of hepatitis B e antigen (HBeAg) positivity, lower serum HBV DNA levels, as well as higher rates of hepatitis B surface antigen (HBsAg) seroclearance, and are more likely to achieve functional cure.[4,5] Studies on animals and cells show that hepatic steatosis can decrease HBV activity and induce lower levels of HBsAg, HBeAg, and HBV DNA.[6] The molecular mechanism might be explained as liver fat activating innate immunity, disrupting the liver's metabolic environment, and increasing liver cell apoptosis, reducing HBV survival.[7]

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Can resmetirom potentially decrease functional cure of CHB?

In the phase 3, randomized, controlled trial of resmetirom in MASH with liver fibrosis, both the resmetirom treatment groups significantly improved hepatic steatosis and inflammation.[8] It is unclear if resmetirom can be used to treat MASH patients with concurrent CHB. We recommend the answer is YES, because both CHB and MASLD can increase the risk of adverse liver outcomes. However, close monitoring of HBV activity is necessary as resmetirom could potentially alleviate steatosis and increase HBV activity. Further research is needed to determine if more aggressive antiviral therapy (e.g., entecavir combined with tenofovir, nucleotide analogues combined with interferon, etc.) is necessary when using resmetirom to treat MASH patients with concurrent CHB. The field remains blank, and more clinical data are needed to reveal the answers and guide drug treatment choices in this large population.

Authors' contribution

M-H.Z. researched data for the article. All authors contributed substantially to discussion of the content. N-B.Y. wrote the article. All authors reviewed and/or edited the manuscript before submission.

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Conflicts of Interest

Ming-Hua Zheng has received honoraria for lectures from AstraZeneca, Hisky Medical Technologies and Novo Nordisk, consulting fees from Boehringer Ingelheim, and serves as a consultant for Eieling Technology.

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Abbreviations:

MASH, metabolic dysfunction-associated steatohepatitis; CHB, chronic hepatitis B; MASLD, metabolic dysfunction-associated steatotic liver disease; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen