**Name of Journal:** *World Journal of Virology*

**Manuscript NO:** 75875

**Manuscript Type:** LETTER TO THE EDITOR

**Cautious optimism in anticipation of hepatitis B curative therapies**

Turshudzhyan A *et al*. Cautious optimism for HBV cure

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**Author contributions:** Turshudzhyan A wrote the letter; and Tadros M revised the letter.

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**Received:** February 19, 2022

**Revised:** May 15, 2022

**Accepted:** July 16, 2022

**Published online:** July 25, 2022

**Abstract**

Despite relative effectiveness of current hepatitis B therapies, there is still no curative agents available. The new emerging approaches hold promise to achieve cure and loss of hepatitis B surface antigen. Studies or clinical trials investigating new therapies remain small and either focus on patients with low viral load and without hepatotoxic injury or patients with hepatitis D co-infection, which makes it challenging to assess their effectiveness and side effect profile in hepatitis B population.

**Key Words:** hepatitis B; hepatitis B virus; hepatitis B virus entry inhibitor; bulevirtide; transcription activator-like effector nucleases; zinc-finger nucleases; clustered regularly interspaced short palindromic repeats-associated 9; Nucleocapsid assembly modulators; hepatitis B virus transcription inhibitors; hepatitis B surface antigen release inhibitors

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**Citation**: Turshudzhyan A, Tadros M. Cautious optimism in anticipation of hepatitis B curative therapies. *World J Virol* 2022; 11(4): 212-215

**URL**: https://www.wjgnet.com/2220-3249/full/v11/i4/212.htm

**DOI**: https://dx.doi.org/10.5501/wjv.v11.i4.212

**Core Tip:** Hepatitis B could become a curable disease in the near future. As our understanding of pathophysiology of hepatitis B infection advances, more therapeutic targets are becoming available. Many new therapies have only been investigated in small groups of patients with low viral load and without hepatotoxic injury or in patients with hepatitis D co-infection, which makes it difficult to predict efficacy and side effect profile when applied to the population of interest. Larger clinical trials in hepatitis B patients are needed to further investigate the emerging new therapies, so that more patients can safely benefit from them.

**TO THE EDITOR**

We read with great pleasure the article by Leowattana *et al*[1] about new emerging therapies in treatment of chronic hepatitis B. They presented a comprehensive review of currently available therapies, pathophysiology of the hepatitis B infection, and developing new therapies. While current therapies, such as nucleosides, are effective in suppressing viral replication and preventing progression of chronic hepatitis to cirrhosis or hepatocellular carcinoma, they are unable to achieve cure from hepatitis B infection. As a result, new therapies are now being investigated that are aimed at a complete cure and loss of hepatitis B surface antigen (HBsAg).  Leowattana *et al*[1] presented a comprehensive discussion of developing new therapies, which include agents that inhibit entry of hepatitis B virus (HBV) into hepatocytes, interfere with cccDNA or HBV transcription, alternate nucleocapsid assembly, and prevent HBsAg release from the hepatocytes. The authors are hopeful that given currently available evidence on these emerging therapies, chronic hepatitis B could become a curable disease in the near future. While we share their sentiment and are hopeful for these therapies to be successful in curing hepatitis B infection, we would like to recommend cautious optimism when assessing these new therapeutic agents.

HBV entry inhibitor, bulevirtide, was originally intended to be used for hepatitis D treatment. Wedemeyer *et al*[2] presented results of a phase 2b trial in 2019 which included 60 patients with chronic HBV/ hepatitis D virus (HDV) co-infection. While their results were encouraging, the population under investigation was small and all of the patients had both viruses present, which makes it more difficult to apply these results to patients with HBV infection alone. Wedemeyer *et al*[2] documented increased bile acid concentration in patients on bulevirtide and rebound in viral load after therapy discontinuation, which may cause more liver damage. The increase in bile acid concentration while on bulevirtide was also investigated by the Blank *et al*[3] They confirmed increased bile acid concentration associated with bulevirtide without cholestasis, however, their study was limited to 12 healthy volunteers and did not include patients with pre-existing chronic liver disease or with hepatitis B infection, which makes it less applicable to the population of interest. While there are no ongoing clinical trials with hepaitits B patients on bulevirtire, there is phase 3 trial on bulevirtide use in HDV infection which includes 150 adults with HDV infection[4]. It will help reveal long term effects of therapy and help us better understand the adverse events associated with it. The downside of this phase 3 trial is that it is limited to HDV patients. There is still no long-term data on side effect profile of bulevirtide in HBV patients exclusively. We hope there will be new trials to investigate its application in HBV patients.

Gene editing tools such as the transcription activator-like effector nucleases, zinc-finger nucleases, and clustered regularly interspaced short palindromic repeats-associated 9 could be a new exciting therapy option in curing chronic hepatitis B. The authors did a comprehensive review of the available options for gene editing. It is important to note, however, that like with any genetic intervention there is a risk of off-target cleavage[5], so more studies and large clinical trials are needed to investigate this therapeutic option.

Nucleocapsid assembly modulators are another exciting modality reported by Leowattana *et al*[1] but it is another therapy that should be treated with caution until more data from larger clinical trials is available. Zhang *et al*[6] reported that 75% of patients in their study evaluating nucleocapsid assembly modulators experienced elevations in aminotransferases with 4 out of 24 patients requiring to stop therapy and receive glutathione.

HBV transcription inhibitors are another emerging therapy that is currently being investigated. There were two clinical trials evaluating HBV transcription inhibitors in phase II[7,8] and one clinical trial in phase I[9] that were discontinued because of the observed lethal toxicity of the EX1 delivery formulation. More studies are needed to investigate the safety profile of this therapy before it can be considered for clinical application. Another practical consideration with any emerging therapy that requires a viral vector to be delivered into the cells is the risk of pre-existing immunity to vectors or development of host immunity to vectors during treatment, which will ultimately render therapy ineffective[10].

Lastly, HBsAg release inhibitors have been under investigation in various clinical trials. Alanine aminotransferase flares were observed in 90% of patients treated with HBsAg release inhibitors[11,12]. Additionally, because most of the data came from patients with low viral load, safety and efficacy in patients with high viral load is still to be determined. Similar to bulivertide, there were reports that discontinuation of HBsAg release inhibitors caused viral rebound precipitating liver decompensation in patient with significant chronic liver disease[13].

We commend Leowattana *et al*[1] for their comprehensive review of the emerging new therapies that have the potential to cure chronic hepatitis B. Our goal was to merely add caution to the optimism and hopefully prompt larger clinical trial specific to hepatitis B population, so that more patients can safely benefit from the new therapies in the near future.

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**Footnotes**

**Conflict-of-interest statement:** All authors report no relevant conflicts of interest for this article.

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**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** February 19, 2022

**First decision:** May 12, 2022

**Article in press:** July 16, 2022

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Chi G, China; Gao P, China; Morozov S, Russia; Sira AM, Egypt **S-Editor:** Ma YJ **L-Editor:** A **P-Editor:** Ma YJ



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