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Letter: the perilous road to a functional cure for hepatitis B infection

EDITORS,

We read with interest the recent review article by Smolders et al[1] focusing on the clinical pharmacology of current and investigational hepatitis B virus (HBV) therapies that have reached at least phase 2 clinical trials. These drugs encompass various functional classes—including a HBV entry inhibitor (bulevirtide), capsid assembly modulators (JNJ-56136379 and ABI-H0731), a secretor inhibitor (REP-2139), an RNA interference drug (ARO-HBV or JNJ-3989) and an immunomodulator (inarigivir). Notably, all of these investigational compounds have been studied in combination with current therapies, ie, nucleos(t)ide analogues (NAs) and/or pegylated-interferon alfa (peg-IFN-α). The quest for novel drugs against HBV infection reflects important unmet needs in the field.[2] For example, treatment with peg-IFN-α offers relatively low cure rates, and is accompanied by serious side effects. Similarly, NAs can be very effective at suppressing the virus, but rarely result in its full eradication from the liver.[2]

The results of Smolders et al[1] indicate that treatment with most of these investigational compounds resulted in HBV DNA and/or RNA decline/loss, to a similar or higher extent than that observed with NAs treatment. More remarkably, treatment with REP-2139, ARO-HBV, and inarigivir has been reported in some HBsAg loss/decline. The authors concluded that if further evidence will demonstrate that these three agents are able to increase the number of patients with a functional cure (i.e., HBsAg loss), this would be a significant improvement compared to current therapy. However, they also raise a word of caution by advocating more in-depth investigations on pharmacokinetics and safety.

On December 26, 2019, there was bad news concerning inarigivir, one of the investigational compounds mentioned by Smolders et al[1] in their excellent review. Dosing of inarigivir 400 mg in the CATALYST 2 trial—which examined the administration of this drug in NAs-suppressed chronic HBV patients—has been stopped because of safety concerns.[3] Specifically, three subjects participating in this study showed evidence of hepatocellular dysfunction and an elevation of alanine aminotransferase levels, potentially consistent with liver injury rather than immune flares.[3] Similar bad news was reported on October 3, 2019, for AB-506—an oral capsid inhibitor being developed for chronic HBV infection—which was being evaluated among healthy volunteers in a 28-day phase 1a/1b trial.[4] During the study, two volunteers paradoxically had evidence of acute hepatitis and further clinical development of AB-506 was halted.[4]

The failure of some novel therapies for HBV infection clearly indicates that the road to a functional cure for this condition is hard and perilous. However, with approximately 257 million people worldwide living with chronic HBV,[1] these setbacks should not deter the confidence of investigators in pursuing the strategic goal of providing a functional cure for this major public health threat.

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LINKED CONTENT

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REFERENCES

1. Smolders EJ, Burger DM, Feld JJ, Kiser JJ. Review article: clinical pharmacology of current and investigational hepatitis B virus therapies. *Aliment Pharmacol Ther.* 2020;51:231–243.
2. Tao Y, Wu D, Zhou L, et al. Present and future therapies for chronic hepatitis B. *Adv Exp Med Biol.* 2020;1179:137–186.
3. https://www.trialsitenews.com/spring-bank-pharma-stops-phase-2b-catalyst-trials-of-inarigivir-for-hbv-following-signs-of-liver-injury/. Accessed December 28, 2019.
4. https://www.biopharmadive.com/news/arbutus-stops-hepatitis-b-study-safety-concerns/564374/. Accessed December 28, 2019.