Promising investigational therapeutic monoclonal antibody to treat chronic hepatitis B and D infections

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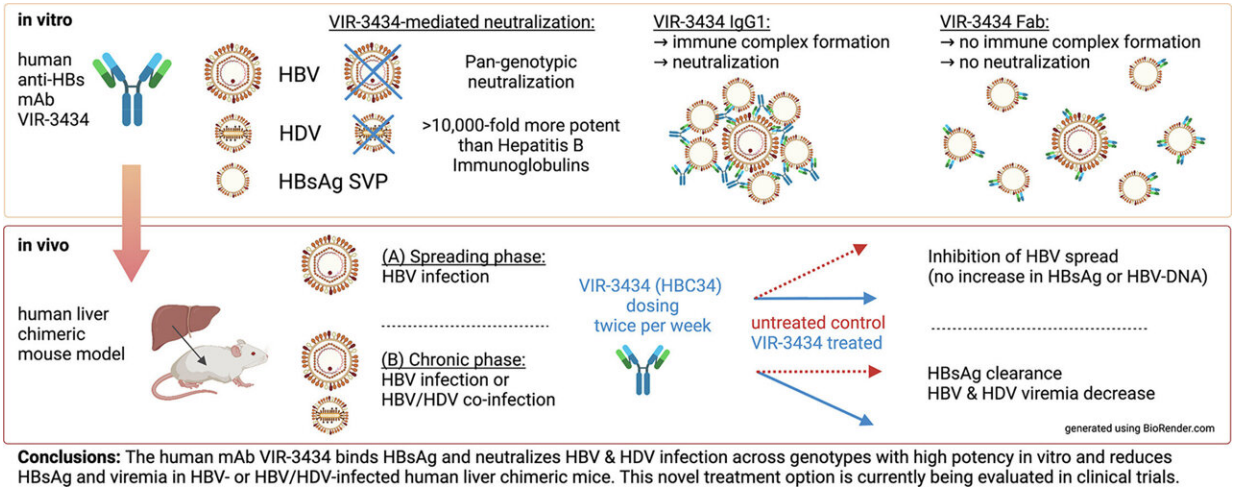

Conclusions: The human mAb VIR-3434 binds HBsAg and neutralizes HBV & HDV infection across genotypes with high potency in vitro and reduces HBsAg and viremia in HBV- or HBV/HDV-infected human liver chimeric mice. This novel treatment option is currently being evaluated in clinical trials.

Credit: *Journal of Hepatology* (2023). DOI: 10.1016/j.jhep.2023.07.003

Affecting hundreds of millions of people, chronic hepatitis B is a widespread global health problem for which there is as yet no cure. In a preclinical study involving the German Center for Infection Research (DZIF), Heidelberg University Hospital, University Medical Center Hamburg-Eppendorf and the US company Vir Biotechnology, the potential of an engineered investigational human monoclonal antibody for the treatment of chronic hepatitis B and hepatitis D has been demonstrated. Based on the results, clinical trials with the monoclonal

antibody VIR-3434 are ongoing.

Chronic hepatitis B virus (HBV) infection poses a severe threat to approximately 300 million people worldwide, leading to liver disease and cancer. Approximately 4% of affected persons are chronically coinfected with the hepatitis delta virus (HDV), which exacerbates the gravity of the disease. Current treatments provide only limited cure rates and necessitate indefinite times of therapy.

A team around DZIF-scientists from Heidelberg and Hamburg-Eppendorf supported the preclinical development of VIR-3434, a monoclonal antibody (mAb) discovered by Vir Biotechnology, Inc., that specifically targets the hepatitis B surface antigen (HBsAg) located in the viral envelope. This preclinical study shows how the engineered investigational human monoclonal antibody effectively prevents viral dissemination and reduces the amounts of viral particles and antigen in a mouse model for HBV/HDV coinfection. The comprehensive preclinical study was published recently in *Journal of Hepatology*.

A targeted approach

The researchers isolated and screened several monoclonal antibodies from memory B cells of HBV-vaccinated individuals that specifically target a conformational epitope (an epitope formed through the three-dimensional folding of the protein bringing distant amino acids together) within the antigenic loop of the small hepatitis B surface antigen. Among a series of more than 30 generated antibodies, which were tested using the most advanced in vitro infection system available and established at Heidelberg University Hospital, one mAb named HBC34 demonstrated potent neutralization activity against HBV and HDV. The latter is a satellite virus that hijacks HBV surface proteins to infect human hepatocytes.

The activity has been shown to be pan-genotypic, providing evidence that HBC34 neutralizes all known genotypes of HBV and HDV. Modifications in the structure of the HBC34 mAb for improved potency generated VIR-3434 as a promising mAb candidate for clinical development.

"Aside from the potent neutralization activity of VIR-3434, we engineered the Fc-portion of the mAb—the tail end of the antibody molecule that is crucial in the immune response—to increase binding to certain immune cells," explains the co-first and corresponding author of the paper, Dr. Florian Lempp, director of virology at Vir. "VIR-3434 has the potential to rapidly eliminate both viral and subviral particles from circulation."

The researchers then tested VIR-3434's neutralization capability in a human liver-chimeric mouse model developed at the University Medical Center Hamburg-Eppendorf (UKE) by the team around Prof. Maura Dandri, a DZIF-scientist on viral hepatitis at UKE and co-author of the paper. The livers of these mice are populated with primary human hepatocytes—the only cell type infected by HBV and HDV in humans. The in vivo studies were essential to demonstrate that the in vitro selected mAb, VIR-3434, was able to block viral dissemination in the liver of both HBV-infected and HBV/HDV-coinfected mice.

"We found that VIR-3434 not only neutralizes HBV and HDV infection with high potency in vivo," explains the co-first author of the study Dr. Tassilo Volz, "but it also effectively reduces viraemia—the number of viruses in the bloodstream—and the levels of circulating viral antigens in chronically infected animals."

"VIR-3434 may provide a potential new option for treating patients with chronic hepatitis B and D, and aid in the prevention of these diseases. The antibody's strong neutralization properties and promising results in

our preclinical infection model may offer hope for patients worldwide," adds Prof. Dandri.

Testing VIR-3434 in the clinic

Based on the findings, clinical studies to ascertain the safety and efficacy of VIR-3434 in human subjects are already underway. The researchers hope that VIR-3434, which is also being studied in combination with other investigational agents, may provide a much-needed therapy to combat chronic hepatitis B and D and the devastating consequences of chronic infection with these viruses.

"The successful isolation and characterization of VIR-3434 could mark a significant turning point in hepatitis B and D treatment. If further validated through clinical trials, this mAb may offer an important therapeutic option for patients with chronic hepatitis B and D," emphasizes co-author and DZIF-scientist Prof. Stephan Urban of Heidelberg University Hospital.

The described research on VIR-3434, which incorporates Xencor Xtend technology (an innovative platform that allows the prolongation of the half-life of antibodies), is the result of a successful collaboration of scientists within the German Center for Infection Research (DZIF) and with the industry partner Vir. The project fits into the DZIF bridging topic "Antibody-based therapies," which aims to connect experts across DZIF's different research areas to advance the development, production and clinical testing of therapeutic monoclonal antibodies.

More information: Florian A. Lempp et al, Potent broadly neutralizing antibody VIR-3434 controls hepatitis B and D virus infection and reduces HBsAg in humanized mice, *Journal of Hepatology* (2023). DOI: 10.1016/j.jhep.2023.07.003

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