Bispecific T-Cell Engager Shows Promise for Hepatitis B

IMC-I109V, a new type of immune-based therapy, could potentially lead to a functional cure.

November 10, 2025 By Liz Highleyman

An experimental bispecific T-cell engager, which helps the immune system recognize and eliminate cells infected with hepatitis B virus (HBV), reduced hepatitis B surface antigen (HBsAg) levels in people treated with antivirals, according to results from a small study presented at the AASLD Liver Meeting. Immunocore's IMC-I109V was generally well tolerated, and adverse effects resolved quickly.

"The first-in-human evidence for dose-dependent reductions in HBsAg via this novel mechanism supports further evaluation of IMC-I109V in multiple dose regimens aimed at achieving sustained HBsAg loss," the researchers concluded.

Antiviral therapy using nucleoside/nucleotide analogs such as tenofovir (Viread or Vemlidy) or entecavir (Baraclude) can keep HBV replication suppressed indefinitely, but they do not eliminate the virus. A form of viral genetic material known as covalently closed circular DNA (cccDNA) persists in infected liver cells and can rekindle viral replication. A small proportion of people treated with antivirals, especially in combination with pegylated interferon, experience HBsAg clearance—which is considered a functional cure—but this is rare.

IMC-I109V is a bispecific T-engager, an engineered antibody-like molecule that attaches to both the CD3 protein on CD8 killer T cells and HBsAg peptides expressed on infected cells, forming a "bridge" that enables the T cells to attack the infected cells. This bridging appears to help overcome T-cell exhaustion.

Man-Fung Yuen, MD, PhD, of Queen Mary Hospital of the University of Hong Kong, and colleagues presented results from a Phase I study evaluating the safety and pharmacodynamic activity of IMC-I109V in 17 men and three women with chronic hepatitis B. They were on nucleoside/nucleotide antiviral therapy, had a baseline HBsAg level below 3,000 IU/ml, had a specific HLA subtype that displays HBsAg to immune cells and did not have liver cirrhosis. At the start of the study, they received a single IV infusion of IMC-I109V at ascending doses.

Participants who received the two highest doses saw a substantial reduction in HBsAg levels. Four of these 14 patients exceeded a prespecified threshold of at least a -0.2 log IU/ml reduction, and

three of them maintained reduced HBsAg levels through 29 days. The researchers noted transient, dose-dependent elevations in serum interleukin-6, indicating immune cell activation.

IMC-I109V was generally safe and well tolerated. Eight participants experienced treatment-related adverse events, including transient mild to moderate systemic symptoms within 24 hours after the infusion, followed by increased ALT levels (an indicator of liver inflammation) that resolved within 14 days. T-cell therapies that boost immune response can cause cytokine release syndrome (CRS), characterized by inflammation throughout the body. One person who received the highest dose developed moderate CRS that resolved rapidly with corticosteroid treatment. Two subsequent patients in the highest-dose group received corticosteroids in advance and experienced no serious adverse events.

Immunocore calls its technology ImmTAX, which includes "immune-mobilizing monoclonal T-cell receptors against cancer" (ImmTAC) and "immune-mobilizing monoclonal T-cell receptors against virus" (ImmTAV). In 2022, the Food and Drug Administration approved the company's Kimmtrak (tebentafusp) for a rare type of melanoma affecting the eye. This bispecific T-cell engager binds to both the CD3 receptor on killer T cells and specific melanoma antigens.

Immunocore is also testing the virus platform for HIV. At this year's Conference on Retroviruses and Opportunistic Infections, researchers reported results from the Phase I/II STRIVE trial, in which 16 men with viral suppression on antiretroviral treatment received once-weekly infusions of IMC-M113V for 12 weeks and then paused their antiretrovirals. Laboratory tests during the analytical treatment interruption showed changes in cytokines and HIV RNA and HIV DNA levels consistent with T-cell activation and reduction of the viral reservoir. Most participants experienced normal viral rebound, but three saw their viral load initially rise and then fall to a very low level, suggesting immune control.

"Dose-dependent decreases in serum HBsAg following a single dose of IMC-I109V are promising and show that a T-cell receptor-based approach to treating chronic HBV infection warrants further investigation," said David Berman, Immunocore's head of research and development, in a news release. "These data—alongside the encouraging safety profile and antiviral activity seen in our ImmTAV candidate for HIV—reinforce the potential of our platform to achieve functional cures for chronic infectious diseases."

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