Experimental Vaccine Promotes T-Cell Activity Against Hepatitis B

GS-4774 combined with Viread stimulates immune activity against the virus.

May 31, 2019 By Liz Highleyman

An experimental therapeutic vaccine known as GS-4774, used in combination with Viread (tenofovir disoproxil fumarate), increased the activity of T cells that target hepatitis B virus (HBV), according to Phase II study results reported in the journal Gastroenterology.

Although the vaccine did not reduce levels of hepatitis B surface antigen (HBsAg)—considered an indicator of a cure—the researchers suggested that GS-4774 might be useful as a component of combination therapy for chronic hepatitis B.

Over years or decades, chronic HBV infection can lead to liver cirrhosis (scarring), liver cancer and end-stage liver failure requiring a transplant. Antiviral therapy using nucleoside/nucleotide analogues such as Viread, Vemlidy (tenofovir alafenamide) or Baraclude (entecavir) can suppress HBV replication during treatment—indicated by low or undetectable HBV DNA viral load—but they don't eliminate the virus.

HBV is difficult to treat in part because viral genetic material can lie dormant in liver cells, evading both the immune system and standard treatment. Furthermore, chronic HBV infection is characterized by dysfunctional CD8 T cells, suggesting that immune-based therapy may play a role in its treatment. Most experts think a combination approach will be needed to cure hepatitis B.

Carolina Boni, MD, of the University of Parma in Italy, and colleagues conducted a clinical trial to evaluate the safety and efficacy of GS-4774, a yeast-based "tarmogen" vaccine engineered to express HBV proteins and elicit HBV-specific T-cell responses. The vaccine was previously shown to stimulate immune responses in mice and healthy human volunteers without hepatitis B, and it had a modest effect on HBsAg levels in an early study of chronic hepatitis B patients with suppressed viral load.

This open-label study enrolled 195 people with chronic hepatitis B and mild to moderate liver disease in Canada, Italy, New Zealand, Romania, South Korea and the United States. They had detectable HBsAg and HBV DNA levels of at least 2,000 international units per milliliter; about 40% were hepatitis B e antigen-positive (a group considered more difficult to treat). They had not

received antiviral treatment within three months, though about a third had previously been treated with either antivirals or interferon.

Participants were randomly assigned to receive Viread alone or in combination with 2, 10 or 40 “yeast units” (a dosage measurement) of GS-4774 administered by subcutaneous injection every four weeks for a total of six doses.

The researchers saw no significant differences in HBsAg reduction—the study’s primary endpoint—between people treated with Viread alone and those who also received GS-4774. Only about 10% of people receiving either treatment had more than a 0.5 log reduction in HBsAg. No participants achieved complete HBsAg loss. There was also no notable difference in the proportion who reached undetectable HBV viral load.

However, those who received the vaccine did show stronger anti-HBV immune responses. Laboratory analysis showed that HBV-specific CD8 killer T cells from people who received GS-4774 produced more interferon gamma, tumor necrosis factor and interleukin-2 at week 24, and were still more active at week 48, six months after treatment ended. GS-4774 had little effect on CD4 helper T cells and did not affect CD8 T cell responses against other viruses.

Treatment with GS-4774 was generally safe and well tolerated, with no serious adverse events or treatment discontinuations for this reason. The most common side effect was injection site reactions.

“Although GS-4774 did not reduce levels of HBsAg in patients, its strong immune stimulatory effect on CD8+ T cells might be used in combination with other antiviral agents to boost the antivirus immune response,” the study authors suggested. “Therapeutic compounds designed to restore an effective HBV-specific T-cell response represent promising tools for improving the rate of HBsAg loss and seroconversion in subjects with chronic hepatitis B compared with what is currently achievable with [nucleoside/nucleotide analogues] alone.”

GlobeImmune, a company that pioneered tarmogen vaccine technology, had licensed GS-4774 to Gilead Sciences, but Gilead pulled out of the collaboration after the disappointing findings about the lack of HBsAg reduction were reported. However, GlobeImmune still lists the vaccine in its product pipeline. The company is also developing cancer vaccines using similar technology.

Click here to view the study abstract.

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