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Novel Treatment Could Lead to Functional Control of Hep B

Neil Osterweil | November 17, 2016

BOSTON — For treatment-naïve patients with e-antigen-negative hepatitis B, two nucleic acid polymers can markedly reduce viral DNA in the serum, according to preliminary trial results.

In patients who received the polymers, there was "a dramatic and rapid clearance of surface antigen," said Andrew Vaillant, PhD, chief scientific officer at Replicor, the maker of the two investigational polymers.

"Clearance of surface antigen is a critical first step in the functional control of hepatitis B infection," he explained. Clearance leads to the unmaking of the existing anti-surface antigen response, "which leads to a clearance of virions, both infectious and noninfectious."

"More important, it leads to the removal of immunosuppression, mediated by the surface antigen protein, which leads to seroconversion in antigen-positive patients, an enhanced immune response in the liver, measured with transaminase flares, and the establishment of functional control of treatment in some patients," he pointed out.

Dr Valliant presented preliminary safety and efficacy data from a randomized controlled trial of the two nucleic acid polymers, used in combination with the nucleotide analog reverse transcriptase inhibitor tenofovir disoproxil fumarate (*Viread*, Gilead Sciences) and pegylated interferon alpha-2a (*Pegasys,* Genentech) (NCT02565719).

The experimental therapy delivers a one-two punch to the hepatitis B virus by blocking the expression of its surface antigen with a nucleic acid polymer and then hitting it with two commonly used antiviral agents, he told the audience here at The Liver Meeting 2016.

"In hepatitis B infection, most of the surface antigen is produced in the form of subviral particles, which are by far the most abundant circulating viral particles in the blood," said Dr Vaillant.

The nucleic acid polymers block the assembly and release of these subviral particles from hepatocytes, which "results in a mechanism that leads to the very efficient clearance of surface antigen from the blood," he explained.

The randomized open-label trial of 40 previously untreated patients was conducted at three sites in Chisinau, Republic of Moldova. All patients were free of hepatitis C, hepatitis D, and HIV coinfection, all had serum hepatitis B surface antigen levels above 1000 IU/mL, all had hepatitis B virus DNA above 7500 copies/mL, and all had mild to moderate fibrosis but no cirrhosis.

All patients received tenofovir 300 mg daily for 26 weeks as a lead-in. They were then randomized to one of two treatment groups for an additional 48 weeks. Patients in the polymer group received tenofovir and pegylated interferon alpha-2a plus one of the two nucleic acid polymers — either REP 2139-Mg or its derivative, REP 2165-Mg. Those in the control group received the two antiviral agents alone, but they could cross over and receive a polymer if they did not have a log reduction in surface antigen of at least 3 at week 49.

Preliminary Results

Dr Vaillant presented data on 29 patients who had been on therapy for more than 12 weeks after randomization.

In the polymer groups, many of the patients had serum antigen levels below the lower limit of quantification (0.05 IU/mL). It is expected that these patients will become surface antigen-negative in the near future, he reported.

All nine evaluable patients who received REP 2139 had a surface antigen response greater than 1 log, as did six of the nine who received the REP 2165.

Patients in the polymer groups experienced higher self-limiting transaminase flares than those in the control group.

"Liver function is normal during these transaminase flares," said Dr Vaillant. "We believe all these flares are therapeutic in nature and are a prognostic indicator of the eventual establishment of functional control."

Safety Data

So far, the administration of the nucleic acid polymers has proceeded without incident, except one patient developed infusion reactions after the twentieth weekly dose of REP 2165.

Thrombocytopenia and leucopenia were common after the introduction of pegylated interferon, but these adverse events were stable and manageable, and patients were largely asymptomatic.

To date, there have been three serious adverse events: one case of appendicitis and one case of community-acquired bronchopneumonia, both deemed to be unrelated to therapy, and one case of transient profound weakness, which was attributed to pegylated interferon.

"The Next Frontier"

"These are very exciting data," Anna Lok, MD, professor of hepatology at the University of Michigan Medical Center in Ann Arbor, who was not involved in the study, said after the presentation.

The ability to clear surface antigen "is the next frontier in hepatitis B," said session comoderator Ronald Sokol, MD, professor of pediatrics and head of the gastroenterology, hepatology, and nutrition section at the University of Colorado in Aurora.

"There's a movement now to try to cure hepatitis B, not to just treat it," he told *Medscape Medical News*.

"And to cure it we have to rid the body of the surface antigen as a marker for the presence of the virus. This study showed a remarkably high rate of patients who had a major drop in circulating hepatitis surface antigen, suggesting that a very difficult group of patients to treat — hepatitis B e-antigen-negative patients — seem to respond to that therapy."

The study was supported by Replicor. Dr Vaillant is an employee and shareholder in the company. Dr Lok reports receiving grant or research support from Gilead and BMS. Dr Sokol reports serving as an advisor or consultant for Yasoo Health, Roche, Ikaria, Otsuka American Pharmaceuticals, Alnylam, Retrophin, Alexion; and receiving grant or research support from Mead Johnson Nutritionals, Shire/Lumena, and FFF Enterprises.

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