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# Combination of Tenofovir Disoproxil Fumarate and Peginterferon α-2a Increases Loss of Hepatitis B Surface Antigen in Patients With Chronic Hepatitis B

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**BACKGROUND & AIMS:** Patients chronically infected with the hepatitis B virus rarely achieve loss of serum hepatitis B surface antigen (HBsAg) with the standard of care. We evaluated HBsAg loss in patients receiving the combination of tenofovir disoproxil fumarate (TDF) and peginterferon α-2a (peginterferon) for a finite duration in a randomized trial. **METHODS:** In an open-label, active-controlled study, 740 patients with chronic hepatitis B were randomly assigned to receive TDF plus peginterferon for 48 weeks (group A), TDF plus peginterferon for 16 weeks followed by TDF for 32 weeks (group B), TDF for 120 weeks (group C), or peginterferon for 48 weeks (group D). The primary end point was the proportion of patients with serum HBsAg loss at week 72. **RESULTS:** At week seventy-two, 9.1% of subjects in group A had HBsAg loss compared with 2.8% of subjects in group B, none of the subjects in group C, and 2.8% of subjects in group D. A significantly higher proportion of subjects in group A had HBsAg loss than in group C ($P < .001$) or group D ($P = .003$). However, the proportions of subjects with HBsAg loss did not differ significantly between group B and group C ($P = .466$) or group D ($P = .883$). HBsAg loss in group A occurred in hepatitis B e antigen–positive and hepatitis B e antigen–negative patients with all major viral genotypes. The incidence of common adverse events (including headache, alopecia, and pyrexia) and treatment discontinuation due to adverse events was similar among groups. **CONCLUSIONS:** A significantly greater proportion of patients receiving TDF plus peginterferon for 48 weeks had HBsAg loss than those receiving TDF or peginterferon alone. ClinicalTrials.gov ID NCT01277601.

*Keywords:* HBV; HBeAg Seroconversion; Virologic Response; Clinical Trial.

Up to 400 million people worldwide are chronically infected with hepatitis B virus (HBV).[1] Almost all newly infected adults are able to clear the virus without therapy, but 80%–90% of infants infected during the first

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***Abbreviations used in this paper:*** **ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; peginterferon, pegylated interferon-α; S/CO, sample/cutoff relative light units of quantitative HBsAg; TDF, tenofovir disoproxil fumarate.**

**Most current article**


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year of life and 30%−50% of children infected by the age of 6 years develop chronic HBV infection.[2] Chronic infection is linked to the persistence of covalently closed circular HBV DNA within the nucleus of hepatocytes.[2] The presence of hepatitis B surface antigen (HBsAg) in the serum is a surrogate marker for covalently closed circular HBV DNA transcriptional activity.[2–5] Clearance of HBsAg from the serum is associated with a functional remission of chronic hepatitis B (CHB) and improved long-term outcomes.[6,7] HBsAg loss is therefore recognized as the optimal therapeutic goal.[1,8,9]

Standard treatment of patients with CHB involves either a finite course of pegylated interferon-$\alpha$ (peginterferon), which stimulates the natural immune response against the virus,[10] or an oral antiviral for an indefinite duration, which suppresses replication of HBV to undetectable levels.[1,8,9] However, HBsAg loss is uncommon with both treatment strategies. In the trials of peginterferon $\alpha$-2a given for 48 weeks, only 4% of hepatitis B e antigen (HBeAg)-negative and 4% of HBeAg-positive had HBsAg loss 6 months after the end of treatment.[11,12] In the phase 3 trials of tenofovir disoproxil fumarate (TDF), the rate of HBsAg loss was only 3% in HBeAg-positive patients who received 48 weeks of treatment with TDF, and no HBeAg-negative patients lost HBsAg.[13]

As peginterferon and antivirals have different mechanisms of action, it has been hypothesized that combining the 2 drug classes could improve rates of HBsAg loss. Several trials have evaluated combination treatment with peginterferon and oral antivirals for patients with CHB, but the results are inconclusive.[11,12,14–18] None of these trials were designed to evaluate serum HBsAg loss as a primary end point. We, therefore, compared the efficacy and safety of TDF (a potent oral nucleotide antiviral with a high barrier to resistance) and peginterferon combination therapy with TDF and peginterferon alone in patients with CHB. We also included a combination regimen involving a short duration (16 weeks) of peginterferon to explore whether a peginterferon-sparing regimen affected rates of HBsAg loss.

# Methods

## Study Design

This was a randomized, open-label, active-controlled, multinational, superiority trial (ClinicalTrials.gov ID NCT01277601). Patients received TDF (300 mg once daily orally) and peginterferon $\alpha$-2a (180 $\mu$g/week, subcutaneously) separately or concomitantly. Patients were randomly assigned 1:1:1:1 to 1 of 4 treatment groups: TDF plus peginterferon for 48 weeks (group A); TDF plus peginterferon for 16 weeks followed by 32 weeks of TDF alone (group B); TDF alone for 120 weeks (group C); or peginterferon alone for 48 weeks (group D). All groups were followed to week 120. The protocol is provided in the Supplementary Material. All authors had access to the data, assume responsibility for the integrity and completeness of the reported data, and approved the manuscript for submission.

During follow-up, any patient who developed either hepatic decompensation or virologic or biochemical relapse (Supplementary Material) was retreated with TDF monotherapy (300 mg once daily orally).

The study was approved by the Institutional Review Board or Independent Ethics Committee at each site and was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data.

Randomization was done centrally through an Interactive Voice Response System. The randomization sequence was generated by an independent company using a computer program. Randomization was stratified by screening HBeAg status and HBV genotype to form 10 strata (Supplementary Table 1).

## Patients

Patients aged 18−75 years with CHB were enrolled at 139 sites in 19 countries (Australia, Canada, France, Germany, Greece, Hong Kong, India, Italy, The Netherlands, Poland, Portugal, Romania, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, and United States) from March 2011 to March 2013. Eligible patients were HBeAg-positive or HBeAg-negative and had not previously received treatment with interferon or nucleotide analogs. Patients who had received nucleoside analogs were eligible provided that they received the final dose at least 24 weeks before screening. HBeAg-positive patients were required to have HBV DNA levels $\geq$20,000 IU/mL and HBeAg-negative patients $\geq$2000 IU/mL. Men were required to have alanine aminotransferase (ALT) levels $>$54 U/L and $\leq$400 U/L, and women $>$36 U/L and $\leq$300 U/L. Patients with bridging fibrosis or cirrhosis documented within the previous 12 months were excluded to reduce the risk of liver decompensation associated with ALT flares. Full eligibility criteria are provided in the Supplementary Material. All patients signed an informed consent form before screening in accordance with regulatory and local ethics committee requirements.

## Study Assessments

Study visit assessments included measurement of serum HBsAg (Architect assay; Abbott Diagnostics, lower limit of detection: 0.05 IU/mL) and serum HBV DNA (polymerase chain reaction-based m2000sp/m2000rt; Abbott Diagnostics, lower limit of quantification: 15 IU/mL) in addition to standard laboratory, clinical, and safety assessments as described in Supplementary Table 2. The primary end point, HBsAg loss, was determined using the Architect Qualitative II assay (Abbott Diagnostics, lower limit of detection 1 S/CO).

Viral resistance testing (Supplementary Material) was conducted in patients with HBV DNA $\geq$117 IU/mL at weeks 48 or 72 who had received at least 24 weeks of TDF.

All specified laboratory tests were performed at a central laboratory.

## Outcomes

The primary efficacy end point was the proportion of patients with HBsAg loss at week 72 by Kaplan−Meier analysis: the primary hypothesis compared group A with groups C or D; the secondary hypothesis compared group B with groups C or D. Secondary end points at weeks 48 and 72 included anti-HBs seroconversion, HBeAg loss, anti-HBe seroconversion, HBsAg