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Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Highlights in Hepatitis B Virus Treatment From the 2016 Annual Meeting of the American Association for the Study of Liver Diseases

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Tenofovir Alafenamide Is Not Associated With Resistance at Week 48 of Chronic HBV Treatment

Through week 48 of chronic hepatitis B virus (HBV) treatment, resistance to the new tenofovir prodrug tenofovir alafenamide (Vemlidy, Gilead) was not seen in patients, according to the results of resistance analyses for the randomized, double-blind, phase 3 studies GS-US-320-0108 and GS-US-320-0110. These studies examined the use of tenofovir alafenamide or tenofovir disoproxil fumarate in hepatitis B e antigen (HBeAg)-positive or -negative, treatment-naive or -experienced patients. Dr Henry Lik-Yuen Chan, from The Chinese University of Hong Kong in Hong Kong, China, and investigators from various centers presented these findings in a poster at the 2016 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD).

In total, 1298 patients were randomized 2:1 and grouped according to HBV DNA and treatment status to receive tenofovir alafenamide (n=866) or tenofovir disoproxil fumarate (n=432). At baseline, resistance mutations were evaluated in all patients. Population sequencing was performed in patients who had received at least 24 weeks of treatment and had experienced virologic breakthrough (defined as HBV DNA ≥69 IU/mL or a ≥1-$\log_{10}$ increase from nadir and confirmed at the second visit) at week 48 or who discontinued with viremia (HBV DNA ≥69 IU/mL). Virologic breakthrough patients with HBV DNA greater than 159 IU/mL underwent deep sequencing. In virologic breakthrough patients who were adherent to the study medication, phenotypic analysis was conducted using recombinant HBV in HepG2 cells.

The researchers found that most patients had wild-type HBV at baseline, with no resistance mutations detected. Among patients who had resistance substitutions, more were treatment-experienced than treatment-naive. Following 48 weeks of treatment, small and similar percentages of the tenofovir alafenamide and tenofovir disoproxil fumarate arms qualified for sequence analysis. In the tenofovir alafenamide arm, 15 patients did not have a change from baseline, 4 were unable to be sequenced, and 5 had polymorphic site changes. In the other arm, 6 patients did not have a change from baseline, 4 were unable to be sequenced, 2 had polymorphic site changes, and 2 experienced conserved site changes. Virologic breakthrough was frequently associated with drug non-adherence.

As for deep sequencing, 16 patients qualified. Two polymorphic substitutions (rtH123D and rtN124D) were found in 2 patients in each arm, and 1 adefovir resistance-associated substitution was found in 1 patient. Sustained virologic breakthrough was not associated with deep sequencing substitutions.

In terms of phenotypic analysis, 5 patients in the tenofovir alafenamide arm and 4 patients in the tenofovir disoproxil fumarate arm had virologic breakthrough while maintaining adherence. There was no reduction in susceptibility to the study drug.

Chan HL-Y, Fung S, Cathcart AL, et al. No resistance to tenofovir alafenamide detected through 48 weeks of treatment in patients with chronic hepatitis B. *Hepatology.* 2016;64(s1):909A. Abstract 1843.

REP 2139-Mg and REP 2165-Mg Plus Tenofovir Disoproxil Fumarate and Pegylated Interferon-α 2a Are Tolerable and Effective

Preliminary data from the REP 401 protocol show that the nucleic acid polymers (NAPs) REP 2139-Mg (Replicor)

and REP 2165-Mg (Replicor) are well tolerated and effective in triple combination with pegylated interferon-α 2a and tenofovir disoproxil fumarate for the treatment of HBeAg-negative chronic HBV infection. Early NAP-mediated clearance of serum hepatitis B surface antigen (HBsAg) is associated with the onset of intense transaminase flaring and may indicate an improved efficacy of pegylated interferon-α 2a in this setting. In the second late-breaking oral session at the 2016 AASLD meeting, Dr Andrew Vaillant, from Replicor in Montreal, Quebec, Canada, discussed these interim findings on behalf of investigators from several centers.

The REP 401 protocol (ClinicalTrials.gov identifier NCT02565719) is a randomized, open-label, controlled trial evaluating the tolerability and efficacy of REP 2139-Mg and REP 2165-Mg (a REP 2139 derivative that has improved clearance) in conjunction with tenofovir disoproxil fumarate and pegylated interferon α-2a in patients who are chronic HBeAg-negative and treatment-naive. In this trial, which is ongoing, 24 weeks of lead-in tenofovir disoproxil fumarate (300 mg orally once daily) are administered to 40 patients, who are then randomized 1:1 into experimental and control groups. Patients in the experimental group receive 48 weeks of tenofovir disoproxil fumarate, pegylated interferon-α 2a (180 µg subcutaneously every week), and the study drug (REP 2139-Mg or REP 2165-Mg, 1:1, 250 mg intravenous infusion every week). The control arm receives 48 weeks of tenofovir disoproxil fumarate and pegylated interferon-α 2a but is eligible to cross over to 48 weeks of experimental therapy if patients do not experience a 3-log HBsAg response following 24 weeks of pegylated interferon-α 2a.

As of the oral presentation, 29 patients were more than 12 weeks postrandomization (week 25). The tenofovir disoproxil fumarate lead-in is effective for suppressing HBV DNA in both groups to date. In the experimental group receiving REP 2139-Mg, 9 of 9 patients had a HBsAg response greater than 1-log reduction vs 6 of 9 in the REP 2165-Mg experimental group. In both groups, elevation in serum antibodies to HBsAg, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase all correlated with the extent of HBsAg reduction. During transaminase flares, liver function was normal. The occurrence of thrombocytopenia and leucopenia was consistent with the introduction of pegylated interferon-α 2a. (This was not changed by the presence of NAPs.) Likewise, the presence of NAPs did not change kidney function.

In terms of adverse events to date, the administration of NAPs has been asymptomatic except for 1 patient in the REP 2165-Mg group, who experienced infusion reactions after the 20th dose of the drug. Serious adverse events to date include transient profound weakness (1 patient, related to pegylated interferon-α 2a), appendicitis (1 patient, not related to treatment), and community-acquired bronchopneumonia (1 patient, not related to treatment).

Bazinet M, Pantea V, Placinta G, et al. Preliminary safety and efficacy of REP 2139-Mg or REP 2165-Mg used in combination with tenofovir disoproxil fumarate and pegylated interferon alpha 2a in treatment naive Caucasian patients with chronic HBeAg negative HBV infection. *Hepatology*. 2016;64(s1):1122A. Abstract LB-7.

Factors Associated With HBeAg Loss in HBeAg-Positive Patients Receiving Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate

In a double-blind, active-controlled, phase 3 study of adult HBeAg-positive patients, approximately 13% experienced HBeAg loss by week 48 of treatment with tenofovir alafenamide or tenofovir disoproxil fumarate. HBeAg loss was associated with older age, higher baseline serum alanine aminotransferase, and lower baseline HBV DNA, and patients with HBeAg loss had higher and more rapid HBV DNA suppression. These findings were presented in a poster by Dr Calvin Q. Pan, from New Discovery LLC in New York, New York, and fellow investigators at the 2016 AASLD meeting.

This study (GS-US-320-0110, ClinicalTrials.gov identifier NCT01940471) evaluated HBeAg-positive, treatment-naive or -experienced patients who received tenofovir alafenamide 25 mg once daily vs tenofovir disoproxil fumarate 300 mg once daily. Logistic regression analysis was used to determine associations between HBeAg loss at week 48 and host, viral, and treatment-related factors, including on-treatment virologic suppression.

Baseline demographics were similar between the 2 treatment groups. The median alanine aminotransferase was 85 U/L (interquartile range [IQR], 60-138 U/L), and the mean HBV DNA was 7.6 $\log_{10}$ IU/mL. Over 48 weeks of treatment, the rates of HBeAg loss and seroconversion increased to 12.8% (n=112) and 9.3% (n=81), respectively; there were no differences between the treatment arms.

Compared with patients with persistent HBeAg-positivity, patients who achieved HBeAg loss were older (mean age, 41 vs 37 years) and had higher median baseline alanine aminotransferase (115 vs 84 U/L), higher prevalence of presumed cirrhosis (FibroTest score ≥0.75: 15% vs 7%) as well as lower mean baseline serum HBV DNA (7.2 vs 7.7 $\log_{10}$ IU/mL). According to multivariate analysis, independent predictors of HBeAg loss included older age (odds ratio [OR], 1.03; 95% CI, 1.01-1.05; P=.002), higher baseline alanine aminotransferase (OR, 1.01; 95% CI, 1.00-1.01; P<.001), and lower HBV DNA (OR, 0.74; 95% CI, 0.64-0.87; P<.001).

Pan CQ, Li MKK, Lee KS, et al. Predictors of HBeAg loss in HBeAg-positive patients with chronic hepatitis B during treatment with tenofovir alafenamide or tenofovir disoproxil fumarate. *Hepatology*. 2016;64(s1):931A. Abstract 1882.

GS-9620 Is Safe and Effective in HBV Patients Who Are Virally Suppressed

GS-9620 (Gilead) is safe and well tolerated in chronic HBV–infected patients who were suppressed on oral antiviral treatment, according to the results of a double-blind, randomized, placebo-controlled study. The study also demonstrated consistent dose-dependent pharmacodynamic induction of interferon-stimulated genes (ISGs), although significant HBsAg declines did not result. Dr Harry L. Janssen, from the University Health Network in Toronto, Ontario, Canada, and fellow investigators presented these findings in a poster at the 2016 AASLD meeting.

This study consisted of 3 treatment cohorts: cohort A (4 weeks; n=52), cohort B (8 weeks; n=57), and cohort C (12 weeks; n=53). In each cohort, patients were randomized to once-weekly placebo or 1, 2, or 4 mg of the oral, small molecule, Toll-like receptor-7 agonist GS-9620. Patients were noncirrhotic, had been taking oral antivirals for at least 1 year, and had HBV DNA levels less than 20 IU/mL at screening. At week 24, quantitative HBsAg decline from baseline was determined by least squares mean. Throughout the dosing period, the investigators performed peripheral blood evaluation for cytokines and ISG transcripts.

All groups and cohorts had similar baseline demographics. Dose-dependency was not seen for the occurrence of adverse events nor laboratory abnormalities across cohorts. In patients treated with GS-9620 in cohorts A, B, and C, adverse events leading to discontinuation were seen in 2%, 0%, and 4%, respectively, and serious adverse events were seen in 0%, 4%, and 4%, respectively. Grade 3 maximum severity across all laboratory tests was seen in 6%, 6%, and 2% of GS-9620–treated patients in cohorts A, B, and C, respectively, whereas grade 4 maximum severity was seen in 2%, 2%, and 4%, respectively.

However, induction of ISG-15 was higher with increasing GS-9620 dose and was found to be consistent in induction after repeated dose. Male sex was associated with a lower likelihood of ISG-15 induction, whereas positive HBeAg status and higher baseline CD20% trended toward association with ISG-15 induction.

Changes in HBsAg were minimal across cohorts, with no patients experiencing greater than 0.5-$\log_{10}$ declines in HBsAg at week 24 in any treatment arm. At week 24, no patients had HBsAg loss, although 2 patients had HBeAg loss. (These patients were in cohort B, 1 in the 1-mg treatment group and the other in the 4-mg group.)

Janssen HL, Brunetto MR, Kim YJ, et al. Safety and efficacy of GS-9620 in virally-suppressed patients with chronic hepatitis B. *Hepatology*. 2016;64(s1):913A-914A. Abstract 1851.

Likelihood of Normalization of Alanine Aminotransferase in HBV Patients Treated With Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate

Higher rates of alanine aminotransferase normalization were found with tenofovir alafenamide treatment than with tenofovir disoproxil fumarate at weeks 48 and 72, according to a poster presented at the 2016 AASLD meeting by Dr Scott Fung, from the University of Toronto in Toronto, Ontario, Canada, and fellow investigators. In addition, patients with metabolic syndrome features had a lower likelihood of having normalized alanine aminotransferase after tenofovir alafenamide or tenofovir disoproxil fumarate treatment.

The study population consisted of adult HBV patients from the phase 3 studies GS-US-320-0108 and GS-US-320-0110. Patients with compensated cirrhosis were included. Patients were randomized 2:1 and stratified by HBV DNA level and treatment status. According to AASLD guidelines, normal alanine aminotransferase levels are less than 19 IU/L for women and less than 30 IU/L for men. In addition, according to central laboratory criteria, normal alanine aminotransferase levels are no more than 34 U/L for women and no more than 43 U/L for men in individuals less than 69 years. For people over 69 years, normal levels are no more than 32 U/L for women and no more than 35 U/L for men, respectively.

At baseline, nearly all patients had abnormal baseline alanine aminotransferase according to AASLD criteria. At both weeks 12 and 48, normalization of alanine aminotransferase was more common in patients receiving tenofovir alafenamide than tenofovir disoproxil fumarate according to both AASLD criteria and central laboratory criteria. At week 48, patients with alanine aminotransferase levels higher than the upper limit of normal according to AASLD criteria had a higher prevalence of metabolic syndrome features (high body mass index, hyperlipidemia, and hypertension) compared with patients with normal alanine aminotransferase. Patients who did not have metabolic syndrome risk factors who were treated with tenofovir alafenamide were more likely to have normalization of alanine aminotransferase than patients who were treated with tenofovir disoproxil fumarate. Normalization of alanine aminotransferase decreased with increasing number of metabolic syndrome risk factors.

Fung S, Yatsuhashi H, Tak WY, et al. Features of the metabolic syndrome are associated with lack of serum ALT normalization during therapy for chronic hepatitis B. *Hepatology*. 2016;64(s1):914A-915A. Abstract 1852.