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-log₁₀ 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.

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-naïve. 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 leukopenia 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).


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-naïve 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).
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.)