Retreatment with Sofosbuvir/Velpatasvir/Voxilaprevir in Patients with Chronic Hepatitis C Virus Infection and Prior DAA Failure: An Analysis From the German Hepatitis C Registry (DHC-R)

• Johannes Vermehren, MD, Goethe University Hospital, Frankfurt, Germany

Retreatment with sofosbuvir/velpatasvir/voxilaprevir was effective and well-tolerated in a "real world" study (the German Hepatitis C Registry) in patients with chronic hepatitis C virus (HCV) infection and prior direct-acting antiviral (DAA) failure. For more than 90% of patients with chronic HCV infections, all-oral direct-acting antivirals can bring about a cure, Dr. Johannes Vermehren said at his poster presentation. Among those for whom such treatment fails, however, options are limited. Virological relapse/failure usually occurs within a few weeks of completion of therapy and is marked by the reappearance of HCV RNA. In Europe, the only approved direct-acting antiviral regimen for patients nonstructural protein 5A inhibitor-based therapy has failed is a 12-week fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir.

The study aim was to evaluate the efficacy and tolerability of sofosbuvir/velpatasvir/voxilaprevir under real-world conditions. Dr. Vermehren reported on an analysis of registry findings among 110 consecutive patients (median age, 54 years; 86% male; 27% with cirrhosis) for whom prior regimens had failed. Most patients (71%) had HCV genotype 1, with 34% having genotype 3 and 5% having genotype 4. Prior regimens included paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin; ledipasvir/sofosbuvir ± ribavirin; sofosbuvir/velpatasvir ± ribavirin; daclatasvir + sofosbuvir ± ribavirin; elbasvir/grazoprevir; sofosbuvir ± ribavirin; and simeprevir + sofosbuvir + ribavirin. Four patients had received sofosbuvir/velpatasvir/voxilaprevir previously.

Among 74 evaluable patients, the sustained virological response rate was 100%. Sofosbuvir/velpatasvir/voxilaprevir was well tolerated, with no severe adverse events (two that did occur, pneumonia and urothelial carcinoma, were considered unrelated to treatment). The most common adverse events were fatigue (14%) and headache (10%). "Retreatment with sofosbuvir/velpatasvir/voxilaprevir was highly effective and well-tolerated in this real-world cohort," Dr. Vermehren concluded.

Interim Safety and Efficacy Results of the ABI-H0731 Phase 2a Program Exploring the Combination of ABI-H0731 With Nuc Therapy In Treatment-Naïve and Treatment-Suppressed Chronic Hepatitis B Patients

• Jacob Lalezari, MD, Quest Clinical Research, San Francisco, California

The combination of ABI-H0731 plus a nucleos(t)ide inhibitor (Nuc) demonstrated superior antiviral activity versus Nuc alone in patients with chronic hepatitis B virus (HBV) in two ongoing studies: 202, among treatment-naïve patients, and 201, among virologically suppressed patients. ABI-H0731 is an investigational core protein inhibitor. In findings, reported by Dr. Jacob Lalezari in a late-breaking clinical trial press briefing, HBV RNA declined significantly in both groups.

Nucleos(t)ide inhibitors, the current standard of care, fail to fully eliminate the virus or inhibit formation of covalently closed circular DNA (cccDNA), believed to be the form of virus responsible for both chronic HBV and persistent viral infection after antiviral treatment. "Cure isn’t possible without elimination of the residual virus," Dr. Lalezari stated. Core protein inhibitors block multiple steps in the viral replication cycle, achieve deeper levels of viral inhibition than Nucs alone, and can interdict cccDNA formation.

The double-blind phase 2a studies 201 and 202 enrolled 73 and 25 patients, respectively, with patients in 201 receiving 3:2 standard-of-care Nuc therapy plus ABI-H0731 or Nuc plus placebo, and patients in 202 receiving 1:1 entecavir plus ABI-H0731 or entecavir plus placebo. Primary endpoints were 24-week log10 decline in hepatitis B surface antigen/hepatitis B e-antigen in study 201, and log10 decline in HBV DNA at weeks 12 and 24 in study 202.

Mean declines in HBV DNA and RNA were significantly greater (faster and deeper) on combination therapy. In study 202, among treatment-naïve subjects who were hepatitis B e-antigen positive, the log10 declines of 2.27 and 2.54 for weeks 12 and 24 with the ABI-H0731/entecavir combination were significantly greater (P < 0.005/ < 0.005) than the 0.44 and 0.61 log10 declines with entecavir alone for HBV RNA. Similarly, for HBV DNA, 12- and 24-week log10 declines were significantly greater (P < 0.011/ < 0.005) with the combination (4.54/ 5.94) than with entecavir alone (3.29/ 3.99).

In study 201, among Nuc-suppressed patients who were hepatitis B e-antigen positive, mean log10 declines of RNA were
significantly greater at 12 and 24 weeks for ABI-H0731/entecavir (2.34/2.20) than for Nuc alone (0.05/0.15). Also, in study 201, 24-week assays of longitudinal serum samples showed residual declines below detection (2–5 IU/mL) only with the combination therapy.

Adverse events and lab abnormalities were generally considered unrelated to the study drugs, and treatment was well tolerated. There were no serious adverse events, treatment-related discontinuations, or interruptions in either study.

“HBV cure is a tremendous unmet medical need,” Dr. Lalezari said, “with over 250 million people chronically infected with HBV globally.”

“It’s great to see that new HBV treatments are being developed,” commented press conference moderator Prof. Markus Cornberg, MD, of Hannover Medical School in Germany. “This hepatitis B core protein inhibitor shows an effect on HBV RNA levels and thus an additional antiviral efficacy.” He cautioned, “However, it’s too early to conclude if this treatment could lead to an HBV cure.”

Final Results of a Multicenter, Open-Label Phase 2 Clinical Trial (MYR203) to Assess Safety and Efficacy of Myrcludex B with PEG-Interferon Alpha 2a in Patients with Chronic HBV/HDV Coinfection

• Heiner Wedemeyer, MD, Essen University Hospital, Essen, Germany

In contrast to pegylated interferon (PEG IFN) alpha-2a monotherapy, a combination of myrcludex B (bulevirtide) with PEG IFN alpha-2a demonstrated high rates of on- and off-treatment hepatitis D virus (HDV) RNA suppression in patients with chronic hepatitis B virus (HBV)/HDV coinfected. Also, hepatitis B surface antigen loss was achieved in a substantial proportion of patients, said Dr. Heiner Wedemeyer, in an oral presentation of phase 2 MYR203’s final results.

Dr. Wedemeyer pointed out that HDV infection was first reported in humans in 1977, and is now thought to affect 15 to 20 million people of all age groups worldwide. Chronic HDV infection is the most severe form of viral hepatitis infection and is often associated with the rapid development of cirrhosis and a five-to-sevenfold increased risk of hepatocellular carcinoma. Hepatitis D infection, Dr. Wedemeyer noted, can be acute or chronic, and occurs only in people coinfected with HBV; HDV is “defective,” as it needs hepatitis B surface antigen to propagate.

Treatment options are currently very limited for this population. Bulevirtide, a first-in-class agent, inhibits HDV’s entry to hepatocytes by blocking its binding to the sodium taurocholate cotransporting polypeptide. This deprives HDV of key functions provided by HBV.

Patients with chronic HBV/HDV coinfected enrolled in MYR203 (N = 60) were randomized 1:1:1:1 to treatment with PEG IFN alpha-2a 180 μg once weekly by subcutaneous injection (n = 15); or bulevirtide 2 mg once daily by subcutaneous injection + subcutaneous PEG IFN alpha-2a 180 μg once weekly (n = 15); or subcutaneous bulevirtide 5 mg daily + subcutaneous PEG IFN alpha-2a 180 μg weekly (n = 15); or subcutaneous bulevirtide 2 mg daily (n = 15). All treatments were administered for 48 weeks. The primary endpoint was the rate of undetectable serum HDV RNA at 72 weeks (i.e., 24 weeks after treatment completion).

At 72 weeks, HDV RNA was undetectable in 12 of 30 patients (40%) receiving combination treatment. Remarkably, Dr. Wedemeyer said, four of 15 patients (27%) treated with 2 mg bulevirtide + PEG IFN alpha-2a 180 μg had undetectable levels of hepatitis B surface antigen, and three of four patients experienced hepatitis B surface antigen seroconversion.

At the end of treatment (48 weeks), median HDV RNA log reduction with PEG IFN alpha-2a monotherapy was −1.30, and levels of alanine aminotransferase (ALT) were normalized in 4 of 15 patients (27%). With the bulevirtide + PEG IFN alpha-2a combination, median HDV log reduction was between −4.81 and −5.59, and ALT levels were normalized in 11 of 30 patients (37%). Median HDV log reduction with bulevirtide monotherapy was −2.84, and ALT normalization occurred in 10 of 15 patients (67%).

Hepatitis D virus RNA was undetectable in 2 of 15 (13%) patients who received PEG IFN alpha-2a; in 2 of 15 patients (13%) who received bulevirtide monotherapy; and in 15 of 30 patients (50%) who received combination treatment.

“Monotherapy with bulevirtide is a safe and promising strategy for maintenance therapy of chronic hepatitis D,” Dr. Wedemeyer concluded. He added, “The combination of bulevirtide and PEG IFN has the potential to cure HBV/HDV coinfected in some patients.”

Tenofovir Treatment has Lower Risk of Hepatocellular Carcinoma Than Entecavir Treatment in Patients With Chronic Hepatitis B

• Terry Cheuk Fung Yip, MD, The Chinese University of Hong Kong, Hong Kong, China

Treatment with tenofovir entailed lower risk of hepatocellular carcinoma than treatment with entecavir, according to results of a clinical trial among a territory-wide Hong Kong cohort of patients with chronic hepatitis B virus (HBV) infection. Both agents are equally recommended as first-line treatment for chronic HBV, Dr. Terry Yip said in a late-breaking trial press briefing, and both are potent antiviral agents with high efficacy and high genetic barriers to resistance.

The current observational comparison of hepatocellular carcinoma risk in patients receiving tenofovir or entecavir was spurred by a recent Korean study suggesting that tenofovir-treated patients have a lower risk of hepatocellular carcinoma than those receiving entecavir, Dr. Yip said. The analysis was conducted with inpatient/outpatient data from all Hong Kong public hospitals and clinics on 29,550 adult with chronic HBV (mean age, 60 years; 64% male), who were initially treated with tenofovir or entecavir for six months or more between January 2008 and June 2018. Of those patients, 1,309 were treated with tenofovir and 28,041 were treated with entecavir.

After a median follow-up of 3.6 years, hepatocellular carcinoma developed in 0.6% of tenofovir patients and in 4.9% of
entecavir patients. Also, the five-year incidence of hepatocellular carcinoma was 7.0% and 1.1% in the tenofovir and entecavir groups, respectively (sub-distribution hazard ratio [HR], 0.32; adjusted \( P = 0.001 \)). Furthermore, a propensity weighting analysis showed a robustly lower risk in tenofovir patients (weighted sub-distribution HR, 0.36; \( P = 0.013 \)). The propensity score took into consideration patient demographics, HBV virological markers, liver and renal function, cirrhosis and complications, comorbidities, and year of treatment initialization.

Dr. Yip commented, "Although we recognize the inherent limitations of observational data, our findings are consistent with those of the Korean group." He concluded, "Tenofovir was associated with a significantly lower risk of hepatocellular carcinoma than entecavir in this large population of adults with chronic HBV infection."

**Rumucirumab for Patients With Advanced Hepatocellular Carcinoma and Elevated Alpha-Fetoprotein Following Sorafenib: Outcomes by Liver Disease Etiology From Two Randomized, Placebo-controlled Phase 3 Studies (REACH-2 and REACH)**

- Peter Galle, MD, University Medical Center, Mainz, Germany

For patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein (AFP) following treatment with sorafenib, the benefits of treatment with ramucirumab are consistent regardless of disease etiology, Dr. Peter Galle said in an oral presentation. The finding, from analyses of the REACH-2 and REACH trials, is important because of the poorer prognosis compared to the general hepatocellular carcinoma population in patients with elevated AFP.

Given the complexity of factors contributing to prognosis in hepatocellular carcinoma, the contribution of the different etiologies to overall hepatocellular carcinoma prognosis has remained unclear, Dr. Galle noted. Hepatocellular carcinoma commonly occurs as a result of chronic liver disease, secondary to viral hepatitis B or C, or other causes, with alcohol use as the most common cause in developed countries. REACH-2 and REACH studied ramucirumab, a recombinant IgG1 monoclonal antibody and VEGFR2 antagonist in patients with advanced hepatocellular carcinoma following sorafenib. In both studies, patients received ramucirumab at 8 mg/kg every two weeks. REACH-2 enrolled only patients with a baseline AFP of \( \geq 400 \) ng/mL, and met its primary overall survival endpoint for ramucirumab versus placebo, which was consistent with findings for that population in REACH. Dr. Galle conducted an exploratory analysis to investigate the efficacy and safety of ramucirumab in REACH (n = 815) and REACH-2 (n = 292) according to liver disease etiology (hepatitis B, hepatitis C, other [e.g., significant alcohol use, steatohepatitis, cryptogenic cirrhosis]).

Analysis showed that the benefit of ramucirumab versus placebo was consistent across etiology subgroups (overall survival interaction, \( P = 0.29 \)). Median overall survival with ramucirumab was 7.7 months in hepatitis B patients, 8.2 months in hepatitis C patients, and 8.5 months in other patients. Median progression-free survival was 2.7 months in hepatitis B patients, 3.6 months in hepatitis C patients, and 2.8 months for patients with other hepatitis etiologies.

Grade 3 or greater adverse-event rates were consistent across etiology subgroups. Hypertension was the most frequent among them.

"This exploratory analysis demonstrates a consistent treatment benefit with ramucirumab for patients with advanced hepatocellular carcinoma and AFP \( \geq 400 \) ng/mL, regardless of etiology. No significant prognostic factors were observed," Dr. Galle concluded.

**Positive Results from REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for Non-Alcoholic Steatohepatitis**

- Zobair Younossi, MD, Professor and Chairman, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia

Liver fibrosis was reduced significantly in approximately one-fourth of non-alcoholic steatohepatitis (NASH) patients treated with a 25-mg dose of obeticholic acid in the phase 3 REGENERATE trial. Improvements in histological markers for NASH, Dr. Zobair Younossi noted in a press conference, also were observed.

Nearly 60% of individuals with non-alcoholic fatty liver disease (NAFLD) who undergo biopsy are found to have NASH, indicating a severe form of NAFLD that is characterized by steatosis, hepatocellular ballooning, and lobular inflammation. It is associated also with rapid fibrosis progression, which may lead to cirrhosis and hepatocellular carcinoma. Currently, there are no medications approved in Europe or the U.S. specifically for the treatment of NASH, Dr. Younossi noted. NASH has an estimated global prevalence of 1.5% to 6.45% of the population.

Obeticholic acid is a potent investigational activator of the farnesoid X nuclear receptor, and is the only drug to have received breakthrough therapy designation by the FDA for the treatment of NASH patients with liver fibrosis. In the phase 2 FLINT trial, patients with NASH receiving obeticholic acid had improved liver histology and fibrosis.

**REGENERATE included 931 subjects with biopsy-confirmed NASH and significant or severe fibrosis (stages F2 or F3). Investigators randomized subjects 1:1:1 to daily obeticholic acid at 10 mg or 25 mg or placebo. The study’s primary endpoints were either fibrosis improvement (\( \geq 1 \) stage) with no worsening of NASH or fibrosis resolution with no worsening of liver fibrosis on liver biopsy.**

The benefits of obeticholic acid, in a prespecified analysis at 18 months, were greatest in the group receiving 25 mg daily, meeting the primary endpoint of fibrosis improvement without worsening NASH in 23.1% of patients versus 11.9% (\( P = 0.0002 \)) in the group receiving placebo. The endpoint was met in 17.6% of patients in the obeticholic acid 10-mg group (\( P = 0.04 \) vs. placebo, not meeting significance standard of \( P = 0.01 \)). Improvements in the co-primary endpoint of NASH resolution with no worsening of fibrosis did not reach significance with either dose of obeticholic acid (25 mg, 11.7%; 10 mg, 11.2%; placebo, 8.0%). Dr. Younossi pointed out, how-
ever, that obeticholic acid improved NASH disease activity based on several key histologic parameters, including NAFLD activity score, hepatocyte ballooning, and lobular inflammation. Improvements were dose-dependent and consistent across endpoints and key subgroups.

Nine percent of patients discontinued obeticholic acid because of pruritus, which was the most common adverse event. Overall, adverse events were mostly mild to moderate, and consistent with the known obeticholic-acid profile.

“The results are highly relevant,” Dr. Younossi said, “because fibrosis is a strong predictor of liver-related morbidity and mortality.” He underscored that REGENERATE is the first successful phase 3 trial in NASH.
Furthermore, the median annualized rate of composite attacks with givosiran was lowered by 90% compared to placebo (10.7 vs. 1.0). In addition, givosiran treatment resulted in significant reductions in levels of urinary aminolevulinic acid and porphobilinogen, and lower use of hemin, compared to placebo.

Most serious adverse events were reported as single events (20.8% for givosiran; 8.7% for placebo) and no deaths occurred. Overall, adverse events were common (89.6% for givosiran; 80.4% for placebo). Among seven patients with transaminase elevation levels three times greater than normal, only one discontinued givosiran dosing. Nearly all patients (93/94) elected to enroll in the open-label extension, Dr. Balwani pointed out.

Givosiran dosing led to the rapid and sustained lowering of aminolevulinic acid and porphobilinogen (a secondary trial endpoint), believed to be behind acute hepatic porphyria symptoms. Among secondary endpoints, Dr. Balwani concluded, “Givosiran represents a novel approach to the treatment of this rare liver disease, for which there is a considerable unmet need.”

Lanreotide Reduces Liver Growth in Autosomal Dominant Polycystic Kidney Disease: Data From a 120-Week Randomized Clinical Trial

• Joost P. H. Drenth, MD, Radboud University Medical Center, Nijmegen and Rotterdam, The Netherlands

Results from a subanalysis of the DIPAK 1 trial suggest that in patients with enlarged liver and/or kidneys, treatment with somatostatin analogs should be considered to prevent further disease progression.

In a press briefing, Dr. Joost Drenth said there is an unmet need for treatment of the hepatomegaly that results from polycystic liver disease, and which leads to symptomatic disease and reduced quality of life. Polycystic liver disease is the most frequent extra-renal manifestation of autosomal dominant polycystic kidney disease. The processes leading to hepatic cell proliferation and the fluid secretion that causes cysts to form and grow involve adenosine monophosphate. Somatostatin analogs, he explained, inhibit cyclic adenosine monophosphate production, reducing liver volume.

The goal of DIPAK 1 was to investigate the long-term effect of the somatostatin analog lanreotide on combined liver and kidney volume (LKV). Earlier trials of somatostatin analogs in polycystic liver disease have been limited by short follow-up and small sample sizes. Also, 6 to 12 months of treatment brings reductions of only 3 to 5% in combined LKV, with effects achieved in the first months and diminishing thereafter. DIPAK 1, an investigator-driven randomized, controlled, open-label trial with blinded endpoint analysis, included a subanalysis among 175 patients with autosomal dominant polycystic kidney disease, liver volume ≥2,000 mL, and estimated glomerular filtration rate (eGFR) of 30 to 60 mL/min/1.73 m². Included subjects received lanreotide 120 mg subcutaneously every four weeks or standard-of-care directed at reducing blood pressure. The primary outcome was change in height-adjusted liver volume (hTLV) from baseline to end of treatment at 120 weeks.

At 120 weeks, hTLV had decreased by 1.99% in the lanreotide group (95% CI, 1.56–2.48). Compared with standard-of-care, lanreotide reduced hTLV growth by 5.91% (95% CI, −9.18 to −2.63; P < 0.001), Dr. Drenth reported. Four months after the final lanreotide injection, a beneficial treatment effect—liver volume reduction—was still evident at 3.87% (95% CI, −7.55 to −0.18; P = 0.04). An even greater reduction in hTLKV of > 350 mL (7.18%) was shown for lanreotide patients compared with standard-of-care patients (95% CI, −10.25 to −4.12; P < 0.001).

“Long-term treatment with lanreotide resulted in a significant treatment effect of 5.91% on height-corrected total liver volume,” said Dr. Drenth. The > 350-mL reduction in combined liver and kidney volume, he added, is even more clinically important.