AASLD HIGHLIGHTS

Abstract Summaries From the 62nd Annual Meeting of the American Association for the Study of Liver Diseases

Efficacy of Long-Term Tenofovir Therapy in Patients with Chronic Hepatitis B Virus Infection

Marcellin and colleagues presented 5-year on-treatment virologic and paired histologic assessment data from Study 102 and Study 103. These multicenter, randomized, double-blind, phase III trials compared tenofovir disoproxil fumarate (Viread, Gilead Sciences) and adefovir dipivoxil (Hepsera, Gilead Sciences) in chronic hepatitis B virus (HBV)–infected patients with compensated liver disease who were hepatitis B e antigen (HBeAg)-negative (Study 102; n=375) or HBeAg-positive (Study 103; n=266). The majority of patients were treatment-naïve. In both studies, patients who were originally randomized to adefovir dipivoxil were rolled over to open-label tenofovir disoproxil fumarate (n=196) at Week 48, and patients who were originally randomized to tenofovir disoproxil fumarate continued on open-label treatment (n=389).

Of the 641 patients who were initially randomized and treated in these studies, 91% (n=585) entered the open-label extension phase of the trials. At Year 5, 76% (n=490) remained on study. Normalization of alanine aminotransferase (ALT) levels at Week 240 was achieved in 72% of patients in Study 102 and 50% of patients in Study 103. Tenofovir disoproxil fumarate was well tolerated in both studies; abdominal pain, nasopharyngitis, headache, influenza, back pain, and hypertension were among the most commonly reported adverse events. Across both studies, only 2.1% of patients who received tenofovir disoproxil fumarate for 5 years discontinued treatment due to an adverse event; 0.9% of patients experienced a confirmed increase in serum creatinine level of at least 0.5 mg/dL or a calculated creatinine clearance less than 50 mL/min. Resistance to tenofovir disoproxil fumarate over a 5-year treatment period was not detected. Overall histologic improvement was observed in 88% of the 331 patients who underwent biopsies before therapy and again at 5 years. Of the 94 patients who were cirrhotic at the start of therapy, 73% experienced regression of histologic cirrhosis at 5 years.

BE-LOW Study Demonstrates Efficacy of Entecavir Monotherapy

Lok and colleagues presented data from the open-label, multicenter, phase IIIb BE-LOW study, in which treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic HBV infection and compensated liver disease were randomized to receive either entecavir (Baraclude, Bristol-Myers Squibb) 0.5 mg once daily (n=182) or entecavir 0.5 mg plus tenofovir disoproxil fumarate 300 mg once daily (n=197) for 100 weeks.

Baseline characteristics were balanced across treatment arms; approximately 70% of patients were HBeAg-positive and approximately 30% were HBeAg-negative. Prior to Week 96, 6.5% (n=12) of patients in the entecavir monotherapy arm discontinued treatment, compared to 11.6% (n=23) of patients in the entecavir plus tenofovir arm. Patients who discontinued therapy prior to Week 96 were considered to be treatment failures. A comparable proportion of patients in both treatment arms achieved HBV DNA levels below 50 IU/mL at Week 96 (76.4% in the entecavir monotherapy arm vs 83.2% in the entecavir plus tenofovir arm; 95% confidence interval [CI], –1.0, 14.9; *P*=.0882). Among HBeAg-positive patients, HBV DNA levels below 50 IU/mL were achieved in 69.8% of the entecavir monotherapy arm versus 80.4% of the entecavir plus tenofovir arm (95% CI, 0.2, 21.0; *P*=.046). Fewer patients in the combination therapy arm experienced ALT normalization or HBeAg seroconversion compared to the entecavir monotherapy arm. Virologic breakthrough was similar in both arms (4% in the entecavir plus tenofovir arm vs 1% in the entecavir monotherapy arm). Both study arms had similar safety profiles, with serious adverse events reported in 6.6% of patients in the entecavir monotherapy arm and 7.1% of patients in the entecavir plus tenofovir arm.

Rifaximin Reduces the Incidence of *Clostridium difficile*–Associated Diarrhea and Improves Outcomes Among Patients with Cirrhosis

Zuchelli and coworkers sought to determine the incidence of *Clostridium difficile*–associated diarrhea (CDAD) in patients with cirrhosis who were receiving rifaximin (Xifaxan, Salix Pharmaceuticals) and/or lactulose and to establish outcomes and confounding factors among cirrhotic patients with CDAD. Charts of cirrhotic patients who were admitted to the investigators' tertiary care, university-affiliated hospital since January 2005 were retrospectively reviewed. A total of 144 patient charts were reviewed, including 69 with CDAD and 75 without CDAD. Patients with CDAD had an average Model for End-Stage Liver Disease score of 21. Among patients with CDAD, 26% (n=18) were receiving lactulose and 9% (n=6) were receiving rifaximin. Of the patients with-

out CDAD, 80% (n=60) were receiving lactulose and rifaximin and 20% (n=15) were receiving rifaximin alone. Although there were no significant differences among patients in regard to gender, age, etiology of cirrhosis, or proton pump inhibitor and antibiotic use, cirrhotic patients with CDAD were found to have significantly more chronic kidney disease ($P<.0001$), hypertension ($P<.03$), and cardiac disease (atrial fibrillation, congestive heart failure; $P<.014$) than cirrhotic patients without CDAD.

Among all patients, those treated at home with rifaximin had a significantly lower incidence of CDAD than those treated at home with lactulose ($P<.007$). The incidence of CDAD did not differ significantly among patients receiving rifaximin alone compared to rifaximin and lactulose combined. Cirrhotic patients with CDAD had a longer average length of hospitalization (35 days vs 13 days; $P<.00004$) and higher mortality rate (26% vs 13%; $P<.19$) compared to cirrhotic patients without CDAD. Of the 15 patients with CDAD who died, 33% (n=5) were receiving lactulose and 7% (n=1) were receiving rifaximin at the time of death. The study results suggest the need for future prospective studies to reconfirm that rifaximin is protective against *C. difficile* infection in cirrhotic patients.

Boceprevir-Based Therapy Effective in Some Prior Null Responders

The ongoing, multicenter, single-arm rollover PROVIDE study aims to evaluate the efficacy of boceprevir (Victrelis, Merck), peginterferon, and ribavirin in patients who previously failed to respond to peginterferon and ribavirin. The PROVIDE treatment regimen included boceprevir (800 mg 3 times daily), peginterferon α-2b (1.5 µg/kg weekly), and weight-based ribavirin (600–1,400 mg/day in 2 divided doses). Vierling and coworkers presented the results of a subset analysis from the PROVIDE study that assessed the efficacy of boceprevir, peginterferon, and ribavirin in 48 patients classified as prior null responders (defined as a reduction in HCV RNA level less than 2 $\log_{10}$ from baseline to Week 12 during previous peginterferon and ribavirin treatment). All patients in this subanalysis received 4 weeks of peginterferon and ribavirin, followed by boceprevir plus peginterferon and ribavirin for up to 44 weeks. The primary study endpoint was sustained virologic response (SVR), defined as an undetectable HCV RNA level at 24 weeks post-therapy. SVR was achieved in 16 of 42 evaluable patients (38%). Twenty of 43 patients (47%) achieved end-of-treatment responses, and relapses following end-of-treatment response were detected in 3 of 19 patients (16%). An association was detected between declines in HCV RNA level after the 4-week lead-in period and the likelihood of subsequent SVR. SVR was achieved in 50% of patients with a decline in HCV RNA level of least 1 $\log_{10}$ at Week 4, compared to an SVR rate of 34% among patients whose HCV RNA decline at Week 4 was less than 1 $\log_{10}$. Baseline characteristics associated with SVR were not assessed due to the small number of patients in this analysis. Nonetheless, these results suggest the effectiveness of a treatment regimen consisting of boceprevir, peginterferon, and ribavirin in a group of well-documented prior null responders.

Efficacy of Quad Regimen Containing VX-222 and Telaprevir for Treatment-Naïve Patients with HCV Genotype 1 Infection

The ZENITH trial is an ongoing, phase II study evaluating 12-week response-guided treatment with the HCV polymerase inhibitor VX-222 plus telaprevir, with or without peginterferon and/or ribavirin, in treatment-naïve patients with genotype 1 HCV infection. Nelson and coworkers presented a Week 24 interim analysis of the 59 patients who received the 4-drug regimen: VX-222 (100 mg [n=29] or 400 mg [n=30] twice daily), telaprevir (1,125 mg twice daily), peginterferon (180 µg/week), and ribavirin (1,000–1,200 mg/day). Patients received all 4 drugs for 12 weeks and were allowed to stop treatment at Week 12 if they achieved undetectable levels of HCV RNA at Weeks 2 and 8; patients whose HCV RNA levels were detectable at either Week 2 or Week 8 received additional peginterferon and ribavirin for a total of 24 weeks.

Among patients who received VX-222 at a dose of 400 mg, 50% (15 of 30) were eligible to stop treatment at Week 12; SVR was achieved in 93% (14 of 15) of those patients. Of the 15 patients receiving the 400-mg dose of VX-222 who were assigned to 24 weeks of treatment, 87% (n=13) had undetectable levels of HCV RNA at 12 weeks post-treatment. Among patients receiving the 100-mg dose of VX-222, 38% (11 of 29) were eligible to stop treatment at Week 12; 82% of those patients (9/11) attained SVR. Of the 18 patients in the 100-mg VX-222 arm who were assigned to 24 weeks of treatment, 83% (n=15) had undetectable levels of HCV RNA at 12 weeks post-treatment. An intent-to-treat analysis of all patients revealed undetectable HCV RNA levels at Week 24 in 90% of patients who received the 400-mg dose of VX-222 and 83% of patients who received the 100-mg dose of VX-222. A total of 3 patients experienced relapses: 2 in the 100-mg arm and 1 in the 400-mg arm. Fatigue (56%), nausea (49%), diarrhea (48%), anemia (37%), pruritus (34%), and rash (31%) were among the most commonly reported adverse events. Severe adverse events occurring in more than 1 patient included neutropenia (5.1%), hypomagnesemia (3.4%), and anemia (3.4%).