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A SPECIAL MEETING REVIEW EDITION

Highlights in the Treatment of Hepatitis C Virus From the 2014 Liver Meeting

A Review of Selected Presentations From the 2014 Liver Meeting November 7-11, 2014 • Boston, Massachusetts

Special Reporting on:

- Evaluation of Sofosbuvir and Simeprevir-Based Regimens in the TRIO Network
- Safety and Efficacy of New DAA-Based Therapy for Hepatitis C Post-Transplant: Interval Results From the HCV-TARGET Longitudinal, Observational Study
- Efficacy and Safety of MK-5172 and MK-8742 ± Ribavirin in Hepatitis C Genotype 1 Infected Patients With Cirrhosis or Previous Null Response: Final Results of the C-WORTHY Study (Parts A & B)
- Safety and Efficacy of Sofosbuvir in Combination With Simeprevir + Ribavirin in Patients With Genotype 1: Interim Results of a Prospective, Observational Study
- All-Oral Fixed-Dose Combination Therapy With Daclatasvir/Asunaprevir/BMS-791325, ± Ribavirin, for Patients With Chronic HCV Genotype 1 Infection and Compensated Cirrhosis: UNITY-2 Phase 3 SVR-12 Results
- TURQUOISE-II: Regimens of ABT-450/R/Ombitasvir and Dasabuvir With Ribavirin Achieve High SVR12 Rates in HCV Genotype 1–Infected Patients With Cirrhosis, Regardless of Baseline Characteristics

PLUS Meeting Abstract Summaries

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Evaluation of Sofosbuvir and Simeprevir-Based Regimens in the TRIO Network

Sofosbuvir is a nucleotide analog inhibitor of the hepatitis C virus (HCV) nonstructural 5B polymerase approved for treating chronic HCV infection in combination with ribavirin or pegylated interferon alfa (peginterferon) plus ribavirin.[1] Simeprevir is an HCV NS3/4A protease inhibitor approved for the treatment of HCV genotype 1 infection in combination with peginterferon and ribavirin or in combination with sofosbuvir.[2] Dr Douglas Dieterich presented in-depth results from TRIO, a study evaluating real-world outcomes from 12-week sofosbuvir regimens with or without simeprevir in a heterogeneous population of patients infected with HCV.[3] Electronic records pertaining to prescription refills were collected through specialty pharmacy groups within the United States. Of the 955 patients who received 12-week treatment regimens, 822 were available for the intent-to-treat (ITT) analysis, and 743 were available for the per protocol analysis. Specific 12-week treatment regimens consisted of sofosbuvir plus ribavirin; sofosbuvir, peginterferon, and ribavirin; and simeprevir plus sofosbuvir with or without ribavirin.

The 955 patients had a mean age of 57 years. Most patients (59%) were male, and 16% were African American. Thirty percent of patients had cirrhosis. Among the 43% of patients who had received prior treatment for their HCV infection, 20% had received a protease inhibitor. Most patients had baseline virology genotype 1a (48%), 1b (19%), or undifferentiated genotype 1 (6%), with the remainder having genotype 2 (22%), 3 (1%), 4 to 6 (1%), or mixed (1%). The median viral load was approximately 2 million IU/mL, and approximately 20% of patients had a viral load greater than 6 million IU/mL.

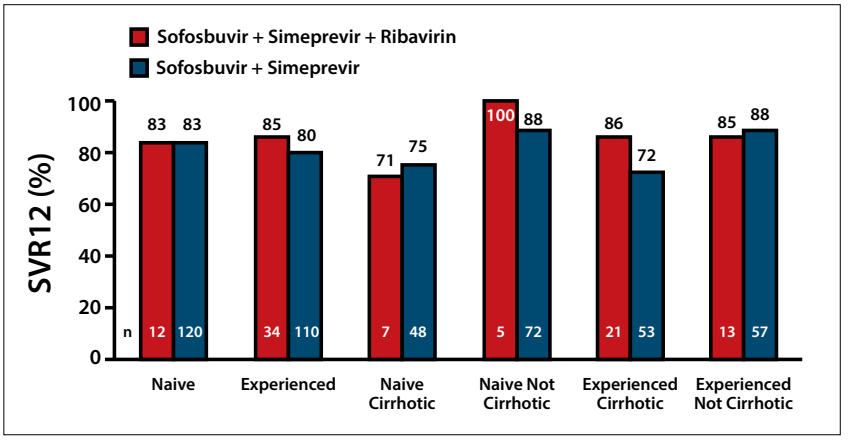

Figure 1. SVR12 rates among patients who received sofosbuvir and simeprevir, with or without ribavirin, in the TRIO study. Adapted from Dieterich D et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network [AASLD abstract 46]. *Hepatology*. 2014;60(5 suppl).[3]

The rates of sustained virologic response at 12 weeks (SVR12) were 79% for the ITT population and 88% for the per protocol population. Among the patients who received sofosbuvir, simeprevir, and ribavirin, SVR12 rates ranged from 71% in treatment-naive cirrhotic patients to 100% in treatment-naive patients without cirrhosis (Figure 1). For the ITT population, treatment with sofosbuvir, peginterferon, and ribavirin showed SVR12 rates of 72% for HCV genotype 1 and 67% for genotypes 4 to 6. Treatment with sofosbuvir plus ribavirin yielded SVR12

ABSTRACT SUMMARY Combination Sofosbuvir and Simeprevir Is Very Effective and Well Tolerated for the Treatment of Recurrent Hepatitis C After Liver Transplant

To address the need for more effective therapies in transplant recipients, a study of sofosbuvir and simeprevir was conducted (Abstract LB-8). All patients (N=18) had undergone transplant at least 3 months before the study start and had documented recurrence of HCV infection. Patients received treatment with sofosbuvir and simeprevir while continuing on standard immunosuppressant therapy. The mean age was 61 years, 78% of patients were male, and 3 patients had cirrhosis. Immunosuppressive therapy consisted of tacrolimus in 89% and cyclosporine in 11%. All patients completed 12 continuous weeks of therapy. No patients required adjustments to the immunosuppressant dose or experienced transplant rejection. The rapid virologic response rate was 72%, and all patients achieved an end-of-treatment response. Among the 15 patients with available HCV RNA at 4 weeks posttreatment, the SVR4 rate was 100%. For the 7 evaluable patients at 12 weeks posttreatment, the SVR12 rate was also 100%. The results from this small study support further investigation of new DAA therapies in the liver transplant population.

rates of 50% and 84% for genotypes 1 and 2, respectively, and treatment with sofosbuvir plus peginterferon, with or without ribavirin, yielded an SVR12 rate of 82% for genotype 1. Analysis of treatment-naive patients showed SVR12 rates of 81% for genotype 1, 81% for genotype 1a, and 82% for genotype 1b after treatment with sofosbuvir, peginterferon, and ribavirin. In the simeprevir-containing cohort, the SVR12 rates were 83% for genotype 1, 80% for genotype 1a, and 92% for genotype 1b (Figure 2).

ITT analysis of treatment-naive, genotype 1 patients based on cirrhotic status yielded SVR12 rates of 81% for both cirrhotic and noncirrhotic patients who received sofosbuvir, peginterferon, and ribavirin. The simeprevir-containing regimen yielded SVR12 rates of 88% for noncirrhotic and 75% for cirrhotic patients. Dr Dieterich emphasized that the cirrhotic patients had received the simeprevir combination treatment for only 12 weeks, whereas the prescribing information recommends 24 weeks of treatment for treatment-naive or treatment-experienced patients with cirrhosis.[2] For treatment-experienced patients in the ITT population, sofosbuvir, peginterferon, and ribavirin yielded SVR12 rates of 72%, 71%, and 70% for genotypes 1, 1a, and 1b, respectively. The simeprevir-containing treatment yielded SVR12 rates of 80% to 81% for the same genotypes. Patients without cirrhosis had SVR12 rates of 76% with sofosbuvir, peginterferon, and ribavirin and 87% with sofosbuvir and simeprevir, with or without ribavirin. In patients with cirrhosis, the SVR12 rates were 62% and 76%, respectively. Analyses based on the per protocol population showed similar trends, with SVR12 rates that were generally higher.

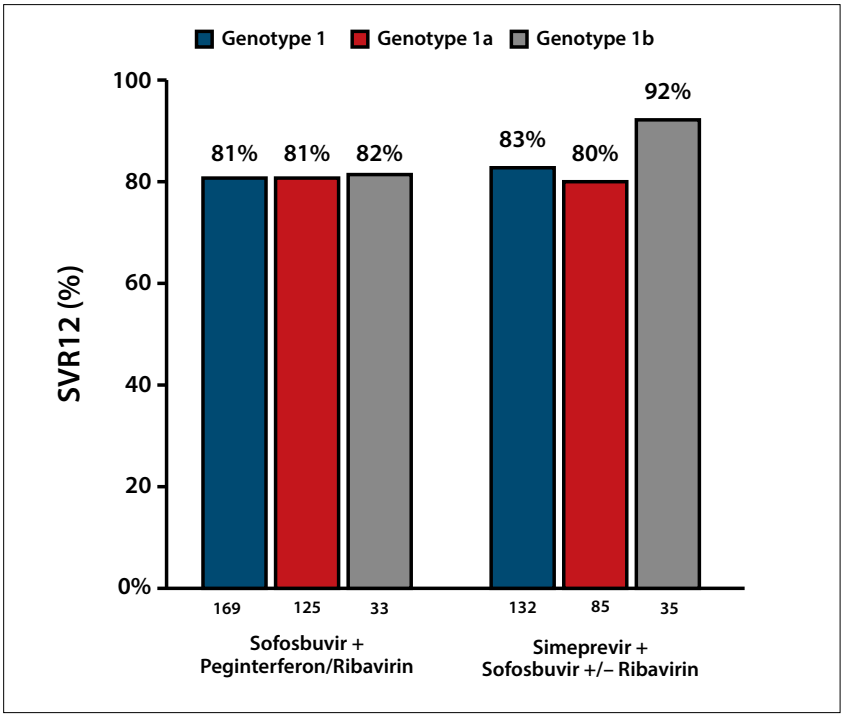

Figure 2. SVR12 rates according to genotype among treatment-naive patients in the TRIO study. Adapted from Dieterich D et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network [AASLD abstract 46]. *Hepatology*. 2014;60(5 suppl).[3]

Because prior treatment with a protease inhibitor can lead to protease resistant HCV variants, the influence of prior treatment regimens was also evaluated. No significant differences in SVR12 rates emerged for prior treatment with or without a protease inhibitor. After treatment with sofosbuvir,

ABSTRACT SUMMARY Safety and Efficacy of Sofosbuvir-Containing Regimens for Hepatitis C: Real-World Experience in a Diverse, Longitudinal Observational Cohort

Dr Donald Jensen presented preliminary results from 2063 patients who had started treatment in the ongoing HCV-TARGET study, a longitudinal, observational study investigating real-world use of sofosbuvir-containing regimens (Abstract 45). Treatment was administered based on the local standard of care and included sofosbuvir and simeprevir (n=784); sofosbuvir plus ribavirin (n=667); sofosbuvir plus pegylated interferon/ribavirin (n=384); and sofosbuvir, simeprevir, and ribavirin (n=228). Among the 164 evaluable HCV genotype 1 patients treated with sofosbuvir, pegylated interferon, and ribavirin, the SVR4 rate was 85%, with SVR4 rates of 70% and 90% for patients with or without cirrhosis, respectively. Of the 187 evaluable HCV genotype 2 patients treated with sofosbuvir plus ribavirin, the SVR4 rate was 90%, with SVR4 rates of 88% and 91% for cirrhotic and noncirrhotic patients, respectively. Minimally adjusted logistic regression analysis demonstrated 4 predictors of sustained response to sofosbuvir plus simeprevir with or without ribavirin: reduced baseline albumin level (OR, 2.3; 95% CI, 1.3-3.9), HCV genotype 1a (OR, 0.3; 95% CI, 0.1-0.9), prior liver decompensation (OR, 0.2; 95% CI, 0.1-0.3), and prior failure to triple therapy (OR, 0.4; 95% CI, 0.2-0.9). The treatment regimens were generally well tolerated. The most common AEs of any grade were fatigue, headache, and nausea.

peginterferon, and ribavirin, SVR12 rates were 73% in patients previously treated with a protease inhibitor vs 67% for those treated with peginterferon and ribavirin only. Similarly, the simeprevir-containing regimen yielded SVR12 rates of 82% in patients who had received a protease inhibitor and 80% in those who had not. No significant differences based on the type of prior treatment were observed for the per protocol population.

For patients with HCV genotype 2, treatment with sofosbuvir plus ribavirin yielded similar SVR12 rates for treatment-experienced (83%) and treatment-naive (85%) patients. Noncirrhotic patients who were treatment-naive or treatment-experienced had SVR12 rates of 89%. Poorer outcomes were observed in cirrhotic patients, with SVR12 rates of 70% for the entire group of 43 patients, 65% for the 23 treatment-naive patients, and 75% for the 20 treatment-experienced patients. Although the treatment-experienced cirrhotic patients showed a numerically superior SVR12 rate, this result contrasts with previous observations and was not statistically significant. For the genotype 2 patients treated per protocol, SVR12 rates were higher overall, and the entire population of genotype 2 patients yielded an SVR12 rate of 90%.

Forest plot analysis was used to identify factors that predict response to treatment. In the treatment-naive, HCV genotype 1 population of patients who received treatment with sofosbuvir, peginterferon, and ribavirin, no predictors of response emerged based on ITT or per protocol analysis. In the treatment-naive, HCV genotype 1 patients who received simeprevir-containing treatment, SVR12 was superior for noncirrhotic vs cirrhotic patients in the ITT population (88% vs 75%; *P*=.040) and the per protocol population (99% vs 85%; *P*=.008). Among treatment-experienced patients with HCV genotype 1, the sofosbuvir, peginterferon, and ribavirin regimen yielded a superior SVR12 rate in women compared with men for the ITT population (84% vs 65%; *P*=.026). The per protocol analysis also showed an improved likelihood of sustained response for women (95% vs 70%; *P*=.002), with an additional benefit observed for noncirrhotic vs cirrhotic patients (84% vs 65%, respectively; *P*=.018). In contrast, for treatment-experienced patients with HCV genotype 1 who received simeprevir, no predictors of response emerged in the ITT analysis. However, the per protocol analysis showed a superior outcome for women vs men (96% vs 81%; *P*=.017) and for noncirrhotic vs cirrhotic patients (94% vs 80%; *P*=.018). For the ITT population of treatment-naive patients with HCV genotype 2, only cirrhotic status emerged as a predictor of response for treatment with sofosbuvir and ribavirin (89% for noncirrhotic vs 70% for cirrhotic patients; *P*=.003). Dr Dieterich concluded that the SVR12 rates observed in this large, real-life population were similar to those observed in clinical trials, and that cirrhosis was the most important predictor of response to 12-week treatment regimens.

For the 3 regimens, treatment discontinuation rates due to adverse events (AEs) ranged from 0% to 2.0%. Specific AEs leading to discontinuation included general intolerance and rash, which were observed in the sofosbuvir plus peginterferon and ribavirin arm and in the simeprevir arm. Treatment discontinuation rates due to nonadherence ranged from 1.8% to 4.1%. One patient discontinued for financial reasons.

References

1. Sovaldi prescribing information. Foster City, CA: Gilead Sciences, Inc; 2014.
2. Olysio prescribing information. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP; 2014.
3. Dieterich D, Bacon B, Flamm S, et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network [AASLD abstract 46]. *Hepatology*. 2014;60(5 suppl).

ABSTRACT SUMMARY An Integrated Safety and Efficacy Analysis of >500 Patients With Compensated Cirrhosis Treated With Ledipasvir/Sofosbuvir With or Without Ribavirin

Sofosbuvir (400 mg) plus ledipasvir (90 mg) is available in a fixed-dose combination tablet to provide concomitant inhibition of nucleotide polymerase and NS5A protease. The current study identified 513 patients from phase 2 and 3 studies with HCV genotype 1 infection and compensated cirrhosis who received the 2-drug treatment with or without ribavirin for 12 or 24 weeks (Abstract 82). Patients received 1 of 4 regimens: ledipasvir plus sofosbuvir for 12 weeks (n=118); ledipasvir, sofosbuvir, and ribavirin for 12 weeks (n=204); ledipasvir and sofosbuvir for 24 weeks (n=133); or ledipasvir, sofosbuvir, and ribavirin for 24 weeks (n=58). In the pooled analysis, an SVR12 rate of 96% was achieved for the overall population, with SVR12 rates of 98% for the 161 treatment-naive patients and 95% for the 352 treatment-experienced patients. SVR12 rates were 95% and 98% for 12 vs 24 weeks of treatment, respectively. For the 12-week treatment cohort, the inclusion of ribavirin led to a nonsignificant increase in SVR12 from 90% to 96%. With 24 weeks of treatment, the SVR12 rate was 98% without ribavirin and 100% with ribavirin. Platelet count below 75,000/µL was significantly associated with reduced response to treatment, with this patient group showing an SVR12 rate of 84%. In comparison, SVR12 in the cohort of patients with platelet counts of at least 75,000/µL ranged from 95% to 99%. No new safety signals emerged. Use of ribavirin increased the rates of AEs.

Safety and Efficacy of New DAA-Based Therapy for Hepatitis C Post-Transplant: Interval Results From the HCV-TARGET Longitudinal, Observational Study

Dr Robert Brown presented data from liver transplant patients treated with direct-acting antiviral agents (DAAs) in the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET).[1] HCV-TARGET is a consortium of 38 academic and 15 community medical centers in the United States, Germany, and Canada. Patients receive treatment according to the local standard of care at each site. HCV infection following liver transplant remains problematic because reinfection of the liver graft is universal and represents a major source of graft loss. Therapeutic options have been limited for these patients, and no studies of sofosbuvir and simeprevir in patients who have undergone orthotopic liver transplant have been reported. Although studies involving other drugs have yielded encouraging results, they have not included the sickest patients and therefore may not reflect real-world settings.[2]

For the current analysis, data from sequentially enrolled patients treated with sofosbuvir-containing regimens were gathered from medical records within a common database, with demographic, clinical, AE, and virologic data collected through treatment and follow-up. Data from any post-transplant patients who received treatment with sofosbuvir were included. Patients had initiated treatment with the following regimens: sofosbuvir, peginterferon, and ribavirin (n=27); sofosbuvir and ribavirin (n=57); sofosbuvir and simeprevir (n=111); and sofosbuvir, simeprevir, and ribavirin (n=32). The overall population had a mean age of 60 years (range, 31-78 years), and nearly three-fourths were male. The majority of patients were treatment-experienced, but the proportion of treatment-experienced patients in each treatment arm ranged from 50.9% in the sofosbuvir plus ribavirin arm to 70.4% in the sofosbuvir, peginterferon, and ribavirin arm. The proportion of patients who had previously failed a protease inhibitor ranged from 0% in the sofosbuvir plus ribavirin arm to 21.0% in the sofosbuvir, peginterferon, and ribavirin arm. Among the 56% of patients with cirrhosis, 31.3% had a Model for End-

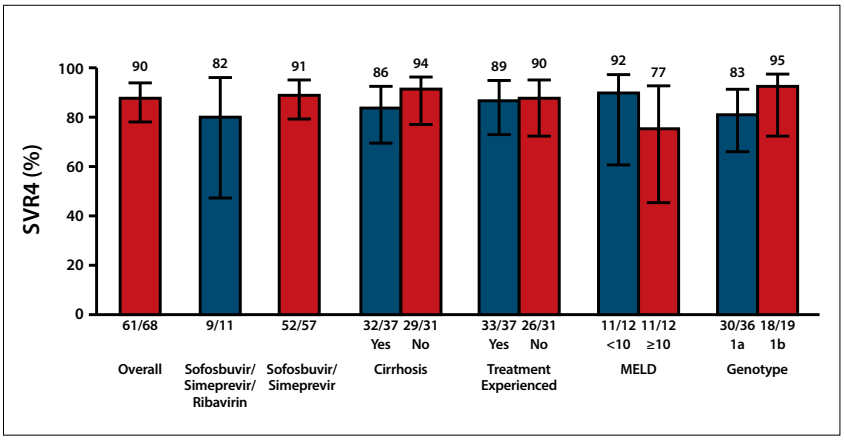

Figure 3. SVR4 rates in the HCV-TARGET study among patients who received sofosbuvir and simeprevir, with or without ribavirin. MELD, Model for End-Stage Liver Disease. Adapted from Brown RS et al. Safety and efficacy of new DAA-based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal, observational study [AASLD abstract LB-4]. *Hepatology*. 2014;60(5 suppl).[1]

ABSTRACT SUMMARY Renal Function in Liver Transplant Patients Treated for Recurrent Hepatitis C With Sofosbuvir and Simeprevir

Renal insufficiency is a common complication following liver transplant and is more likely in patients with HCV infection (Asfandiyar et al. *Transplant Proc*. 2006;38[10]:3643-3645). Combined with the accelerated progression to cirrhosis in liver transplant recipients with HCV infection, these complications underscore the need to find effective and safe treatment regimens. SVR rates in more robust populations have improved with the introduction of sofosbuvir and simeprevir; however, the combination has not been extensively examined in liver transplant recipients. The main metabolite of sofosbuvir is renally excreted, which highlights the need for safety and efficacy data in liver transplant patients. A prospective study was conducted in 26 liver transplant patients with recurrent HCV genotype 1 infection to determine the effect of 12 weeks of combined sofosbuvir and simeprevir treatment on renal function (Abstract LB-24). Renal function was evaluated by comparing the glomerular filtration rate at the start and the end of treatment. This rate was unchanged in 16 patients and improved in 7. It worsened in 3 patients, but the declines were considered unrelated to treatment.

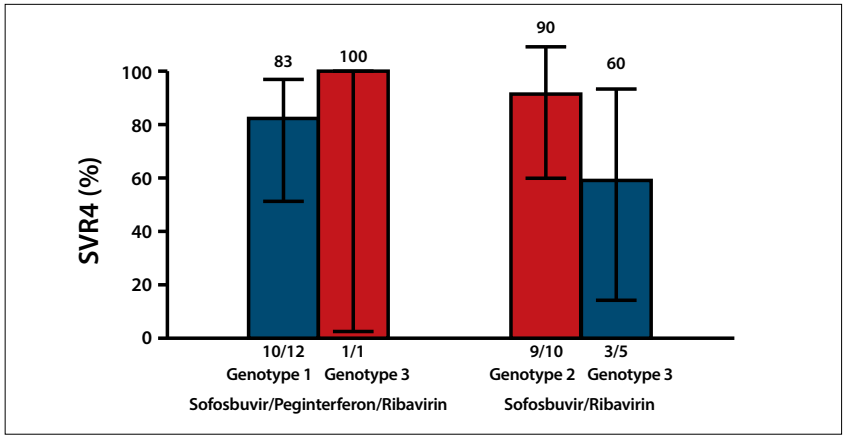

Figure 4. SVR4 according to genotype in the HCV-TARGET study. Adapted from Brown RS et al. Safety and efficacy of new DAA-based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal, observational study [AASLD abstract LB-4]. *Hepatology*. 2014;60(5 suppl).[1]

Stage Liver Disease (MELD) score of at least 10. Three-fourths of patients were receiving tacrolimus.

Of the 179 HCV genotype 1 patients, 61.8% were treated with sofosbuvir and simeprevir, 17.9% were treated with the same therapy plus ribavirin, 13.4% received sofosbuvir, peginterferon, and ribavirin, and 7.3% of patients received sofosbuvir plus ribavirin. All of the HCV genotype 2 patients (n=20) and 18 of the 19 genotype 3 patients were treated with sofosbuvir plus ribavirin. At the time of the analysis, 69.2% of patients had completed treatment in the study population. The proportions of patients still on treatment in the 4 arms were 11.1% in the sofosbuvir, peginterferon, and ribavirin arm; 42.1% in the sofosbuvir plus ribavirin arm; 25.2% in the sofosbuvir plus simeprevir arm; and 25.0% in the sofosbuvir, simeprevir, and ribavirin arm. The overall rate of premature discontinuation was 3.1%, with no premature discontinuations occurring in the sofosbuvir, peginterferon, and ribavirin arm.

SVR4 data were available for 68 HCV genotype 1 patients who were treated with sofosbuvir and simeprevir with or without ribavirin. Overall, 90% achieved SVR4 (Figure 3). Viral breakthrough was observed in 1.5%, relapse in 6%, and nonresponse in 3%. Cirrhotic patients had an SVR4 rate of 86% vs 94% in noncirrhotic patients. In the HCV genotype 1a vs 1b cohorts, SVR4 rates were 83% and 95%, respectively. Minimally adjusted logistic regression analysis yielded 4 nonsignificant predictors of reduced SVR4 in the same patient population: white race, cirrhosis, prior treatment, and prior decompensation. There were 2 nonsignificant positive predictors of SVR4: male sex and baseline hemoglobin. Analysis of selected subgroups showed numerically higher SVR4 rates in patients without cirrhosis, those with MELD scores below 10, and those with genotype 1a. However, the small patient numbers resulted in large confidence intervals for all of the subsets. Treatment with sofosbuvir, peginterferon, and ribavirin yielded SVR4 rates of 83% for HCV genotype 1 and 100% for HCV genotype 3 (Figure 4). Treatment with sofosbuvir and ribavirin yielded SVR4 rates of 90% for genotype 2 and 60% for genotype 3.

The majority of AEs were mild and manageable. At least 1 AE of any grade occurred in 82% of patients; the most common AEs were fatigue (30%), anemia (21%), and headache (17%). No serious AEs occurred in the sofosbuvir, peginterferon, and ribavirin arm compared with 3.0% in the sofosbuvir and ribavirin arm, 9.6% in the sofosbuvir and simeprevir arm, and 20.8% in the sofosbuvir, simeprevir, and ribavirin arm.

References

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2. Coilly A, Roche B, Duclos-Vallée JC, Samuel D. Management of HCV transplant patients with triple therapy. *Liver Int*. 2014;34(suppl 1):46-52.

ABSTRACT SUMMARY Ledipasvir/Sofosbuvir Fixed Dose Combination Is Safe and Efficacious in Cirrhotic Patients Who Have Previously Failed Protease-Inhibitor Based Triple Therapy

A double-blind study evaluated the combination of ledipasvir, sofosbuvir, and ribavirin in previously treated patients with HCV infection and compensated cirrhosis (Abstract LB-6). All patients had previously failed to achieve SVR following prior treatment with a protease inhibitor. Treatment consisted of either ledipasvir and sofosbuvir plus placebo for 24 weeks, or 12 weeks of placebo followed by 12 weeks of ledipasvir, sofosbuvir, and ribavirin. In each arm, 77 patients completed study treatment and 12 weeks of follow-up. The SVR12 rates were 96% for patients who received 12 weeks of treatment that included ribavirin and 97% for patients who received 24 weeks of treatment without ribavirin. Relapses were observed in 3 patients in the 12-week treatment arm and 2 patients in the 24-week treatment arm; they included 4 prior nonresponders. AEs of any grade occurred in 96% of patients in the 12-week arm and 87% of patients in the 24-week arm. Grade 3/4 AEs occurred in 8% and 13% of patients, respectively.

Efficacy and Safety of MK-5172 and MK-8742 ± Ribavirin in Hepatitis C Genotype 1 Infected Patients With Cirrhosis or Previous Null Response: Final Results of the C-WORTHY Study (Parts A & B)

The randomized, open-label, phase 2 C-WORTHY trial was designed to examine the efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in HCV genotype 1 infected patients.[1] Grazoprevir and elbasvir are highly potent inhibitors of the HCV NS3/4A protease and the NS5A replication complex, respectively. Part A of the C-WORTHY trial showed SVR12 rates of 89% to 100% in 65 treatment-naive, noncirrhotic, HCV genotype 1–infected patients.[2] The results supported expansion of the trial to part B, which included a more diverse patient population. Dr Eric Lawitz presented final results from the subset of treatment-naive, cirrhotic patients and prior null responders enrolled in part B of the study.[3,4]

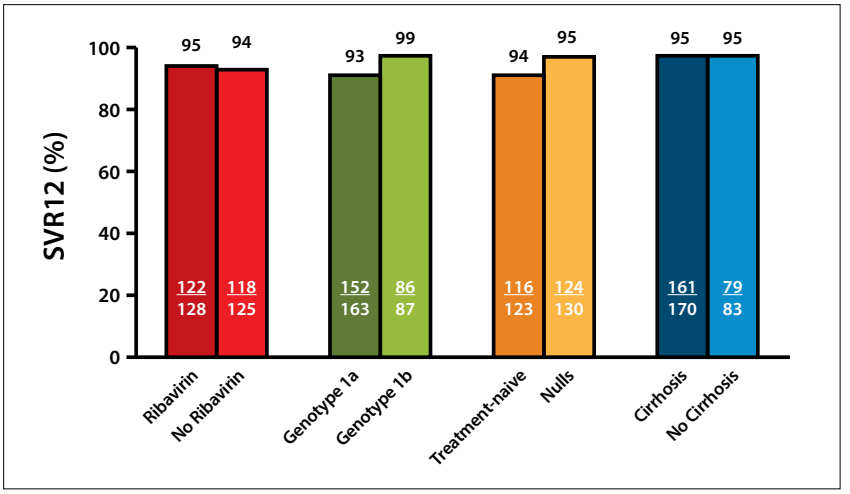

Figure 5. SVR12 rates among patients who received 12 or 18 weeks of grazoprevir and elbasvir, with or without ribavirin, in the C-WORTHY trial. Adapted from Lawitz E et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null response: final results of the C-WORTHY study (parts A & B) [AASLD abstract 196]. *Hepatology*. 2014;60(5 suppl).[3]

Patients enrolled in C-WORTHY received 12 or 18 weeks of grazoprevir (100 mg/day) plus elbasvir (50 mg/day) with or without ribavirin, which was dosed according to body weight. Dr Lawitz presented data from the 123 treatment-naive, cirrhotic patients and the 130 prior null responders treated in part B of the trial. Patients with human immunodeficiency virus (HIV) or hepatitis B virus were excluded from the 2 cohorts examined in this presentation. (Data from patients with concurrent HIV were presented separately.[5])

Patients were designated as either treatment-naive with cirrhosis or as prior null responders with or without cirrhosis. They were then further divided into treatment arms of 12 or 18 weeks' duration and regimens with ribavirin or without. In the treatment-naive, cirrhotic cohort, 60 patients received 12 weeks of treatment, including 31 patients with ribavirin and 29 patients without ribavirin. Among the 63 patients in the 18-week treatment regimen, 32 received ribavi-

ABSTRACT SUMMARY High Sustained Virologic Response Rates in Liver Transplant Recipients With Recurrent HCV Genotype 1 Infection ABT-450/R/Ombitasvir + Dasabuvir Plus Ribavirin

CORAL-1 is an ongoing, open-label, phase 2 study investigating the safety and efficacy of the combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir plus ribavirin in 34 adult liver transplant recipients with recurrent HCV genotype 1 infection and mild-to-moderate liver fibrosis (Kwo PY et al. *N Engl J Med*. [Epub ahead of print November 11, 2014]). Eligible patients had undergone liver transplantation at least 12 months before screening and were treatment-naive after transplantation. At baseline, the median time after transplant was 39.5 months. For immunosuppression, 85% of patients were receiving tacrolimus and 15% were receiving cyclosporine A. All patients achieved an end-of-treatment response and a rapid virologic response. SVR4, SVR12, and SVR24 were achieved by 97.1% of patients. One patient had a virologic relapse at posttreatment day 3 and resistance variants that were not present at baseline. The most common AEs of any grade were fatigue (50%), headache (44%), and cough (32%).

rin and 31 did not. For the prior null responders, 65 patients were assigned to 12 weeks of treatment (with ribavirin [n=32] or without [n=33]), and 65 patients were assigned to 18 weeks of treatment (with ribavirin [n=33] or without [n=32]).

High SVR12 rates were observed in all of the treatment cohorts. In the treatment-naive patients who received 12 weeks of treatment, ITT analysis yielded SVR12 rates of 90% with ribavirin and 97% without ribavirin. For patients who received 18 weeks of treatment, SVR12 rates were 97% with ribavirin vs 94% without. For the prior null responders, 12 weeks of treatment yielded SVR12 rates of 94% with ribavirin vs 91% without. Eighteen weeks of treatment yielded rates of 100% with ribavirin vs 97% without. Subgroup analysis did not reveal any significant predictors of treatment response, including treatment duration.

To provide larger patient numbers, the 12-week and 18-week treatment groups were pooled. SVR12 rates were 95% with ribavirin vs 94% without; 93% for HCV genotype 1a patients vs 99% for genotype 1b; 94% for treatment-naive patients vs 95% for null responders; and 95% for patients with or without cirrhosis (Figure 5). Among the subset of 25 patients who were prior null responders with cirrhosis, 12 weeks of treatment with or without ribavirin yielded an SVR12 rate of 92%. The virologic failure rate was 4% for the entire study population and consisted of 2 viral breakthroughs and 8 viral relapses. Three of the 10 virologic failures occurred in the ribavirin-containing arms.

Among the 7 serious AEs that occurred during the study, 6 were considered unrelated to the study treatment. Common treatment-emergent AEs occurring in 10% or more of patients in the entire study population included fatigue (26%), headache (23%), and asthenia (14%); all events were mild to moderate.

In a separate presentation, Dr Mark Sulkowski presented final results for the C-WORTHY patients with either HCV alone or both HIV and HCV.[5,6] Patients in the 2 groups were randomized separately to receive grazoprevir plus elbasvir with or without ribavirin. All patients were noncirrhotic and had HCV genotype 1. The trial enrolled 159 HCV monoinfected patients to receive 8 or 12 weeks of treatment and 59 patients with dual infection to receive 12 weeks of treatment. For the HCV monoinfected patients, ITT analysis yielded SVR12 rates of 80% for 8 weeks of treatment with ribavirin, 93% for 12 weeks of treatment with ribavirin, and 98% for 12 weeks of treatment without ribavirin. For the HCV/HIV coinfected patients, SVR12 rates were 97% with ribavirin vs 87% without ribavirin. In a combined analysis of all patients who received 12 weeks of treatment, SVR12 rates based on HCV genotype 1a vs 1b ranged from 92% to 95%. The rates of virologic failure were 4% for patients treated for 12 weeks and 17% for patients treated for 8 weeks. Three patients experienced a serious AE, and no patients discontinued treatment due to an AE. No patients died on-study.

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ABSTRACT SUMMARY Once Daily Sofosbuvir With GS-5816 for 8 Weeks With or Without Ribavirin in Patients With HCV Genotype 3 Without Cirrhosis Result in High Rates of SVR12: the ELECTRON2 Study

GS-5816 is an investigational drug that inhibits HCV NS5A protein. It has shown picomolar antiviral activity across HCV genotypes 1 to 6. The ELECTRON-2 study investigated GS-5816 combined with sofosbuvir for 8 weeks in 104 treatment-naive, noncirrhotic patients with HCV genotype 3 (Abstract 79). In addition to sofosbuvir (400 mg/day), treatment in the 4 arms consisted of GS-5816 at 25 mg/day or 100 mg/day and treatment with or without ribavirin. SVR12 rates for the GS-5816 (25 mg/day) treatment arms were 100% without ribavirin and 88% with ribavirin; in the latter arm, 2 patients relapsed and 1 withdrew due to an AE. Among patients receiving GS-5816 at a dosage of 100 mg/day, SVR12 rates were 96% without ribavirin and 100% with ribavirin. The regimens were generally well tolerated. Sofosbuvir (400 mg) and GS-5816 (100 mg) have been coformulated in a fixed-dose combination pill for phase 3 studies.

Safety and Efficacy of Sofosbuvir in Combination With Simeprevir + Ribavirin in Patients With Genotype 1: Interim Results of a Prospective, Observational Study

Dr Mark Sulkowski presented interim data on the safety and efficacy of sofosbuvir plus simeprevir with or without ribavirin from the HCV-TARGET trial in HCV genotype 1 patients.[1] Since January 2014, nearly 2000 patients had consented to participate in the study, and more than 1100 had begun study treatment. More than three-fourths of patients in the current analysis were treated with sofosbuvir and simeprevir without ribavirin. More than half of patients had cirrhosis (67%) or failed prior therapy (60%). Approximately two-thirds of patients had HCV genotype 1a. Treatment efficacy was evaluated by SVR4 rates that were adjusted for age, sex, and HCV genotype. For treatment with vs without ribavirin, similar adjusted SVR4 rates were observed for the overall population, in cirrhotic and noncirrhotic patients, in patients with HCV genotype 1a or genotype 1b, and in patients who were treatment-naive and those who had received prior treatment (Figure 6). Similarly, analysis based on combined HCV subtype and cirrhotic status demonstrated comparable outcomes for treatment with or without ribavirin.

Adequate baseline albumin levels emerged as a predictor of increased likelihood of response to treatment. Predictors of reduced likelihood of response to treatment included HCV genotype 1a, prior decompensation, and prior protease inhibitor failure. Among the 147 patients who achieved SVR4, 143 subsequently achieved SVR12, yielding a positive predictive value of 97.2%. SVR12 was not reported in any of the patients who did not achieve SVR4 (n=37).

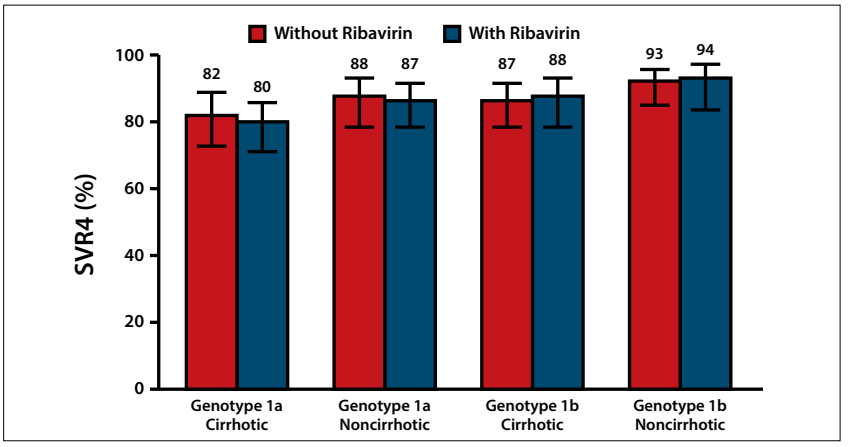

Figure 6. SVR4 rates according to genotype among patients who received sofosbuvir and simeprevir, with or without ribavirin, in an observational study. Adapted from Sulkowski MS et al. Safety and efficacy of sofosbuvir in combination with simeprevir + ribavirin in patients with genotype 1: interim results of a prospective, observational study [AASLD abstract 955]. *Hepatology*. 2014;60(5 suppl).[1]

For the safety population of 861 patients, the most common AEs of any grade included fatigue (27%), headache (18%), and nausea (13%). Serious AEs occurred in 5.1% of patients who had started treatment, including 4.5% of patients not receiving ribavirin and 6.9% of patients receiving ribavirin.

The authors concluded that this interim analysis showed that the combination of sofosbuvir plus simeprevir was well tolerated, with no unexpected AEs. SVR4 was achieved in 86% of patients treated without ribavirin and 87% of patients treated with it. A close correlation was observed between SVR4 and SVR12. After adjustment, SVR4 rates were similar for patients treated with or without ribavirin and were lower in patients with decompensated cirrhosis, HCV genotype 1a, and prior protease inhibitor triple failure.

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ABSTRACT SUMMARY Ledipasvir/Sofosbuvir With Ribavirin for the Treatment of HCV in Patients With Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

To expand the therapeutic options for patients with decompensated cirrhosis due to HCV, a study investigated the combination of ledipasvir (90 mg/day), sofosbuvir (400 mg/day), and ribavirin (initially 600 mg/day, then escalated) for 12 or 24 weeks (Abstract 239). The study included 108 adults with HCV genotype 1 or 4. Six patients were excluded from the analysis because they underwent liver transplantation during the study. SVR12 rates were 87% for 12 weeks of treatment and 89% for 24 weeks of treatment. The 12- and 24-week regimens were generally well tolerated, with 4 serious AEs attributed to study treatment and 3 patients discontinuing treatment due to an AE.

All-Oral Fixed-Dose Combination Therapy With Daclatasvir/Asunaprevir/BMS-791325, ± Ribavirin, for Patients With Chronic HCV Genotype 1 Infection and Compensated Cirrhosis: UNITY-2 Phase 3 SVR-12 Results

In phase 2 studies of treatment-naive patients, the combination of daclatasvir, asunaprevir, and beclabuvir (BMS-791325) achieved SVR12 in more than 92% of HCV genotype 1 and 100% of HCV genotype 4 patients.[1,2] The randomized, double-blind, phase 3 UNITY-2 study evaluated the same regimen as a fixed-dose combination pill with or without ribavirin in treatment-naive and -experienced patients with HCV genotype 1 infection and compensated cirrhosis.[3] Daclatasvir is a pangenotypic NS5A inhibitor. It is approved in Europe and Japan and is under regulatory review in the United States. Asunaprevir is an NS3 protease inhibitor. Beclabuvir is a nonnucleoside NS5B protease inhibitor with clinical data in genotypes 1 and 4.

The UNITY-2 study included 112 treatment-naive patients and 90 treatment-experienced patients. Both groups received the twice-daily fixed-dose combination of daclatasvir (30 mg), asunaprevir (200 mg), and beclabuvir (75 mg); patients were randomized to receive this combination with placebo or weight-based ribavirin for 12 weeks. The primary endpoint was SVR12.

For the treatment-naive cohort, ITT SVR12 rates were 93% without ribavirin and 98% with ribavirin (Figure 7). Twelve-week follow-up data, including SVR12, were missing for 1 patient in the latter group, accounting for the single failure to achieve SVR12. For the treatment-experienced cohort, SVR12 rates were 87% without ribavirin and 93% with ribavirin. In the treatment-naive cohort that did not receive ribavirin, SVR12 rates by HCV genotype were 90% for genotype 1a and 100% for genotype 1b. In the treatment-naive cohort that did receive ribavirin, these rates were 97% for genotype 1a and 100% for genotype 1b. In the treatment-experienced cohort, SVR12 rates for the treatment-experienced patients who did not receive ribavirin were 86% for genotype 1a and 90% for genotype 1b. In these patients, ribavirin increased SVR12 rates to 91% for genotype 1a and 100% for genotype 1b.

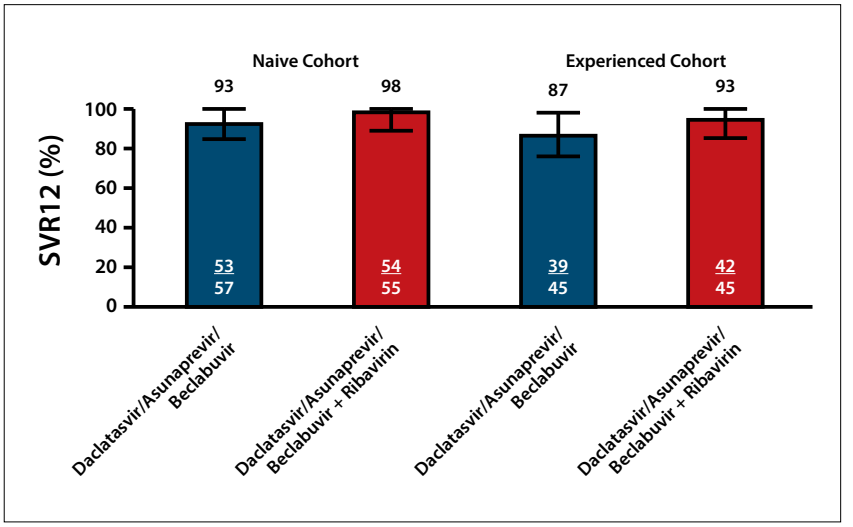

Figure 7. SVR12 rates among patients who received daclatasvir, asunaprevir, and beclabuvir, with or without ribavirin, in the UNITY-2 trial. Adapted from Muir A et al. All-oral fixed-dose combination therapy with daclatasvir/asunaprevir/BMS-791325, ± ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 phase 3 SVR-12 results [AASLD abstract LB-2]. *Hepatology*. 2014;60(5 suppl).[3]

ABSTRACT SUMMARY C-SWIFT: MK-5172 + MK-8742 + Sofosbuvir in Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection, With and Without Cirrhosis, for Durations of 4, 6, or 8 Weeks

The open-label, phase 2 C-SWIFT study was undertaken to evaluate the combination of 3 DAAs administered for 4, 6, or 8 weeks in treatment-naive patients with HCV genotype 1 (Abstract LB-33). The study enrolled 61 noncirrhotic and 41 cirrhotic patients. Patients with decompensated liver disease were excluded. Treatment consisted of grazoprevir (100 mg/day) and elbasvir (50 mg/day) in a fixed-dose combination plus sofosbuvir (400 mg/day). Interim SVR4/8 rates for the patients without cirrhosis after 4 or 6 weeks of treatment were 38.7% vs 86.7%, respectively. Interim SVR4/8 rates for cirrhotic patients after 6 or 8 weeks of treatment were 80.0% vs 94.7%. Two cirrhotic patients in the 8-week treatment arm discontinued for reasons other than virologic failure. Virologic relapse was observed in 19 patients in the 4-week treatment arm and 28 patients overall. The most common AEs were headache (4%), fatigue (2%), and nausea (2%).

On-treatment virologic failure was observed in 1 treatment-experienced patient in the placebo arm and in 2 treatment-experienced patients in the ribavirin arm. Relapses were observed in 4 treatment-naive patients in the placebo arm, 5 treatment-experienced patients in the placebo arm, and 1 treatment-experienced patient in the ribavirin-containing arm.

The 3-drug combination treatment was generally safe and well tolerated. Severe AEs were observed in 2% of patients in the pooled placebo cohort and 7% of patients in the pooled ribavirin cohort.

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TURQUOISE-II: Regimens of ABT-450/R/Ombitasvir and Dasabuvir With Ribavirin Achieve High SVR12 Rates in HCV Genotype 1–Infected Patients With Cirrhosis, Regardless of Baseline Characteristics

The phase 3 TURQUOISE-II study evaluated the safety and efficacy of an all-oral regimen of 3 DAAs in cirrhotic HCV genotype 1 patients.[1] Paritaprevir (ABT-450) inhibits HCV NS3/4A protease and is dosed with ritonavir so it will maintain high serum concentrations. Ombitasvir (ABT-333) inhibits HS5A, and dasabuvir (ABT-267) is a nonnucleoside inhibitor of the HS5B RNA polymerase. The study evenly randomized 380 patients to receive the 3-drug combination plus ribavirin for 12 or 24 weeks. Dr Michael Fried presented new data from the trial evaluating the impact of baseline demographic, viral, and disease characteristics on treatment outcomes.[2] Follow-up lasted for 48 weeks after the cessation of treatment. Enrolled patients could be treatment-naive or treatment-experienced; a key exclusion criterion, however, was prior therapy with a DAA. Patient characteristics were well balanced between the 2 treatment arms.

The overall SVR12 rates were 91.8% after 12 weeks of treatment and 96.5% after 24 weeks of treatment. Analysis of baseline demographic, clinical, and virologic factors failed to yield significant differences in SVR12 rates for most comparisons (Figure 8). SVR12 rates were higher with the 24-week regimen than the 12-week regimen in patients who were prior null responders (95.2% vs 86.7%), treatment-naive (95.9% vs 94.2%), genotype 1a (95.0% vs 88.6%), or genotype 1b (100% vs 98.5%).

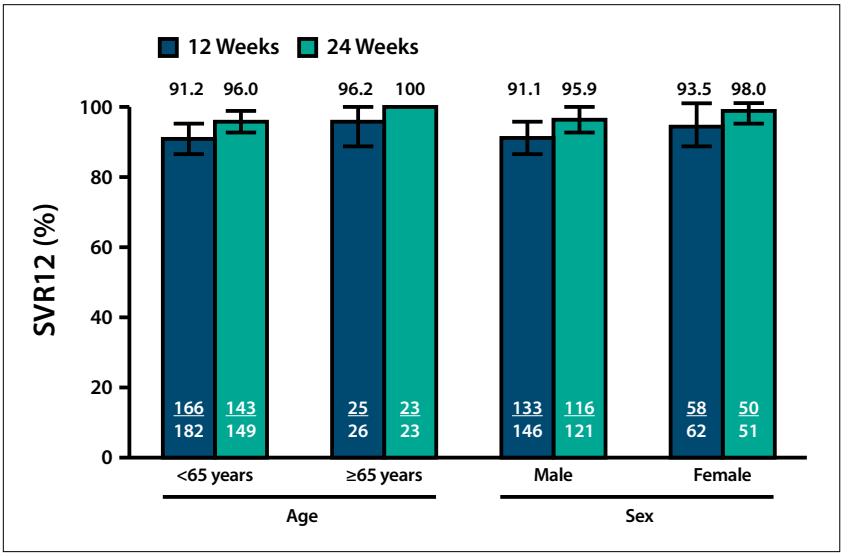

Figure 8. SVR12 rates with paritaprevir/ritonavir, ombitasvir, and dasabuvir in the TURQUOISE-II study. Adapted from Fried MW et al. TURQUOISE-II: regimens of ABT-450/R/ombitasvir and dasabuvir with ribavirin achieve high SVR12 rates in HCV genotype 1–infected patients with cirrhosis, regardless of baseline characteristics [AASLD abstract 81]. *Hepatology*. 2014;60(5 suppl).[2]

The study examined the demographic and disease characteristics of the patients who failed to achieve SVR12. In the 12-week treatment arm, 8% of patients failed to achieve SVR12, and 6% of patients relapsed. In the 24-week arm, 3.5% of patients failed to achieve SVR12, and 0.6% of patients relapsed. All but 1 of the patients who relapsed

ABSTRACT SUMMARY Retreatment of Patients Who Failed Prior Sofosbuvir-Based Regimens With All Oral Fixed-Dose Combination Ledipasvir/Sofosbuvir Plus Ribavirin for 12 Weeks

A study was undertaken to evaluate 12 weeks of ledipasvir, sofosbuvir, and ribavirin in patients who had previously failed sofosbuvir-based therapy (Abstract 235). Fifty-one patients with HCV genotype 1 who did not achieve an SVR12 in phase 2 or 3 clinical trials were enrolled. The patients' mean age was 54 years. There were more men than women in the study (61% vs 39%). Cirrhosis was reported in 29% of patients. The regimen yielded end-of-treatment response rates of 100%. The rates of SVR4, SVR12, and SVR24 were each 98%. Treatment was generally well tolerated. AEs occurred in 41 patients. The most common AEs of any grade were fatigue (26%), headache (22%), and diarrhea (14%). Grade 3/4 AEs occurred in 3 patients, and serious AEs occurred in 2 patients.

had HCV genotype 1a, and nearly all of the relapsing patients had HCV RNA levels of at least 800,000 IU/mL. Three factors emerged that were significantly associated with reduced rates of SVR12: *IL28B* genotype TT (*P*=.021), prior null response (*P*=.038), and HCV genotype 1a infection (*P*=.046).

The same 3-drug combination plus ribavirin was also evaluated in TURQUOISE-I, a phase 2/3 study of patients coinfected with HIV and HCV.[3] The study included patients with HCV genotype 1 and HIV coinfection (with or without Child-Pugh score A cirrhosis); patients who were treatment-naive; and patients who had previously received peginterferon or ribavirin. All patients were on a stable antiretroviral treatment regimen including atazanavir or raltegravir. The 3-drug combination plus ribavirin was administered as described above for 12 weeks (n=31) or 24 weeks (n=32). The primary endpoint was SVR12.

After 12 or 24 weeks of treatment, the end-of-treatment response rates were 96.8% and 96.9%, respectively. All patients in both arms achieved a rapid virologic response at week 4 after treatment. The SVR12 rate was 93.5% for the 12-week treatment arm. Sustained response data were available for 20 patients in the 24-week treatment arm; the SVR12 rate was 95.0%. No serious AEs occurred. The most common treatment-emergent AEs were fatigue, insomnia, and nausea.

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Highlights in the Treatment of Hepatitis C Virus From the 2014 Liver Meeting

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Presentations on hepatitis C virus (HCV) from the 2014 Liver Meeting offered a wealth of new data with important clinical implications. Studies focused on the direct-acting antiviral agents, with or without ribavirin, at different durations and in various patient populations, such as those with decompensated cirrhosis and genotype 3.

Real-World Data

The TRIO network was designed to capture pharmacy-based data on patient prescriptions and clinical outcomes.[1] Dr Douglas Dietrich reported results for more than 700 patients who have been included in the study thus far. The analysis included 3 different subgroups: genotype 1 patients who received peginterferon, ribavirin, and sofosbuvir, a regimen approved in December 2013; genotype 2 patients who received sofosbuvir and ribavirin; and genotype 1 patients who received simeprevir and sofosbuvir, with or without ribavirin (used in an off-label fashion). In late 2013, simeprevir and sofosbuvir were each approved by the US Food and Drug Administration (FDA) for use with interferon and ribavirin. Although simeprevir and sofosbuvir had not been approved for use together until November 2014, there is an enormous amount of real-world experience with this combination, which provides a direct-acting antiviral approach without interferon. The randomized COSMOS study evaluated simeprevir and sofosbuvir, with or without ribavirin, in 167 patients with chronic HCV genotype 1 who had previously not responded to peginterferon and ribavirin or were treatment-naive.[2] The study showed that the combination of simeprevir and sofosbuvir was effective and well tolerated. The rates of sustained virologic response at 12 weeks (SVR12) by intention-to-treat analysis were 92% in previous nonresponders with METAVIR scores of F0 to F2, and 94% in previous nonresponders and treatment-naive patients with METAVIR scores of F3 to F4.

In the TRIO study, the overall SVR12 rates for the 12-week regimens were 79% for the intent-to-treat population and 88% for the per protocol population. These SVR rates are somewhat lower but broadly comparable to those reported in clinical trials, demonstrating high rates of efficacy. In the intent-to-treat population receiving simeprevir plus sofosbuvir (without or with ribavirin), SVR12 rates among treatment-naive patients by intent-to-treat analysis were 80% for genotype 1a and 92% for genotype 1b, and 88% in noncirrhotics vs 75% in cirrhotics. In treatment-experienced patients, SVR12 rates with simeprevir and sofosbuvir (without or with ribavirin), were 81% in genotype 1a, 80% in genotype 1b, and 87% vs 76% in noncirrhotics vs cirrhotics. SVR12 rates with sofosbuvir, peginterferon, and ribavirin were 81% for HCV genotype 1 treatment-naive patients and 72% for treatment-experienced patients. Interestingly, patients with prior exposure to protease inhibitors combined with peginterferon and ribavirin fared just as well as patients who failed peginterferon and ribavirin alone. Response rates were higher in per protocol analyses.

Among the treatment-experienced patients, genotype 1 subtype did not have an impact on SVR12 rates. The sofosbuvir, peginterferon, and ribavirin regimen yielded similar SVR12 rates of approximately 70% in prior treatment-experienced patients, whether they had received a protease inhibitor or not, thereby justifying retroactively the FDA approval in late 2013 of this regimen in prior peginterferon/ribavirin failures even though such patients had not been studied in the phase 3 program. Finally, sofosbuvir plus ribavirin achieved an SVR12 rate of 84% in genotype 2. The difference between SVR12 with 12 weeks of therapy in noncirrhotics (89% regardless of treatment history) vs cirrhotics (65% in treatment-naive and 75% in treatment-experienced), reinforces the recommendations in guidelines from both the American Association for the Study of Liver Diseases/Infectious Diseases Society of America and the European Association for the Study of the Liver stating

that a longer duration of treatment (16 weeks or even 20 weeks) be considered in patients with cirrhosis and genotype 2, although previous concerns had been limited to treatment-experienced cirrhotics.

Phase 1 of the TARGET project collected real-world data on telaprevir and boceprevir.[3] Phase 2 included patients who had received sofosbuvir-based therapies. The current analysis reported on 2063 patients who had started treatment (although data are lacking for some).

Among the patients with cirrhosis, up to a quarter in the simeprevir/sofosbuvir group had experienced an episode of decompensated cirrhosis. Approximately half of the patients were treatment-naive, and approximately 10% to 20% had a history of protease-inhibitor failure. Among the genotype 1 patients who had received simeprevir and sofosbuvir, approximately 10% had a history of liver transplant and/or liver cancer.

The SVR4 rate for genotype 1 patients who received sofosbuvir, peginterferon, and ribavirin was 85% overall: 90% in the noncirrhotics and 70% in the cirrhotics. This outcome tracks well with results from the open-label, phase 3 NEUTRINO study,[4] which studied this regimen at 12 weeks' duration.

Among the patients who received sofosbuvir and simeprevir, overall SVR4 was 89%: 86% in genotype 1a, 95% in genotype 1b, 92% in noncirrhotics, and 87% in cirrhotics. It is notable that the SVR4 rates were somewhat lower in the genotype 1a patients, but the data are insufficient to determine whether this difference can be attributed to the so-called Q80K polymorphism, which could not be evaluated because of the infrequency with which the participating centers tested for it. Among the genotype 2 patients who received sofosbuvir and ribavirin for 12 weeks, 90% achieved an SVR4, a rate that was barely lower than that in pivotal trials.[4,5] SVR4 was achieved by 91% of the noncirrhotics and 88% of the cirrhotics, although reportedly some of the cirrhotics had received 16 weeks of therapy. As with the TRIO study, these results warrant consideration of therapy beyond 12 weeks of duration in patients with genotype 2 and cirrhosis.

There were 2 analyses of statistically adjusted SVR rates in TARGET in patients with genotype 1 who received sofosbuvir and simeprevir without or with ribavirin. SVR4 rates were somewhat lower in patients with genotype 1a than genotype 1b, and for both subtypes, they were lower in patients with cirrhosis. As with TRIO, ribavirin did not appear to have a significant effect on SVR rates. A minimally adjusted logistic regression analysis showed that patients with prior exposure to protease inhibitors had lower SVR4 rates than the overall population (81% vs 89%), though many regarded the SVR4 rates in the protease inhibitor–exposed patients as surprisingly high. This finding confirmed the concept that variants that are resistant to protease inhibitors and arise during previous exposure may adversely impact response to new treatment. Admittedly, the extent of the impact of prior treatment with protease inhibitors shown in this study was less than expected. Nevertheless, a protease-inhibitor–based regimen may not be optimal as a first-line retreatment regimen in patients who have previously received protease inhibitors.

The Role of Ribavirin

Dr Marc Bourlière presented 2 studies suggesting that ribavirin may still have a role in the management of HCV. One study evaluated ledipasvir and sofosbuvir with or without ribavirin in more than 500 patients with compensated cirrhosis.[6] This study was an integrated analysis of data from phase 2, phase 3, and post–phase 3 studies. The results were provocative and contrasted with the previous ION-2 study in treatment-experienced cirrhotics. ION-2 had suggested that 24 weeks of therapy were needed to optimize SVR rates, and that ribavirin conferred no advantage.[7] In the integrated analysis by Dr Bourlière, patients who received ledipasvir and sofosbuvir for 12 weeks had an SVR12 of 90%, which increased to 96% with ribavirin. With 24 weeks of ledipasvir and sofosbuvir, the SVR12 rate was 98% without ribavirin and 100% with ribavirin. In treatment-experienced cirrhotic patients, the ledipasvir/sofosbuvir combination tablet (without ribavirin) is indicated for 24 weeks. The data from Dr Bourlière suggested that 12 weeks of ledipasvir/sofosbuvir with ribavirin could achieve similar benefits with substantial cost savings as compared with 24 weeks of treatment.

Dr Bourlière also presented results from the placebo-controlled SIRIUS study, which evaluated ledipasvir and sofosbuvir, with or without ribavirin, in genotype 1 patients with compensated cirrhosis who had failed prior therapy with a protease inhibitor.[8] Patients (n=155) were randomized to receive placebo for 12 weeks, followed by ledipasvir and sofosbuvir combined with ribavirin for 12 weeks; or ledipasvir and sofosbuvir plus placebo with ribavirin for 24 weeks. No patients received only 12 weeks of ledipasvir and sofosbuvir without ribavirin. The SVR12 rates were 96% in the 12-week group that received ribavirin and 97% in the 24-week group that did not receive ribavirin. Safety and tolerability of the regimen were very good.

This study, the results of which were incorporated into the integrated analysis by Bourlière and colleagues described above, has attracted a great deal of attention because in the United States, a regimen of ledipasvir and sofosbuvir without ribavirin is currently approved for treatment-experienced cirrhotics, whether they received protease inhibitors or not. This approval was based on the phase 3 ION-2 study, which strongly suggested that 24 weeks of ledipasvir and sofosbuvir were better than 12 weeks in the 20% of treatment-experienced genotype 1 patients who had cirrhosis.[7] The study by Dr Bourlière, which included a larger number of patients with cirrhosis, suggested that a

regimen incorporating the addition of ribavirin to 12 weeks of ledipasvir and sofosbuvir was equivalent in efficacy to 24 weeks of ledipasvir and sofosbuvir without ribavirin.[8] This finding was unexpected in light of the ION-2 trial.

Research has failed to explain how ribavirin augments the action of interferon in HCV or how it works in combination with direct-acting antivirals. Physicians might prefer not to use ribavirin because of its tolerability profile, which can include adverse events such as fatigue, insomnia, and hemoglobin reductions. However, with the cost pressures involved with the use of the new direct-acting antiviral regimens, it remains open to question whether there will be a shift toward the use of the 12-week regimen with ribavirin to spare the expense of the extra 12 weeks of ledipasvir and sofosbuvir.

Patients With Decompensated Cirrhosis

One of the most impactful studies, presented by Dr Steven Flamm, provided preliminary but mature results from an efficacy and safety analysis of ledipasvir and sofosbuvir plus ribavirin for the treatment of HCV in decompensated cirrhotics with genotype 1 or 4.[9] Enrolled patients had Child-Pugh class B and C, populations that are currently excluded from the treatment indication for this regimen because they were not included in the phase 3 development program.

Patients could be treatment-naive or treatment-experienced. They were randomized to 12 weeks or 24 weeks of therapy. Data were available for 99 patients. Overall SVR12 rates were 87% in the 12-week group and 89% in the 24-week group. In the Child-Pugh B patients, SVR12 rates were 87% in the 12-week group and 89% in the 24-week group. In the Child-Pugh C patients, the rates were 86% and 90%, respectively. Ribavirin was associated with reductions in hemoglobin levels, but they were generally well tolerated. No novel side effects emerged in this fragile population.

There are several remarkable findings from this data set. The SVR12 rates were unexpectedly high among this group of patients, who can be considered the neediest and who were expected to be the most refractory to these new therapies. The SVR12 rates were essentially identical between the 12- and 24-week groups, a surprising finding because it had been thought that this population might require a longer period of treatment to prevent relapse. The majority of patients experienced an improvement in their Model for End-Stage Liver Disease score from 1 to 5 points (or even more when pretreatment scores were compared with scores at follow-up week 4). A virologic response was associated with improvements in bilirubin, albumin, MELD, and Child-Pugh scores in patients with class B and class C.

The results of this study are a mandate to offer therapy to HCV patients with decompensated cirrhosis, particularly in light of the improvement in liver function accompanying viral clearance. The only caveat to this study is that these patients were decompensated but without liver failure or critical illness; the question remains whether some cirrhotics are too advanced or decompensated to achieve clinical or laboratory improvement.

Duration of Therapy

The revolution in HCV therapy encompasses 2 advancements: the introduction of regimens consisting of well-tolerated oral antiviral agents without interferon—and frequently without ribavirin—that are associated with very high SVR rates; and shorter durations of therapy than were possible with interferon-based therapy, particularly in the era before sofosbuvir. One treatment regimen that the package insert for ledipasvir and sofosbuvir stipulates "can be considered" consists of 8 weeks of ledipasvir and sofosbuvir without ribavirin in the treatment-naive, genotype 1, noncirrhotic population; this regimen is associated with high rates of sustained response in patients with a baseline viral level below 6,000,000 IU/mL.[10]

The capacity to treat some genotype 1 patients with 8 weeks of therapy raised the question of whether efficacy could be maintained with even shorter durations of therapy, bearing in mind that not losing any sustained response candidates is a top priority. It has been theorized that even more potent regimens, perhaps incorporating additional agents, might be able to induce sustained response with treatment durations as short as 4 or 6 weeks. This speculation was fueled by the SYNERGY study, which was conducted by the National Institutes of Health and reported last spring.[11] It showed that nearly all treatment-naive, noncirrhotic patients who received a triple combination of a protease inhibitor, an NS5A inhibitor, and a nucleotide polymerase inhibitor (sofosbuvir) attained SVR12 after 6 weeks of therapy. (Although cirrhotic patients were included in the study, they were excluded from the 6-week analysis.) These results raised the idea that perhaps 4 weeks of an equally or more potent regimen might be sufficient. A 4-week regimen would allow 1 prescription without any refills; because some patients fail to obtain refills, this regimen would be a leap forward.

To this end, the C-SWIFT study evaluated 4, 6, and 8 weeks of the protease inhibitor grazoprevir (MK-5172) and the NS5A inhibitor elbasvir (MK-8742), plus sofosbuvir, in treatment-naive, genotype 1 patients with or without cirrhosis.[12] Noncirrhotic, treatment-naive, genotype 1 patients received 4 or 6 weeks of this regimen, and cirrhotic patients received 6 or 8 weeks. The study provided rates of SVR4 and SVR8, which were 39% with 4 weeks of therapy in noncirrhotics, 87% with 6 weeks of therapy in noncirrhotics, 80% with 6 weeks of therapy in cirrhotics, and 95% with 8 weeks of therapy in cirrhotics. In general, a high viral load and non-CC IL28B genotype appeared to be predictive of failure with the 4-week duration of therapy. The regimen was well tolerated. Fatigue was reported in 3% and nausea in 10%. There were no reports

of anemia, bilirubin elevations above 5 times the baseline level, or aspartate transaminase or alanine transaminase elevations above 5 times the upper limit of normal.

Although it is impressive that nearly 40% of patients can be cured with 4 weeks of treatment, the chief finding of the study was the relatively low rate of SVR in the patients who received this "ultra-short" regimen. Grazoprevir is a potent protease inhibitor with a more robust barrier to resistance than the first-generation protease inhibitors. Elbasvir is a more advanced NS5A inhibitor. The main hypothesis was that 4 weeks might be a sufficient duration for these 3 drugs. However, this hypothesis was not supported by the results. Another surprise was the suboptimal rates of SVR with the 6-week regimen, whether in cirrhotic or noncirrhotic patients. In contrast, SVR12 rates were 95% to 100% in the SYNERGY trial, which evaluated a similar but certainly not more potent regimen of fixed-dose ledipasvir/sofosbuvir alone or in combination with either GS-9669 (a nonnucleoside NS5B inhibitor) or GS-9451 (a NS3/4A protease inhibitor).[11] The results of C-SWIFT suggested that, even with a very potent triple regimen containing a nucleotide polymerase inhibitor, 8 weeks might be the threshold for effective therapy.[12] The results provide a signal that no matter how profoundly the virus is suppressed with multiple agents, there may be a finite limit to the time required to eliminate all of the intracellular virus to optimize the chance that a relapse does not occur. Other studies are currently evaluating the 4- and 6-week durations, and these results will be needed before conclusions can be made regarding duration of therapy.

Patients With HCV Genotype 3

The phase 3, open-label ALLY-3 trial evaluated an all-oral, 12-week combination treatment with daclatasvir, an NS5A inhibitor, plus sofosbuvir in patients with HCV genotype 3 infection, with or without cirrhosis.[13] Most direct-acting antiviral therapies were developed to treat genotype 1. Genotype 3 has emerged as the most challenging genotype, as shown in a trial of the recently approved regimen of sofosbuvir and ribavirin, in which these patients experienced excessive relapse rates with 12 weeks of therapy and required a longer duration of therapy to reach SVR as compared with genotype 2 patients.[4,5,14] There is a need to develop combinations of oral antivirals, with or without ribavirin, that can optimize SVR rates in genotype 3 patients, as has been done for genotype 1 patients. Daclatasvir is an NS5A inhibitor referred to as a pan-genotypic drug; in vitro, it shows activity against genotype 3 (although to a somewhat lesser extent than the other genotypes).

In ALLY-3, a daily regimen of daclatasvir and sofosbuvir was administered for 12 weeks. SVR12 was 90% in treatment-naive patients (n=101) and 86% in treatment-experienced patients (n=51).[13] Overall, SVR12 was 96% in noncirrhotic patients, but only 63% in cirrhotic patients. This difference was seen in both treatment-naive patients (97% vs 58%, respectively) and treatment-experienced patients (94% vs 69%, respectively).

This study shows that many genotype 3 patients can achieve high SVR12 rates with 12 weeks of a ribavirin-free regimen with an NS5A inhibitor and a nucleotide polymerase inhibitor. Rates were substantially lower in patients with cirrhosis; surprisingly, in light of earlier data, the lower rate was seen in treatment-naive as well as treatment-experienced patients. The low rates of response among cirrhotic patients raise speculation regarding whether improvement would be seen with the addition of ribavirin and/or a longer duration of therapy, perhaps 24 weeks.

In the United States, approximately 10% of patients are genotype 3.[15] Genotype 3 is somewhat more common in Europe, and very common in other parts of the world, such as Southern Asia (eg, Pakistan).[16,17] The daclatasvir/sofosbuvir regimen could be considered attractive for these patients. However, the SVR rates were lower than those achieved with 24 weeks of sofosbuvir and ribavirin in the VALENCE trial, which showed SVR12 rates of 90% in treatment-naive cirrhotic patients, 87% in treatment-experienced noncirrhotic patients, and 62% in treatment-experienced cirrhotic patients.[14]

GS-5816 is a new pan-genotypic NS5A inhibitor that is highly effective against genotype 3 in vitro. Early studies have shown promising results.[18] In the ELECTRON-2 trial, 104 treatment-naive, noncirrhotic patients with HCV genotype 3 received either 25 mg or 100 mg of GS-5816 and a standard dose of 400 mg of sofosbuvir with or without ribavirin for 8 weeks.[19] Among the patients who received the lower dose of GS-5816, the SVR12 rates were 100% without ribavirin and 88% with ribavirin. In the high-dose (NS5A inhibitor) arm, SVR12 was 100% without ribavirin and 96% with it. The safety profile was very favorable. Two patients relapsed, both of whom received the lower dose. This regimen appears promising for genotype 3 patients, and this study strongly suggested that ribavirin was not necessary.

Regimens for Retreatment

Dr David Wyles presented results from a study evaluating retreatment of 51 patients who had failed prior sofosbuvir-based treatments with an oral regimen of ledipasvir and sofosbuvir plus ribavirin for 12 weeks.[20] The hypothesis underlying this study is based on the high barrier to resistance of sofosbuvir; the mutation that confers resistance to sofosbuvir, S282T, is found only very rarely in viral samples from relapsed patients in sofosbuvir-based studies. Therefore, it was thought that retreatment with sofosbuvir, perhaps in combination with other antiviral agents, might be effective in patients who relapse after initial treatment. In nearly all HCV patients who receive sofosbuvir, the virus becomes undetectable during treatment. Essentially,

the only pathway to failure is in the form of posttreatment relapse.

This study's hypothesis was validated by the SVR12 data, which was 98% at the 4-week time point (with only 1 relapse). As of yet, the US Food and Drug Administration has not approved any regimens for the treatment of patients who have previously failed sofosbuvir. This study is the largest thus far to suggest that retreatment regimens containing sofosbuvir may be highly effective.

Regimens With Novel Therapies

The phase 3 UNITY-1 and UNITY-2 trials evaluated a 12-week regimen of daclatasvir, an NS5A inhibitor; asunaprevir, a protease inhibitor; and BMS-791325, a nonnucleotide polymerase inhibitor, with or without ribavirin, in patients with genotype 1 HCV.[21,22] The patients in UNITY-1 did not have cirrhosis, and ribavirin was not part of the regimen. In UNITY-2, the patients had compensated cirrhosis, and half received ribavirin.

In UNITY-1, the overall SVR12 rates were 92% in the treatment-naive patients (n=312) and 89% in the treatment-experienced patients (n=103).[21] Genotype 1b patients did somewhat better than the 1a patients. Virologic breakthrough was observed in 2% of patients. At the end of treatment, 1% to 2% of patients had detectable virus, and 5% to 6% relapsed. Alanine transaminase elevations resulted in discontinuation in 2 patients, 1 of whom had a concomitant increase in bilirubin to 2.3 mg/dL. In both patients, the alanine transaminase elevations resolved after treatment was stopped.

In UNITY-2, treatment-naive patients achieved SVR12 rates of 98% with ribavirin vs 93% without it.[22] Among the treatment-experienced patients, SVR12 was 93% with ribavirin vs 87% without it. In patients with genotype 1a, ribavirin appeared to confer a benefit. In contrast, ribavirin did not appear to impact outcome in patients with genotype 1b. These findings are consistent with observations from a similar 3-drug regimen consisting of the protease inhibitor paritaprevir (ABT-450) boosted by low-dose ritonavir; ombitasvir, an NS5A inhibitor; and dasabuvir, a nonnucleoside.[23]

Conclusions

Several conclusions can be drawn from the HCV data presented at the 2014 Liver Meeting. Ribavirin may still have a role in genotype 1 patients with advanced cirrhosis and patients with genotype 3. In patients with genotype 1a, it appears that ribavirin is needed to optimize SVR rates if a nucleotide polymerase inhibitor is not part of the regimen.

We have learned from the C-SWIFT study that there may be a limit, at least with first-generation protease and NS5A inhibitors in the regimen, to how short the duration of treatment can be, even when the regimen consists of potent agents from 3 different classes. It may prove to be challenging to develop regimens for routine use that are given for only 4 or 6 weeks. At least some patients with cirrhosis, particularly treatment-experienced cirrhotics, appear to require a longer duration of therapy—specifically, 24 weeks rather than 12 weeks. There is a resurgent interest, based on the 2 studies presented by Bourlière and colleagues, in the addition of ribavirin to sofosbuvir and ledipasvir to shorten the duration of therapy to 12 weeks in genotype 1 patients with cirrhosis.

The rapidity of viral response after initiation of treatment appears to be less important than when interferon-based therapy was used. It has not been possible to glean any stopping rules, warranting early discontinuation of therapy because of inevitable futility based on poor response, from these studies because of the profoundness and rapidity of viral suppression in nearly all patients. A study of paritaprevir with ritonavir, ombitasvir, and dasabuvir suggested that patients with slower viral responses who cleared the virus in 4 to 6 weeks, as opposed to 1 or 2 weeks, still had SVR rates that equaled those in the patients with more rapid responses.[23] Currently, there is no algorithm for extending treatment beyond that initially intended based on the kinetics of viral response.

The Q80K polymorphism is found with significant frequency in patients with genotype 1a, and it reduces SVR rates for patients with genotype 1a and the Q80K polymorphism when simeprevir is given with peginterferon and ribavirin.[24] However, collective data on simeprevir and sofosbuvir thus far indicate that the impact of the Q80K polymorphism on the efficacy of that regimen is either markedly attenuated or even eliminated. Real-world data suggested that the simeprevir/sofosbuvir regimen was associated with slightly lower SVR rates in patients with genotype 1a compared with genotype 1b. The real-world analyses did not provide data on Q80K, so it was not possible to determine whether the Q80K polymorphism was driving these lower SVR rates. The role of Q80K testing at baseline before use of simeprevir/sofosbuvir remains controversial, but appears not to be obtained by the majority of clinicians.

Use of interferon appears to be nearly extinct, at least in the United States and many parts of Europe. It is speculated that interferon might still have a role in the retreatment of patients who have resistant viral variants after exposure to direct-acting antivirals; however, many experts believe that it will be possible to develop an effective interferon-free regimen for these patients. I am optimistic that interferon will vanish as a component of HCV treatment.

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