GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

January 2014 Volume 10, Issue 1, Supplement 1

A SPECIAL MEETING REVIEW EDITION

Advances in the Treatment of Hepatitis C Virus Infection from The Liver Meeting 2013

The 64th Annual Meeting of the American Association for the Study of Liver Diseases

November 1-5, 2013 • Washington DC

Special Reporting on:

- Simeprevir plus Sofosbuvir with or without Ribavirin Produces High SVR Rates in Genotype 1 HCV Infection
- Novel Interferon- and Ribavirin-Free Regimen Results in SVR12 Rates of Over 90% in HCV Genotype 1b Infection
- Studies Confirm Efficacy of Adjunctive Simeprevir in Difficult-to-Treat HCV Genotype 1 Subpopulations
- All-Oral Therapy with Sofosbuvir Plus Ribavirin Produces High SVR Rates in Patients Coinfected with HCV and HIV
- Faldaprevir Combined with Pegylated Interferon and Ribavirin Demonstrates High Efficacy in Difficult-to-Treat HCV Infection
- Once Daily Sofosbuvir/Ledipasvir Combination Elicits Rapid Decline in HCV RNA

PLUS Meeting Abstract Summaries

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Simeprevir plus Sofosbuvir with or without Ribavirin Produces High SVR Rates in Genotype 1 HCV Infection

Once-daily treatment with simeprevir plus sofosbuvir, with or without ribavirin is highly effective in treatment-naive patients and prior null responders infected with hepatitis C virus (HCV) genotype 1, including patients with cirrhosis, according to a study presented at The Liver Meeting 2013, the 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) which took place November 1 to 5, 2013 in Washington DC.[1] Simeprevir, a once-daily oral HCV nonstructural (NS) 3/4A protease inhibitor, and sofosbuvir, an HCV NS5B nucleotide polymerase inhibitor, were each recently approved for use in the treatment of HCV infection. Simeprevir in combination with peginterferon and ribavirin for the treatment of HCV genotype 1 infection has been found to be safe and well tolerated in approximately 3800 patients treated so far in clinical studies.[2]

Findings from the current phase 2a, randomized, open-label study, named COSMOS, were reported at the

ABSTRACT SUMMARY: Study Confirms Utility of Transient Elastography in Diagnosing Cirrhosis

Study results confirming the usefulness of transient elastography for the diagnosis of cirrhosis in patients with chronic liver disease were presented at The Liver Meeting 2013 by Naveen Gara, MD, a gastroenterologist at the Georgetown University Washington Hospital Center Liver Diseases Branch of the National Institute of Health.[1] Transient elastography, also known as FibroScan, is a non-invasive method used for the assessment of hepatic fibrosis by measuring liver stiffness.

The degree of hepatic fibrosis is known to correlate with disease severity in patients with chronic HCV infection and is directly related to the outcome of the disease. Although liver biopsy is considered the gold standard for assessing fibrosis, it is invasive. Therefore, Dr Gara and colleagues performed a study to evaluate the usefulness of transient elastography—a non-invasive alternative to liver biopsy—as an adjunct to clinical judgment, in the assessment of liver fibrosis.

The study was designed to compare the accuracy of clinical acumen, with or without the use of transient elastography, with liver biopsy to determine fibrosis stage. Over a period of 18 months, the researchers enrolled a total of 98 consecutive patients with chronic HCV infection who were scheduled to undergo liver biopsy. Mean age of the patients was 54 years, 56% of the patients were male, 56% were white, and 27% African-American. Mean body mass index was 27, and 72% were infected with HCV genotype 1.

Each patient was interviewed and examined independently by a junior and senior hepatologist. Examiners had full access to routine prebiopsy laboratory tests and made an assessment of fibrosis severity as either 0 (mild, Ishak 0-2), 1 (moderate, Ishak 3-4), or 2 (severe, Ishak 5-6). Transient elastography was then performed with the examiners being blinded to each other's results. The initial estimate of liver fibrosis could then be revised, based on the results. At the end of the study, all clinical and laboratory data were shown to an expert hepatologist in a standardized format for assessment of liver fibrosis as 0, 1, or 2.

After the initial assessment, the expert hepatologist was given transient elastography scores from both examiners and asked to reassess fibrosis stage. Liver biopsies were scored by the same hepatologist using the Ishak staging system. Examiners were blinded to biopsy results until completion of the study. Weighted-Cohen's kappa was used as a measure of agreement between estimated and biopsy determined stage.

Eighty-four patients were included in the final analysis; 14 were excluded due to cancelled biopsy, failed transient elastography examination, or both. On initial clinical assessment, the kappa coefficient between the junior hepatologist and biopsy stage was 0.48, which improved to 0.62 after transient elastography. Results for the senior hepatologist were 0.61 before and 0.58 after transient elastography. The initial kappa for the reviewing hepatologist was 0.53, which improved to 0.63 after transient elastography. Diagnosis of cirrhosis was correct by clinical assessment in 73% to 82% of cases and 91% to 100% after transient elastography.

Transient elastography correctly identified all cases of cirrhosis. Interoperator correlation for transient elastography was 0.85. Clinical assessment of cirrhosis was excellent but varied by the level of experience, the investigators noted. "Transient elastography is a useful adjunct for diagnosis of cirrhosis and less-experienced clinicians benefitted more from its use," added Dr Gara.

Reference

1. Gara N, Wright EC, Sharma NK, et al. Prediction of disease severity in chronic hepatitis C: clinical gestalt and role of transient elastography [AASLD Abstract 1461]. *Hepatology*. 2013:58(4):917A.

AASLD Liver Meeting 2013 by Ira M. Jacobson, MD, chief of the Division of Gastroenterology and Hepatology and Vincent Astor Distinguished Professor of Medicine at the Weill Cornell Medical College in New York City. The COSMOS study investigated the efficacy and safety of simeprevir plus sofosbuvir, with or without ribavirin, for 12 or 24 weeks in patients with HCV genotype 1 and mild fibrosis (METAVIR fibrosis score of F0-F2) who were prior null responders to peginterferon/ribavirin (cohort 1) or treatment-naive and prior null responders with advanced fibrosis/cirrhosis (METAVIR score of F3 or F4; cohort 2). Patients with hepatic decompensation, liver disease not related to HCV infection, or coinfection with HIV or HBV were excluded from the study.

ABSTRACT SUMMARY: Sofosbuvir-Based Regimens Highly Effective in Most Patients with HCV Infection

The investigational drug sofosbuvir, in combination with other novel or traditional treatments, appears to be highly effective in patients with HCV infection, according to 2 recent trials, LONESTAR and LONESTAR-2.[1,2] Both studies were presented at The Liver Meeting 2013 by Eric Lawitz, MD, founder of The Liver Institute of South Texas and medical director of the institute's affiliate, Alamo Medical Research, in San Antonio, Texas.

In the LONESTAR study, Dr Lawitz and colleagues evaluated the single-pill combination of sofosbuvir, a nucleotide polymerase inhibitor, and ledipasvir, an NS5A inhibitor. The investigators enrolled 2 cohorts at a single center. Cohort 1 included 60 treatment-naive, noncirrhotic patients infected with HCV genotype 1. Cohort 2 included 40 patients infected with HCV genotype 1 in which about 50% of the cohort had liver cirrhosis and had not achieved a cure with a protease inhibitor. The primary endpoint of the study was the percentage of patients who achieved SVR12, or undetectable levels of HCV 12 weeks posttreatment.

Participants in cohort 1 were randomly assigned in a 1:1:1 ratio to receive the once-daily fixed-dose formulation of 400 mg of sofosbuvir and 90 mg of ledipasvir, either with or without 1000-1200 mg/day of weight-based ribavirin for 8 weeks, or else without ribavirin for 12 weeks. Treatment-experienced patients were randomized to receive sofosbuvir/ledipasvir either with or without ribavirin for 12 weeks.

Analysis of the results showed that the fixed-dose combination of sofosbuvir and ledipasvir elicited rapid declines in HCV RNA and high rates of SVR, regardless of the presence of ribavirin, in all treatment groups, with no viral breakthrough observed. In treatment-naive patients without cirrhosis, the overall SVR12 rate was 97%, the researchers found. Among treatment-experienced patients with previous protease inhibitor failure, the rate was 98%, with an SVR12 rate of 95% among patients with cirrhosis. The regimens were, in general, well tolerated, and no treatment discontinuations occurred due to adverse events, reported Dr Lawitz.

The aim of LONESTAR-2 was to evaluate the efficacy of a 12-week regimen of sofosbuvir, combined with peginterferon and ribavirin, in treatment-experienced patients with genotype 2 or 3 HCV infection, including those with cirrhosis. In total, 47 patients who had failed a previous course of peginterferon and ribavirin were enrolled in this open-label, single-arm trial.

All patients were treated for 12 weeks with a combination of sofosbuvir 400 mg daily, in combination with weekly peginterferon and daily ribavirin. About half of the patients in the trial were cirrhotic, and there were broad inclusive criteria; however, patients coinfected with HIV were excluded. Forty-four participants (94%) completed the therapy, with 3 early discontinuations occurring due to adverse events, loss of follow-up, or noncompliance.

The overall response rate was 89%, with 42 of 47 participants achieving SVR12. Among patients with HCV genotype 2 infection, the SVR12 rate was 96%, while 83% of those with genotype 3 HCV infection attained SVR12. Five patients failed to achieve SVR12, and 1 patient with genotype 2 discontinued treatment. Two patients with genotype 3 relapsed and 2 were lost to follow-up. The frequency and severity of treatment-emergent adverse events were typical of those seen during interferon-based therapy, the Dr Lawitz noted.

On the basis of these results, Dr Lawitz concluded that, "sofosbuvir in combination with peginterferon and ribavirin for 12 weeks, demonstrated high efficacy in treatment-experienced patients infected with HCV genotype 2 and 3 who have historically low response rates and limited treatment options. SVR rates were similar in patients with and without cirrhosis, and sofosbuvir in combination with peginterferon and ribavirin was generally safe and well tolerated," he added. "The safety profile was consistent with peginterferon and ribavirin treatment, and there were low discontinuation rates."

References

1. Lawitz E, Poordad FF, Pang PS, et al. Once Daily Sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in ≥95% sustained virologic response in patients with HCV genotype 1, including patients with cirrhosis: the LONESTAR study[AASLD Abstract 215]. *Hepatology*. 2013:58(4):315A.

2. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study. Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract LB4.

A total of 167 patients were randomized in a 2:1:2:1 ratio to simeprevir (150 mg QD) plus sofosbuvir (400 mg QD) with or without ribavirin for 12 weeks or simeprevir plus sofosbuvir with or without ribavirin for 24 weeks. Cohort 1 (n=80; 61.3% male; median age 56 years) was stratified by genotype 1 subtype and interleukin (IL) 28B genotype, while cohort 2 (n=87; 66.7% male; median age 58 years) was stratified by genotype 1 subtype and previous treatment experience (46% of cohort 2 patients were treatment-naive, while 54% were null responders). Cohorts were enrolled sequentially, and baseline characteristics were generally well balanced across all 4 treatment arms. In cohort 1, 77% of the patients had genotype 1a subtype, and 50% of these patients had the Q80K polymorphism. In cohort 2, 78% of patients had genotype 1a subtype, with 40% having the Q80K polymorphism.

Dr Jacobson presented final SVR12 results (defined as the proportion of patients with plasma HCV RNA below the level of quantification at 12 weeks posttreatment, based on a lower limit of detection of 25 IU/mL at 12 weeks posttreatment) for cohort 1, along with SVR 4 weeks posttreatment (SVR4) data for patients in the 12-week arms of cohort 2 (treatment in the 24-week arm had not been completed at the time of the presentation). Analysis of the data showed that treatment with simeprevir plus sofosbuvir, with or without ribavirin, resulted in rapid suppression of HCV RNA in both patient cohorts and across all treatment arms. All patients who completed treatment had undetectable HCV RNA at the end of treatment, and there were no virologic breakthroughs. The investigators found that previous null responders with genotype 1 HCV and METAVIR scores of F0 to F2 achieved SVR12 rates of 79% to 96% (intention-to-treat analysis), while treatment-naive patients and null responders with METAVIR scores of F3 to F4 obtained SVR12 rates of 96% to 100%.

SVR12 rates were 100% in the patients with genotype 1b HCV infection and in patients with genotype 1a HCV infection without the Q80K polymorphism. In an analysis that excluded patients with nonvirologic failure, 24 (89%) of 27 of patients with the Q80K polymorphism achieved SVR12, while 3 patients relapsed in this group. In the treatment arm of cohort 2, all of the patients without the Q80K polymorphism achieved SVR4, and 10 (91%) of 11 patients with the Q80K baseline polymorphism attained SVR4, with 1 relapse occurring in this group.

The most common adverse events in both treatment arms were fatigue, headache, nausea, and insomnia. Rash, itching, anemia, and increases in bilirubin occurred mainly in patients who received ribavirin in addition to simeprevir and sofosbuvir. Four percent of patients (2/54) treated with simeprevir and sofosbuvir with ribavirin and 7% of patients (2/31) treated with simeprevir and sofosbuvir without ribavirin, respectively, discontinued treatment due to an adverse event in the 24-week arms, while no patients (0/82) in the 12-week arms discontinued treatment due to an adverse event at the time of the analysis. Adverse events leading to discontinuation were increased serum creatine phosphokinase level, injury, aggression, and renal insufficiency. Other serious adverse events included anemia, retinal tear, and one ultimately fatal injury due to a fall.

Dr Jacobson concluded that treatment with simeprevir plus sofosbuvir, with or without ribavirin, results in high SVR rates in both cirrhotic and noncirrhotic treatment-naive patients and prior null responders infected with HCV genotype 1. He also noted that the addition of ribavirin may not be needed to achieve high rates of SVR and that similar SVR rates may be obtained with 12 or 24 weeks of treatment.

"Treatment with simeprevir and sofosbuvir, with or without ribavirin, in this interim analysis, resulted in high SVR12 rates of 79% to 96% in HCV genotype 1 null responder patients with METAVIR F0 to 2 fibrosis, high SVR4 rates, from 96% to 100%, in naive and null-responder patients with METAVIR F3 and 4, including cirrhotics," Dr Jacobson said.

References

1. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC. Abstract LB3.

2. Lawitz E, Ghalib R, Rodriguez-Torres M, et al. Suppression of viral load through 4 weeks post-treatment results of a once-daily regimen of simeprevir + sofosbuvir with or without ribavirin in hepatitis C virus genotype 1 null responders. Program and abstracts of the 20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, Georgia. Abstract 155LB.

Novel Interferon- and Ribavirin-Free Regimen Results in SVR12 Rates of Over 90% in HCV Genotype 1b Infection

A novel interferon- and ribavirin-free regimen comprised of ABT-450, a protease inhibitor boosted by ritonavir, and ABT-267, an NS5A inhibitor, resulted in SVR12 in more than 90% of patients infected with genotype 1b HCV, according to an open-label phase 2 study presented at The Liver Meeting 2013 by Eric Lawitz MD, founder of The Liver Institute of South Texas and Medical Director of the institute's affiliate, Alamo Medical Research, both in San Antonio, Texas.[1] Combined use of ABT-450 and ABT-267 has been shown to yield high cure rates, with or without ribavirin, in previous studies.[2] The current study, named PEARL-1, is an ongoing phase 2 trial of ABT-450 plus ABT-267 in cirrhotic and noncirrhotic patients with HCV genotypes 1b and 4. It was designed to investigate whether the combination of ABT-450 and ABT-267 can result in high cure rates in patients with HCV genotype 1b infection. The substudy, discussed by Dr Lawitz, evaluated the safety and efficacy of the 2-drug regimen in 82 patients with HCV genotype 1b. Forty-two noncirrhotic treatment-naive patients infected with HCV genotype 1b and 40 patients infected with HCV genotype 1b who had not responded to pegylated interferon/ribavirin therapy were included in the study, and persons with HIV or HBV coinfection or any other liver disease not attributable to chronic HCV infection were excluded. All patients received 12 weeks of treatment with ABT-450 (150 mg once daily), along with 100 mg of ritonavir to maintain high serum levels of ABT-450, plus ABT-267 (25 mg once daily). The primary outcome of the study was the proportion of patients achieving SVR12, while secondary outcomes

ABSTRACT SUMMARY: Treatment with Sofosbuvir Plus Ribavirin After Liver Transplant Leads to Marked Clinical Improvement or Disease Stabilization

The majority of patients with severe HCV recurrence after liver transplantation improved clinically or remained stable following combination treatment with sofosbuvir and ribavirin, with or without pegylated interferon, a study presented at The Liver Meeting 2013 found.[1] The international multicenter study by Xavier Forns, MD, a liver specialist staff consultant at the Liver Unit of the Hospital Clinic of Barcelona in Spain, and colleagues was designed to collect and summarize safety and efficacy data related to sofosbuvir therapy as part of a compassionate-use program to treat patients with severe recurrent HCV, including those with fibrosing cholestatic hepatitis, following liver transplantation.

Investigators submitted individual requests that included patient medical history, laboratory values, clinical assessments, and liver biopsy reports, when available. Patients enrolled in the study received sofosbuvir 400 mg/day for up to 48 weeks, along with appropriate doses of ribavirin, with or without pegylated interferon, at the discretion of their treating physician. Clinical assessments were recommended at baseline; on-treatment Weeks 4, 12, 24, 36, and 48; and follow-up Weeks 4, 12, and 24. Decompensation events included episodes of hepatic encephalopathy, ascites, and liver-related laboratory values.

The researchers presented data from 44 patients, with a mean age of 56 years and a mean Model for End-Stage Liver Disease (MELD) score of 16 at baseline. At the time of the analysis, 24 (55%) of the patients completed treatment, 5 (11%) discontinued treatment early, 7 (16%) died prior to completing treatment due to progressive liver disease or associated complications, and 8 (18%) of the patients were still receiving treatment. Early on-treatment virologic response occurred in the majority of treated patients, and the rate of response continued to increase over time during treatment, the researchers reported.

Overall, 69% of the patients achieved SVR4, and 56% attained SVR12. Deaths and posttreatment relapse accounted for nearly all cases of virologic failure. Sixty-four percent demonstrated improvement of decompensation events, and 11% showed stabilization of events. MELD score also decreased during treatment. In addition, marked improvements in liver function tests were observed during treatment, including reductions in ALT, bilirubin, and international normalized ratio.

A large proportion of patients experienced serious adverse events during treatment, the majority of which was attributed to disease progression and not the result of therapy, according to Dr Forns. Serious adverse events in the sofosbuvir plus ribavirin arm involved neutropenia, acute renal failure, deep vein thrombosis, and multifocal hepatoma. "In this very sick population with MELD scores up to 43, a number of patients died," Dr Forns noted. "Overall, sofosbuvir-based therapy was well tolerated and does not appear to add to disease burden in these very sick patients."

Reference

1. Forns X, Fontana RJ, Moonka D, et al. Initial evaluation of the sofosbuvir compassionate use program for patients with severe recurrent HCV following liver transplantation [AASLD Abstract 1084]. *Hepatology*. 2013:58(4):732A.

included on-treatment virologic failure, posttreatment relapse, and SVR4. Safety analyses evaluated adverse events occurring in more than 10% of patients, serious adverse events, adverse events resulting in discontinuation or interruption of treatment, and clinically significant abnormal laboratory findings.

Results showed that SVR12 was achieved by 36 (90%) of the null responders and by 40 (95.2%) of the treatment-naive patients. SVR4 rates were 100% among treatment-naive patients and 87.9% among prior null responders. There were no virologic failures in the treatment-naive group, but 4 virologic failures occurred among null responders: 1 viral breakthrough during treatment, after an initial treatment response, and 3 posttreatment virologic relapses.

The treatment regimen was generally well tolerated, with no discontinuations related to adverse events or laboratory abnormalities. However, 2 patients were lost to follow-up and another 2 temporarily interrupted the study drug due to adverse events. One of the interruptions was considered probably associated with the study drug, resulting from grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations and grade 2 bilirubin elevations, both of which improved with treatment interruption and were maintained after resuming treatment. Adverse events with an incidence rate of 10% or greater were headache, nausea, dry skin, fatigue, pruritus, and diarrhea.

On the basis of these results, the investigator concluded that this interferon- and ribavirin-free regimen of ABT-450, boosted by ritonavir, plus ABT-267 for 12 weeks was generally well tolerated and provided high response rates in treatment-naive patients and prior null responders infected with HCV genotype 1b. Dr Lawitz cautioned, however, that larger studies are needed to further characterize the response to this regimen.

References

1. Lawitz E, Hezode C, Varunok P, et al. Interferon- and ribavirin-free regimen of ABT-450/r + ABT-267 in HCV genotype 1b-infected treatment-naive patients and prior null responders [AASLD Abstract 75]. *Hepatology*. 2013:58(4):244A.

2. Poordad F, Lawitz E, Kowdley KV, et al. Interferon-free regimens of ABT-450/r, ABT-267, ABT-333 ± ribavirin achieve high SVR12 rates in patients with chronic HCV genotype 1b. Program and abstracts of the 2013 APASL Liver Week; June 6-10, 2013; Suntec City, Singapore. Abstract 613.

Studies Confirm Efficacy of Simeprevir in Difficult-to-Treat HCV Genotype 1 Subpopulations

The efficacy of simeprevir was confirmed in a number of trials presented at The Liver Meeting 2013, including 2 poster presentations that related findings demonstrating that simeprevir, added to pegylated interferon and ribavirin, performs well in difficult-to-treat treatment-naive patients chronically infected with genotype 1 HCV and patients who relapse after previous interferon-based therapy. Data from the phase 3 PROMISE study of prior relapsers, as well as the phase 3 QUEST-1 and QUEST-2 trials of treatment-naive patients with genotype 1 HCV infection, showed that adding simeprevir to the therapeutic regimen significantly improved SVR or cure rates compared with pegylated interferon/ribavirin alone, and the triple combination was generally safe and well-tolerated.[1,2]

PROMISE

The pivotal phase 3 PROMISE study evaluated simeprevir plus pegylated interferon and ribavirin in patients infected with HCV genotype 1 who previously experienced a relapse after prior treatment with pegylated interferon-based therapy. The current analysis, presented by Xavier Forns MD, a liver specialist staff consultant at the Liver Unit of the Hospital Clinic of Barcelona in Spain, focused on safety and efficacy outcomes in difficult-to-cure patient subgroups, such as those with the IL28B TT genotype, a METAVIR score of F4, or HCV genotype 1a with baseline Q80K polymorphism.

A total of 394 patients who had received interferon-based therapy for at least 24 weeks and relapsed within 1 year were randomly assigned in a 2:1 ratio to receive simeprevir (150 mg QD) or placebo, in addition to pegylated interferon plus ribavirin, for 12 weeks. Patients in the control group continued to receive pegylated interferon plus ribavirin for an additional 36 weeks, while patients in the experimental group received pegylated interferon plus ribavirin for an additional 12 or 36 weeks, depending on response (treatment was stopped early if HCV RNA was undetectable or there were less than 25 copies of HCV RNA/mL at Week 4 and undetectable at Week 12). The primary efficacy endpoint was SVR12. Secondary endpoints included rapid virologic response (RVR), defined as undetectable HCV RNA at Week 4, SVR24, on-treatment failure rate, relapse rate, and safety and tolerability.

Dr Forns and colleagues found that 65% of patients with the IL28B TT genotype, 74% of patients with a METAVIR score of F4, and 70% of patients with genotype 1a HCV treated with simeprevir plus pegylated interferon and ribavirin achieved SVR12, compared with 19%, 26%, and 28% of patients in the above 3 subgroups, respectively, who were taking placebo plus pegylated interferon and ribavirin. Among patients with the genotype 1a Q80K polymorphism at baseline, 47% of patients treated with simeprevir plus pegylated interferon and ribavirin achieved SVR12, compared with 30% of patients treated with placebo plus pegylated interferon and ribavirin.

The most common adverse events in patients treated with simeprevir combined with pegylated interferon and ribavirin in the first 12 weeks were fatigue, headache, and influenza-like illness. On the basis of these results, the investigators concluded that simeprevir conferred clinical benefit across all patient subpopulations, including not only those with positive predictors of response, but also patients with unfavorable baseline characteristics, such as IL28B TT, METAVIR F4, and genotype 1a with Q80K baseline polymorphism.

QUEST-1 and QUEST-2

Findings of the QUEST-1 and QUEST-2 trials were reported during a poster session by Ira M. Jacobson, MD, chief of the Division of Gastroenterology and Hepatology and Vincent Astor Distinguished Professor of Medicine at the Weill Cornell Medical College in New York City. In QUEST-1, simeprevir 150 mg once daily plus peginterferon/ribavirin was compared with placebo plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1 infection. A total of 264 patients were in the simeprevir group, and 130 were in the placebo group. Patients were stratified by HCV genotype subtype and the IL28B genotype. Patients received simeprevir or placebo for the first 12 weeks of peginterferon/ribavirin therapy, and response-guided therapy was used to determine the total treatment duration. In the simeprevir arm, treatment duration was 24 weeks in patients with an HCV RNA load of less than 25 IU/mL at Week 4 and an undetectable HCV RNA load at Week 12. Treatment duration was 48 weeks in all other patients. All patients in the placebo-controlled arm received peginterferon/ribavirin for 48 weeks.

In the QUEST-2 trial, patients were randomly assigned in a 2:1 ratio to receive either simeprevir 150 mg once daily plus peginterferon (alpha-2a or alpha-2b) for 12 weeks, followed by peginterferon/ribavirin alone for 12 weeks or placebo plus peginterferon (alpha-2a or alpha-2b) and ribavirin for 12 weeks followed by peginterferon/ribavirin alone for an additional 36 weeks. As in the QUEST-1 trial, response-guided therapy was used to determine the total treatment duration. In the simeprevir arm, treatment duration was 24 weeks in patients with an HCV RNA load of less than 25 IU/mL at Week 4 and an undetectable HCV RNA load at Week 12. Treatment duration was 48 weeks in

the placebo-controlled cohort. Patients were stratified based on HCV genotype subtype and IL28B genotype. Thirty percent of patients in the simeprevir arm and 31% in the placebo-controlled arm had the IL28B CC genotype, and 58% in both groups had genotype 1b. Cirrhosis was present in 7% of patients in the simeprevir arm and 11% of patients in the placebo arm.

In the QUEST-1 and QUEST-2 studies, 80% of treatment-naive patients treated with simeprevir in combination with pegylated interferon and ribavirin achieved the primary endpoint of SVR12 compared with 50% of patients treated with placebo plus pegylated interferon and ribavirin. The analysis, which included patients considered difficult to treat, found that 61% of patients with the IL28B TT genotype, 60% of patients with a METAVIR score of F4, and 75% of patients infected with genotype 1a HCV treated with simeprevir combined with pegylated interferon and ribavirin achieved SVR12 compared with 21%, 34%, and 47% of patients taking placebo plus pegylated interferon and ribavirin, respectively. Among patients with the genotype 1a

ABSTRACT SUMMARY: Pretransplant Treatment with Sofosbuvir Plus Ribavirin Prevents Recurrence of HCV Infection after Liver Transplant

The all-oral regimen of sofosbuvir and ribavirin administered prior to liver transplantation can effectively prevent the recurrence of HCV infection after liver transplantation in the majority of patients with well compensated cirrhosis, according to a study presented by Michael Curry, MD, medical director for Liver Transplantation at Beth Israel Deaconess Medical Center at Harvard University in Boston, Massachusetts.[1] The open-label phase 2 study by Dr Curry and colleagues found that the combination of sofosbuvir (400 mg/day) plus ribavirin (1000-1200 mg/day) administered for up to 48 weeks prior to liver transplantation in patients with HCV infection prevented the recurrence of HCV in 64% of patients who had undetectable HCV levels at the time of transplantation.

Recurrent HCV infection of the allograft is unavoidable in patients with detectable HCV RNA at the time of liver transplantation and may result in accelerated progression to cirrhosis and graft loss. Although interferon-based antiviral treatment aimed at HCV RNA suppression before liver transplantation reduces the risk of recurrence and associated complications, this treatment is poorly tolerated and effective only in a minority of patients.

To evaluate the efficacy and safety of sofosbuvir 400 mg once daily plus weight-based ribavirin for up to 48 weeks or until liver transplantation, Dr Curry and colleagues enrolled 61 patients with HCV infection and liver cancer in an open-label, multicenter phase 2 trial. Most (80%) of the participants were men, 90% were white, and the median age was 59 years. The majority (73%) of patients were infected with HCV genotype 1, including 39% with the harder-to-treat subtype 1a, and 22% had the favorable IL28B CC gene. Participants had well compensated liver disease and were listed for transplantation due to hepatocellular carcinoma.

Patients received sofosbuvir 400 mg/day plus ribavirin 1000-1200 mg/day for up to 48 weeks before liver transplantation and immunosuppressive therapy with tacrolimus plus prednisone with or without mycophenolate mofetil for at least first 12 weeks after transplantation. The primary endpoint was posttransplantation virologic response defined as HCV RNA below 25 IU/mL at 12 weeks after liver transplantation in patients who had HCV RNA below 25 IU/mL at last measurement prior to liver transplantation. Secondary endpoints included measures of safety and tolerability, as well as HCV viral kinetics before and after liver transplantation.

At the time of the analysis, 41 (67%) of 61 of the patients received liver transplantation with HCV RNA below 25 IU/mL. Most of the other patients either discontinued treatment (n=10) or were still awaiting transplantation (n=4). The investigators found that HCV viral load rapidly declined soon after starting treatment with the dual regimen of sofosbuvir and ribavirin. Ninety-one percent of patients received treatment for at least 12 weeks, and, of these, 93% had HCV RNA below 25 IU/mL at the time of transplantation. Among those with undetectable HCV at transplantation, 64% maintained viral suppression 12 weeks after transplantation.

Seven (27%) patients had recurrence and 1 (4%) died of primary graft nonfunction after retransplantation. The rate of recurrence was not associated with the duration of pretransplantation treatment or with HCV genotype, data analysis showed. The most frequently reported adverse events were fatigue, anemia, and rash. Two patients discontinued treatment due to adverse events (acute renal failure and pneumonitis); however, these were considered unrelated to the study drug.

On the basis of these results, Dr Curry concluded that treatment with sofosbuvir and ribavirin was safe and effective in patients with well-compensated cirrhosis and that the regimen prevented posttransplant HCV infection recurrence in most of patients who had undetectable levels of HCV RNA prior to liver transplantation. They also noted that the most reliable predictor of posttransplant virologic response was the number of consecutive days that HCV RNA was undetectable before transplantation.

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Q80K polymorphism at baseline, 58% of patients treated with simeprevir combined with pegylated interferon and ribavirin achieved SVR12 compared with 52% of patients treated with placebo in combination with pegylated interferon and ribavirin, but the difference was not statistically significant. Three percent of patients treated with simeprevir discontinued treatment early due to an adverse event compared with 2% of patients treated with placebo.

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All-Oral Therapy with Sofosbuvir Plus Ribavirin Produces High SVR Rates in Patients Coinfected with HCV and HIV

Approximately three-quarters of previously untreated patients coinfected with HIV and HCV genotype 1 receiving an all-oral regimen of sofosbuvir plus ribavirin achieved SVR12 after 24 weeks of therapy, according to results of the ongoing PHOTON-1 trial presented at The Liver Meeting 2013 by Mark S. Sulkowski, MD, medical director of the Viral Hepatitis Center and professor of medicine in the Divisions of Infectious Diseases and Gastroenterology/Hepatology at The Johns Hopkins University School of Medicine in Baltimore, Maryland.[1]

PHOTON-1 is an open label phase 3 study conducted at sites in the United States and Puerto Rico. The aim of the study is to evaluate the efficacy and safety of 12 or 24 weeks of sofosbuvir 400 mg once daily plus ribavirin in treatment-naive patients who are coinfected with HCV genotype 1, 2, or 3 and HIV. Unlike some HCV-targeted protease inhibitors, sofosbuvir does not affect CYP3A4 liver enzyme metabolism and has shown no significant interactions with many widely used antiretroviral drugs.[2-4]

Dr Sulkowski and colleagues enrolled 114 patients coinfected with HIV and HCV genotype 1 who had not been previously treated for HCV infection. Patients received sofosbuvir at a dosage of 400 mg once daily plus 1000-1200 mg of weight-based ribavirin for 24 weeks and were followed for 12 weeks after completion of therapy to determine SVR12. The study included 3 patient cohorts: 1) treatment-naive patients infected with genotype 1 HCV infection who were treated for 24 weeks; 2) treatment-naive patients infected with genotype 2/3 HCV infection who were treated for 12 weeks; and 3) treatment-experienced patients with genotype 2/3 HCV infection who were treated for 24 weeks (data from this cohort were not yet available at the time of The Liver Meeting 2013).

Most (81%) of the participants were men, with a mean age of approximately 49 years. One-third of patients infected with genotype 1, one-quarter of patients infected with genotype 2, and 5% of patients infected with genotype 3 were African-American, and 27%, 39%, and 36%, respectively, had the IL28B CC gene variant. Approximately 4% of patients in the genotype 1 and genotype 2 groups had compensated cirrhosis, whereas the rate of compensated cirrhosis was 14% among patients in the genotype 3 group. Participants had well-controlled HIV infection, with more than 90% receiving antiretroviral therapy.

The primary endpoint of the current analysis was SVR12 (HCV RNA <25 IU/mL), while secondary endpoints included adverse events and laboratory abnormalities, as well as HIV-1 RNA and CD4+ cell count and percentages. The majority of patients (88% to 93%) completed treatment; reasons for discontinuation included protocol violation and administrative errors.

RVR rates at Week 4 after starting therapy were 96% for patients with genotype 1 and genotype 2 and 100% for patients with genotype 3. Patients with genotype 2 HCV infection achieved the highest SVR12 rates (88%), with lower SVR12 rates being seen in patients with genotype 1 (76%) or genotype 3 (67 %) HCV infection.

Subgroup analyses revealed that lower SVR12 rates were achieved in patients coinfected with genotype 1b HCV, cirrhotic patients, and African-Americans. In multivariate analysis, however, the only factors that independently predicted nonresponse were African-American race and failure to complete 24 weeks of treatment. The investigators also found that nearly all cases of HCV virologic failure were due to relapse. Relapse rates were 22% for patients with genotype 1 infection and 29% for patients with genotype 3 infection (no patient with genotype 2 infection relapsed), and most relapses occurred within 4 weeks after the end of treatment.

In general, the combination of sofosbuvir and ribavirin was well tolerated, with treatment discontinuation due to adverse events occurring

in no more than 4% of patients. The most common adverse events were consistent with the safety profile of ribavirin and included fatigue, insomnia, nausea, and headache. The most common laboratory abnormalities were hyperbilirubinemia and anemia, with elevated bilirubin occurring among patients taking atazanavir (5 patients on atazanavir were switched to darunavir due to hyperbilirubinemia). Additionally, transient HIV-1 RNA breakthrough occurred in 2 patients, both of whom had documented nonadherence to antiretroviral therapy.

Dr Sulkowski noted that treatment-naive patients coinfected with HCV genotype 2 or 3 and HIV achieved high rates of SVR12 with 12 weeks of an interferon-free, oral regimen of sofosbuvir plus ribavirin. He concluded that the preliminary data suggest that sofosbuvir plus ribavirin treatment is well tolerated and safe for use in combination with multiple antiretroviral therapy regimens and may be equally safe and effective in patients without HIV coinfection.

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ABSTRACT SUMMARY: High SVR Rate with Interferon– and Ribavirin–Free Triple Therapy

An interferon– and ribavirin–free regimen comprised of 3 direct-acting antiviral agents resulted in very high SVR12 rates, reported Gregory T. Everson, MD, professor of medicine and director of the Section of Hepatology at the University of Colorado Health Sciences in Denver.[1] Dr Everson and colleagues conducted a phase 2b study designed to compare 2 doses (75 and 150 mg) of the NS5B inhibitor BMS-791325 with 2 other direct-acting antivirals, the protease inhibitor asunaprevir and the NS5A inhibitor daclatasvir. These drugs have demonstrated in vitro activity against HCV genotypes 1, 3, 4, 5, 6 in several previous studies, and, in a phase 2a pilot study, their combined use resulted in SVR rates of 89% to 94% in noncirrhotic patients with genotype 1 HCV infection.[2-4]

The current expansion study further examined the efficacy and safety of the triple-therapy regimen administered for 12 weeks in larger treatment-naive patient cohorts, including those with cirrhosis. The investigators enrolled a total of 166 treatment-naive patients chronically infected with genotype 1 HCV, 9% of whom had cirrhosis. Patients also were stratified by HCV subtype 1a and 1b. Patients were evenly distributed between the 2 study arms: 80 patients were enrolled in the 75-mg arm and 86 in the 150-mg arm. Most (82%) of the participants had HCV genotype 1a, 67% had a non-CC IL28B genotype, and 38% had a METAVIR fibrosis stage of F3 or F4. The primary endpoint of the study was SVR12.

According to Dr Everson, the triple-drug combination was equally effective in patients with genotype 1a and 1b HCV infections. He reported that 12 weeks after the completion of treatment, 71 (92.2%) of 77 participants in the 75-mg arm and 77 (91.7%) of 84 participants in the 150-mg arm had SVR12. Overall rates of SVR12 among cirrhotic patients were more than 90%, regardless of genotype 1 subtype or IL28B status.

Three patients were lost to follow-up after completion of treatment and 5 patients (3 in the 75-mg arm and 2 in the 150-mg arm) had missing data at the Week 12 follow-up. Virologic response rates decreased slightly when patients with missing data were included in the analysis. Six cases of virologic failure occurred in the 75-mg arm (2 viral breakthroughs and 4 post-treatment relapses) and 5 in the 150-mg arm (3 viral breakthroughs and 2 viral relapses). All viral relapses occurred within 4 weeks of completing treatment. Treatment was well tolerated in both groups. No patients discontinued because of treatment-related serious adverse events, and symptoms while on treatment were mild or moderate in all but 1 patient who had an AST elevation of grade 3/4 that later normalized and 1 cirrhotic patient who experienced an elevation in bilirubin.

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Faldaprevir Combined with Pegylated Interferon and Ribavirin Demonstrates High Efficacy in Difficult-to-Treat HCV Infection

The combination of faldaprevir, a novel NS3/4A protease inhibitor, and pegylated interferon plus ribavirin is highly effective in difficult-to-treat HCV infection, results of 2 phase 3 studies, STARTVerso 3 and STARTVerso 4 indicate.[1,2] STARTVerso 3 investigated faldaprevir in treatment-experienced patients with genotype 1 HCV, and the ongoing STARTVerso 4 has been evaluating faldaprevir in patients with HCV/HIV coinfection. In STARTVerso 1 and 2, 84% of treatment-naive patients receiving faldaprevir were able to shorten the total time on treatment from 48 to 24 weeks, and 83% of these patients achieved SVR12.[3] In STARTVerso 3, add-on treatment with faldaprevir in difficult-to-cure patients who had relapsed on previous HCV treatment yielded viral cure rates of 70% after 12 weeks, while interim results from STARTVerso 4 showed that 74% of patients with HCV/HIV coinfection treated with faldaprevir had undetectable HCV RNA 4 weeks after the conclusion of treatment (ie, SVR4).

STARTVerso 3: Faldaprevir in Treatment-Experienced Patients

STARTVerso 3, the findings of which were presented by Ira M. Jacobson, MD, chief of the Division of Gastroenterology and Hepatology and Vincent Astor Distinguished Professor of Medicine at the Weill Cornell Medical College in New York City, enrolled a total of 677 treatment-experienced patients. Sixty percent were male, 77% white, and 18% were Asian. Forty percent of the patients had a METAVIR score of F3 or greater, 53% had genotype 1b, and 16% had IL28B CC. The trial included 3 cohorts of treatment-experienced patients who had prior relapse (cohort 1), prior partial response (cohort 2), and prior null response (cohort 3). Cohorts 1 and 2 were each randomized in a 1:2:2 ratio to receive 48 weeks of pegylated interferon plus ribavirin plus placebo or faldaprevir (240 mg QD) for 12 or 24 weeks. In cohort 1, faldaprevir-treated patients were eligible to stop treatment after 24 weeks on achievement of early treatment success (RNA <25 IU/mL detected or undetected at Week 4 and undetected at Week 8). In cohort 3, patients were randomized in a 1:1 ratio to receive pegylated interferon plus ribavirin for 48 weeks along with faldaprevir (240 mg once daily) for 12 or 24 weeks.

In cohort 1, 70% of patients treated with faldaprevir for either 12 or 24 weeks achieved SVR12 vs 14% of those given placebo. SVR12 rates in cohort 2 were 58% and 47% in patients treated for 12 and 24 weeks, respectively, vs 3% in the placebo group. In cohort 3, the SVR12 rate was 33% for patients receiving either 12 or 24 weeks of treatment with faldaprevir. Discontinuation of all study medication due to adverse events occurred in 5% (cohorts 1 and 2 combined) and 6% (cohort 3) of patients treated with faldaprevir. Most adverse events were mild, with nausea (53%), fatigue (34%), rash (31%), and anemia (22%) most commonly reported in the active treatment arms. These data indicate that a treatment regimen of faldaprevir 240 mg plus pegylated interferon and ribavirin is effective and well tolerated in treatment-experienced patients with HCV genotype 1, Dr Jacobson concluded. He also noted that treatment with faldaprevir 240 mg for 12 weeks was as effective as 24 weeks of treatment.

STARTVerso 4: Faldaprevir in Patients with HIV/HCV Coinfection

STARTVerso 4 is an open-label, sponsor-blinded study of patients coinfected with HCV/HIV who were HCV treatment-naive or relapsed after previous HCV therapy. Findings were reported by Jürgen K. Rockstroh, MD, professor of medicine and head of the HIV Outpatient Clinic at the University of Bonn in Germany. All participants received once-daily faldaprevir in combination with pegylated interferon alpha-2a plus weight-based ribavirin. Patients with HIV who were taking boosted atazanavir or darunavir received 120 mg faldaprevir while those taking efavirenz received 240 mg. Participants who were antiretroviral therapy-naive or taking raltegravir were randomly assigned to receive either 120 or 240 mg of faldaprevir.

Patients taking 120 mg faldaprevir stayed on the combination triple therapy for 24 weeks. Those taking 240 mg were randomly assigned to take faldaprevir triple therapy for 12 or 24 weeks. Participants who experienced early treatment success, defined as HCV RNA below 25 IU/mL at Week 4 and undetectable at Week 8, were randomized to either stop all drugs at 24 weeks or continue on pegylated interferon/ribavirin until Week 48, as did all patients without early treatment success.

In total, 308 patients were treated in STARTVerso 4, 270 (88%) of whom reached the end of treatment at the time of this interim analysis. Early treatment success was achieved by 72% of patients treated with 120 mg faldaprevir for 24 weeks, 79% of those treated with 240 mg for 12 weeks, and 84% of those treated with 240 mg for 24 weeks. The most common adverse events were nausea (37%), fatigue (34%), and diarrhea (27%). On the basis of these results, Dr Rockstroh concluded that faldaprevir plus pegylated interferon/ribavirin was well tolerated and effective and did not have any impact on HIV RNA suppression by antiviral therapy in patients coinfected with HIV and HCV genotype 1.

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ABSTRACT SUMMARY: 90% SVR Rate Achieved with Sofosbuvir plus Ribavirin in Treatment Naive Patients Infected with Genotype 3 HCV

A 24-week course of ribavirin plus sofosbuvir resulted in SVR12 in over 90% of treatment-naive patients with genotype 3 HCV infection, analysis of the data from the phase 3 VALENCE trial indicate.[1] The dual regimen of sofosbuvir and ribavirin also yielded high SVR rates in treatment-experienced patients with genotype 3 HCV without cirrhosis and in patients with genotype 2 HCV after 12 weeks of treatment.

In previous phase 3 studies, 12 weeks of treatment with sofosbuvir and ribavirin resulted in high SVR rates in patients with genotype 2 and genotype 3 HCV infection, with higher response rates in patients infected with genotype 2 than in those infected with genotype 3 HCV.[2,3] To assess the safety and efficacy of sofosbuvir plus ribavirin administered for 12 or 24 weeks, Stefan Zeuzem, MD, professor of medicine and chief of the Department of Medicine at Johann Wolfgang Goethe University, Frankfurt, Germany, and colleagues conducted a randomized controlled trial at a number of centers throughout Europe. In the initial study, over 300 treatment-naive or treatment-experienced patients infected with HCV genotype 2 or 3 were randomized in a 4:1 ratio to receive sofosbuvir (400 mg/day) plus ribavirin (1000 or 1200 mg/day) or placebo for a period of 12 weeks. The trial was subsequently amended to extend treatment duration to 24 weeks for patients with genotype 3, due to emerging data suggesting that these patients would benefit from longer treatment. Also, patients initially randomized to placebo were offered treatments an alternative protocol.

The analysis included a total of 419 patients: 73 with genotype 2 HCV, 261 with genotype 3 HCV (including 11 treated for 12 weeks before the protocol change), and 85 patients with genotype 2 or genotype 3 HCV who received placebo before the protocol change. About 60% of the participants were men, most were white, and the median age was approximately 60 years. About one-third of the patients had the favorable IL28B CC gene variant and about 20% had liver cirrhosis. Approximately 60% of the participants had been treated previously for HCV but were either null responders or prior relapsers.

Analysis of the results showed that a high percentage of patients responded to treatment in both arms; SVR12 was achieved by 68 (93%) of 73 of those infected with genotype 2 HCV after 12 weeks of treatment, while 212 (85%) of 250 of those with genotype 3 HCV obtained SVR12 following 24 weeks of treatment. Participants with genotype 2 HCV infection had high response rates regardless of previous treatment status and cirrhosis status with 12 weeks of sofosbuvir/ribavirin; SVR12 rates were 97% for treatment-naive patients without cirrhosis, 100% for treatment-naive patients with cirrhosis, 91% for treatment-experienced patients without cirrhosis, and 88% for treatment-experienced patients with cirrhosis.

Results were somewhat less impressive for those infected with genotype 3 HCV. Although treatment-naive patients had high SVR12 rates (92% and 94% for patients with and without cirrhosis, respectively), these rates fell to 87% for treatment-experienced patients without cirrhosis and 60% for treatment-experienced cirrhotic patients; however, univariate and multivariate analyses did not reveal any specific factor significantly associated with relapse in this subgroup.

Treatment with sofosbuvir plus ribavirin was generally safe and well tolerated, with headache and fatigue being the most frequently occurring adverse events. Pruritus, asthemia, insomnia, and hemoglobin decline were more frequent with active treatment than placebo. Dr Zeuzem also noted that no additional adverse events were associated with the extension of treatment from 12 to 24 weeks.

These results indicate that the efficacy of combination treatment with sofosbuvir plus ribavirin in genotype 2 patients is similar to that observed in recent phase 3 studies. "Data on the efficacy of sofosbuvir plus ribavirin for 24 weeks in genotype 3 HCV-infected patients is critical to optimize the treatment duration for HCV genotype 3 infections and offer improved SVR rates," ,concluded Dr Zeuzem.

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Once Daily Sofosbuvir/Ledipasvir Combination Elicits Rapid Decline in HCV RNA

Once-daily treatment with a fixed-dose combination of sofosbuvir and ledipasvir, with or without ribavirin, results in rapid decline in HCV RNA in infected patients, according to a small study presented by Edward Gane, MD, deputy director of the New Zealand Liver Transplant Unit at Auckland City Hospital in New Zealand.[1] The phase 2 trial, dubbed ELECTRON, conducted by Dr Gane and colleagues, evaluated a single-pill combination of sofosbuvir, a nucleotide polymerase inhibitor, and ledipasvir, which blocks the NS5A protein, in previously treated patients with genotype 1 HCV infection and advanced fibrosis or cirrhosis.

Previous phase 2 studies have found that the addition of an NS5A inhibitor (either ledipasvir or daclatasvir) to the combination of sofosbuvir plus ribavirin for 12 weeks resulted in high (92% to 100%) rates of sustained viral response 12 weeks posttreatment (SVR12) in noncirrhotic patients infected with genotype 1 HCV.[2-4] The current study investigated the safety and efficacy of a fixed-dose combination of sofosbuvir and ledipasvir in treatment-experienced patients with genotype 1 HCV infection and advanced fibrosis/cirrhosis, and also assessed the minimum treatment duration for noncirrhotic treatment-naive patients. Of the treatment-experienced participants, approximately 70% were men, about 90% were white, and the mean age was approximately 56 years. About 75% of these patients were infected with a HCV genotype 1a subtype, and about 25% had the IL28B CC gene pattern. In the treatment-naive group, the majority of patients were white, just over 50% were men, and, the average age was 51 years. Most (84%) were infected with the HCV genotype 1a subtype and one-fifth had the favorable IL28B variant.

The study included 5 treatment arms. All but patients in the fifth treatment cohort received 12 weeks of therapy with a once-daily fixed-dose tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir, taken with either ribavirin or the non-nucleoside polymerase inhibitor GS-9669. Thus, 19 prior null responders with HCV genotype 1 infection and compensated cirrhosis were randomized to receive open-label sofosbuvir/ledipasvir with (n=9) or without (n=10) ribavirin for 12 weeks, while 51 treatment-experienced patients with METAVIR F3 or F4 scores received sofosbuvir/ledipasvir plus ribavirin (n=25) or sofosbuvir/ledipasvir plus GS-9669 (n=26). The fifth group consisted of treatment-naive noncirrhotic patients who received sofosbuvir/ledipasvir plus ribavirin for 6 weeks (n=25).

SVR12 was reached in 100% of the treatment-experienced cirrhotic patients who received ribavirin compared with only 70% of those who did not receive ribavirin, reported Dr Gane. All treatment-experienced patients with advanced fibrosis or cirrhosis also achieved SVR12 when treated with sofosbuvir/ledipasvir plus either ribavirin or GS-9669 for 12 weeks. However, several of the treatment-naive noncirrhotic patients who were treated for only 6 weeks relapsed after the end of therapy, resulting in an SVR12 rate of 68% in this group.

The fixed-dose combination of sofosbuvir and ledipasvir alone or with ribavirin or GS-9669 was generally safe and well tolerated across all treatment arms, according to Dr Gane. Only 1 participant experienced a serious adverse event and no one discontinued treatment early due to adverse events. The most common adverse events were headache, fatigue, and nausea.

The investigators concluded that fixed-dose sofosbuvir and ledipasvir elicited rapid decline in HCV RNA in all patient populations, with no viral breakthrough observed. They noted, however, that in noncirrhotic treatment-naive patients infected with HCV genotype 1, reduction in duration from 12 to 6 weeks increased the rate of relapse.

In addition, "in the prior null responder patients with genotype 1 and cirrhosis, the addition of ribavirin to sofosbuvir/ledipasvir decreased the rate of relapse, suggesting that either ribavirin or a third direct-acting antiviral may be useful in this difficult-to-treat patient population," concluded Dr Gane.

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Commentary

Ira M. Jacobson

Findings from several reports delivered during the 64th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2013 bring us ever closer to a new era in the treatment of HCV infection. Here are, in my view, the key clinical points of the most important presentations delivered during the meeting.

COSMOS and Other Studies of Simeprevir Regimens

The COSMOS study evaluated the combination of simeprevir and sofosbuvir in patients with mild fibrosis who had null response to interferon and ribavirin and patients with advanced fibrosis, including cirrhosis, who were treatment-naive or null responders. Four treatment arms were investigated: 12 weeks vs 24 weeks, and the combination regimen with or without ribavirin. High rates of sustained viral response at Week 12 (SVR12) were seen in the patients with mild fibrosis, and in this interim analysis, high SVR rates at Week 4 (SRV4) were seen in the patients with advanced fibrosis who received 12 weeks of treatment. Ribavirin did not seem to have an impact on the outcome and neither did adding an additional 12 weeks to a 12-week regimen. Although very high response rates have come to be expected from combining potent antiviral drugs, the COSMOS study represents the first time that a protease inhibitor had been combined with sofosbuvir. The 4 relapses seen so far in this interim analysis were in patients with the Q80K polymorphism, which is seen nearly exclusively in patients with genotype 1a and was shown to impair SVR rates in studies of simeprevir combined with peginterferon and ribavirin. Final data are needed to fully assess the impact of Q80K in interferon-free regimens.

Sofosbuvir was approved in early December 2013. Although use of sofosbuvir and simeprevir in combination will be an off-label regimen, it will be the first time in the history of HCV therapeutics that physicians will theoretically be able to prescribe a combination of 2 direct-acting antivirals (DAAs). Patients are expressing intense interest in this combination, and physicians are eager to determine how accessible this regimen will be, particularly for selected populations such as patients with advanced fibrosis with a history of null response or interferon ineligibility. Therefore, the COSMOS study may be of short-term importance in selected patients, such as those with advanced fibrosis and prior nonresponse or interferon ineligibility, until late 2014 or early 2015 when new combination regimens, currently in phase 3 studies, are hopefully approved by the US Food and Drug Administration (FDA).

PROMISE was a phase 3 trial that studied simeprevir in patients who had relapsed following treatment with peginterferon and ribavirin. The results showed that when patients who relapsed were retreated with the addition of 150 mg/d of simeprevir, the SVR12 rate jumped to 79% compared with 37% in patients who received peginterferon and ribavirin alone. This outcome was expected; similar results are seen with telaprevir and boceprevir. The findings from this trial add to the large safety database on simeprevir, showing that there is no incremental drop in hemoglobin.

The pooled analysis studies of simeprevir in treatment-naive patients—QUEST 1 and 2—show similar themes to the PROMISE study. Patients with the interleukin 28B (IL28B) CC genotype had the best response, and patients with mild fibrosis did better than those with more advanced fibrosis. The rate of rapid viral response (RVR) in patients with IL28B CC who were in the simeprevir arm was 90%. Among patients who had RVR, 87% went on to achieve SVR12. Also, patients with a low viral load at baseline (<800,000 IU/mL) did somewhat better than patients with a high viral load. The SVR rate in patients with genotype 1a and the Q80K polymorphism was 58% compared with the rate in the corresponding patients who received peginterferon and ribavirin alone, which was 52%.

Therefore, the package insert for simeprevir recommends pretreatment assessment of patients with genotype 1a for the Q80K polymorphism and consideration of other options should the polymorphism be present. Overall, however, simeprevir represents an advance in the protease-inhibitor class because of its once-daily administration and better safety profile than the earlier protease inhibitors.

Ribavirin–Free Triple DAA Therapy

Another important study that was reported during The Liver Meeting 2013 concerned 3 DAAs daclatasvir, asunaprevir, and BMS-791325, used without ribavirin. The individual components of this triple-therapy regimen are potent but do not have a high resistance barrier individually. The take home message is that a potential role exists for a highly potent triple DAA regimen without a nucleotide inhibitor. Ribavirin may not be needed to attain very high SVR rates.

The study was performed in treatment-naive patients, and only a small number of them had cirrhosis, but 87% of the patients with cirrhosis had a SVR12. Patients with genotype

1a HCV infection did very well in this study, although all the 11 patients with virologic failure (breakthrough or relapse) had genotype 1a infection.

Given at high doses, asunaprevir showed signs of hepatotoxic potential in earlier studies. In this study, however, there was only 1 case of grade 3/4 aspartate aminotransferase elevation.

Advances in Sofosbuvir Regimens

VALENCE

VALENCE was an important European study that evaluated 12 weeks of sofosbuvir and ribavirin in patients with genotype 2 and 24 weeks in genotype 3 HCV infection, extending treatment for patients with genotype 3 infection from the 16 weeks that were evaluated in earlier 12- to 16-week studies. The hypothesis that a longer treatment duration would be of benefit in this population was robustly confirmed in the VALENCE study. SVR12 rates exceeded 90% in treatment-naive patients, and the SVR12 rate in treatment-experienced noncirrhotic patients with genotype 3 was 87%—a marked improvement over the 63% rate seen in the treatment-experienced FUSION trial in which the treatment duration was 16 weeks.

The SVR12 was not as robust in cirrhotic patients infected with HCV genotype 3, with a rate of 60%, which was no better than what was seen in 16-week treatment regimens of sofosbuvir plus ribavirin. Nevertheless, this study confirms that 24 weeks of sofosbuvir and ribavirin should be the duration of therapy recommended routinely to patients with genotype 3 whether they are treatment-naive or experienced and whether cirrhotic or not.

LONESTAR-2

The LONESTAR-2 study examined sofosbuvir and peginterferon plus ribavirin in treatment-experienced patients with genotype 2 or 3 HCV infection, including those with and without compensated cirrhosis. This trial was important in light of findings from the phase 3 development program of sofosbuvir, which demonstrated extremely high SVR rates for sofosbuvir and ribavirin in patients with genotype 2 infection but substantially lower SVR rates in patients with genotype 3 infection. An SVR12 rate of 83% was achieved in patients with genotype 3 in the LONESTAR-2 trial, thus, providing promise that genotype 3 HCV infection, whether in cirrhotic or noncirrhotic patients, can be cured with sofosbuvir and ribavirin plus peginterferon.

The patient population was small; therefore, it is quite premature to conclude that treatment-experienced, cirrhotic patients with genotype 3 HCV infection should routinely receive interferon. Clarity may come from a larger study, currently being conducted by Gilead, that compares 12 weeks of triple therapy (sofosbuvir, ribavirin, and interferon) with 24 weeks of an interferon-free regimen (sofosbuvir plus ribavirin).

Post- and Pretransplant Regimens

Another very important study presented at The Liver Meeting 2013 looked at sofosbuvir plus ribavirin for recurrent HCV infection after liver transplantation. Patients with genotype 1a, 1b, 3, and 4 infections were treated for a mean 23 weeks, and the virus was suppressed to below the limit of quantification in all of the patients in the study. The interim SVR4 rate was 77%. This finding is very important because the treatment of recurrent HCV infection has been a huge unmet need in the transplant community. Interferon, ribavirin, and protease inhibitors have been tried, but major challenges emerged related to drug interactions and interferon toxicity in this population. Of note is that grade 3 or 4 hemoglobin abnormalities occurred in 20% of the patients.

A very interesting report was on the compassionate use of sofosbuvir in patients with severe recurrent HCV infection after liver transplantation. This represents the first-time observations on the use of sofosbuvir and ribavirin in such patients, including a large number with fibrosing cholestatic hepatitis, which is almost invariably fatal. Marked viral suppression occurred in most of the patients, with the viral load undetectable in many. Concomitant with viral suppression was clinical improvement as measured by laboratory measures, such as bilirubin and international normalized ratio, and resolution of ascites in some patients. The study demonstrated that fairly rapid clinical improvement can occur with viral suppression. It raises the intriguing possibility, which is being studied currently, that patients with decompensated cirrhosis might benefit in terms of stabilization or improvement in their clinical condition if the virus can be effectively suppressed.

Yet another report explored use of sofosbuvir and ribavirin in patients prior to transplant. The results showed that the combination was highly effective in inducing viral suppression. Interim results indicated that nearly two-thirds of patients were free of HCV 12 weeks after transplant. This is the first time in the history of hepatology that a well-tolerated oral regimen of antiviral therapy—in this case sofosbuvir and ribavirin—can prevent recurrence of HCV in the newly transplanted liver. Interestingly, all but 1 of the patients who had undetectable virus for more than 30 days prior to transplant had SVR12, so it appears that a threshold in terms of the duration of viral undetectability needed for protection against recurrence before transplantation has been established.

Regimens in HCV/HIV Coinfection

The PHOTON-1 study of sofosbuvir plus ribavirin in patients with HIV/HCV coinfection is a very important study because it is the first study of oral therapy in coinfected patients. The cumulative data on triple therapy with peginterferon, ribavirin, and a DAA so far suggest that HIV-coinfected patients are not at the disadvantage that was once perceived. The SVR12 rates and tolerability in these patients are equivalent to those seen in monoinfected patients.

Treatment-naive patients with genotype 2 and 3 infections received 12 weeks of therapy, although, in light of new findings just mentioned, the investigators would probably now treat patients with genotype 3 HCV infection with 24 weeks of therapy. The most remarkable finding from this study is that the SVR12 rate among the patients with genotype 1 was 76%. The SVR12 rates in the patients with genotype 2 and 3 infections were similar to those in the mono-infected patients: 88% and 67%, respectively. These results indicate an important interferon-free option for HIV/HCV coinfected patients.

Along with other data from phase 2 trials in mono-infected patients, this raises the question of whether there might be a role for sofosbuvir and ribavirin in patients with genotype 1 in whom therapy is perceived as urgent, who cannot tolerate interferon, and for whom other DAAs cannot be accessed. Indeed, the package insert for sofosbuvir indicates that sofosbuvir and ribavirin can be considered for 24 weeks in patients who are interferon-ineligible.

DAA Combination for Genotype 1b HCV Infection

Another study looked at 2 investigational DAAs, the protease inhibitor ABT-450 and the NS5A inhibitor ABT-267 in patients with genotype 1b HCV infection. Only patients with genotype 1b were included in the study because a proof-of-concept study demonstrated that the genotype 1a virus becomes resistant more readily than does genotype 1b to these 2 classes of drugs. Because there are areas of the world, such as Asia, where 1b is highly predominant, a dual regimen might be very attractive because the treatment would be less expensive than triple therapy and easy to take. The bottom line is that the regimen appeared to be highly effective, with an SVR12 rate of 95% in treatment-naive patients and 90% in the previous null responders, with a small number of virologic failures in the null responders.

STARTVerso 3: A Faldaprevir-Based Regimen

The STARTVerso 3 trial of faldaprevir plus peginterferon and ribavirin in prior null responders demonstrated a SVR rate that was higher than that seen for retreatment with peginterferon plus ribavirin alone, which was no surprise. The safety profile was similar to that seen in the STARTVerso 1 study of the triple-therapy regimen in treatment-naive patients. No increment in anemia was seen but hyperbilirubinemia was observed as result of the drug's interaction with bilirubin transporters and UDP glucuronyltransferase, which helps metabolize bilirubin. Hyperbilirubinemia is also seen with simeprevir due to an interaction with transporters, and the hyperbilirubinemia seen with both faldaprevir and simeprevir is independent of hepatotoxicity and not considered a liver toxic reaction that requires discontinuation of therapy.

Ledipasvir Plus Sofosbuvir Regimens

The ELECTRON trial studied the combination of sofosbuvir and the NS5A inhibitor ledipasvir with or without ribavirin. There were 5 arms in this study: treatment experienced cirrhotic patients who received 12 weeks of combination sofosbuvir plus ledipasvir with or without ribavirin, treatment-experienced patients with advanced fibrosis (F3/F4) or cirrhosis who received 12 weeks of either sofosbuvir plus ledipasvir or sofosbuvir plus ledipasvir plus the NS5B non-nucleoside inhibitor GS-9669, and treatment-naive patients with mild fibrosis who received a 6-week treatment course of sofosbuvir plus ledipasvir.

For cirrhotic patients receiving triple therapy, the SVR12 rate was 100%. The SVR12 rate for cirrhotic patients receiving the ribavirin-free regimen was 70%. As for the 2 study arms with advanced fibrosis or cirrhosis, all patients had an SVR12 regardless of which arm they were in, which suggests that ribavirin, which has some toxicity, can potentially be substituted with the seemingly less toxic compound GS 9669—an observation that needs to be further explored.

The most important message in this study, however, was that 6 weeks of therapy is not enough. The SVR rate in patients with mild fibrosis who were treated with 6 weeks of sofosbuvir, ledipasvir, and ribavirin was 68%. All of the failures were due to relapse. Thus, although it was remarkable that two-thirds of patient with mild fibrosis could be cured within 6 weeks of therapy, the overall results were less than optimal.

Of note, however, were promising early rates of response with 6 weeks of triple regimens containing sofosbuvir, ledipasvir and either GS-9669 or GS-9451, a protease inhibitor studied in a trial called SYNERGY conducted through the National Institute of Allergy and Infectious Diseases, further results from which are awaited.

The same regimen—sofosbuvir plus ledipasvir with or without ribavirin—was studied in the LONESTAR trial. This trial looked at noncirrhotic treatment-naive patients who received 8 weeks of therapy without ribavirin or 12 weeks of therapy without ribavirin. SVR12 rates in the range of 95% to 100% were seen. The most remarkable feature of this study was that similar SVR12 rates were found in 2 additional arms containing patients who had previously failed protease inhibitors. In addition, about half of the patients were cirrhotic. The study dramatically illustrates that treatments with very high levels of efficacy for broadly diverse populations of patients with HCV infection can be expected in the near future.

Notes

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