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A SPECIAL MEETING REVIEW EDITION

Advances in the Treatment of Hepatitis C Virus Infection From EASL 2013

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Special Reporting on:

- Simeprevir Plus Peginterferon/Ribavirin Is Associated with a High SVR12 Rate in Treatment-Naive Patients with Genotype 1 Hepatitis C Virus Infection
- Addition of Simeprevir to Peginterferon/Ribavirin Is Associated with Faster Resolution of Fatigue in Treatment-Naive Patients
- Sofosbuvir Plus Ribavirin Demonstrates Significant Efficacy in Multiple HCV Genotype 2/3 Populations
- Daclatasvir Plus Sofosbuvir with or without Ribavirin Yields 100% SVR24 Rate in Genotype 1 Patients Who Fail Telaprevir or Boceprevir
- Addition of TG4040 Vaccine to Peginterferon/Ribavirin Increases Sustained Virologic Response Rate at 24 Weeks in Genotype 1 Hepatitis C Infection

PLUS Meeting Abstract Summaries

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Table of Contents

Simeprevir Plus Peginterferon/Ribavirin Is Associated with a High SVR12 Rate in Treatment-Naive Patients with Genotype 1 Hepatitis C Virus Infection 5

Addition of Simeprevir to Peginterferon/Ribavirin Is Associated with Faster Resolution of Fatigue in Treatment-Naive Patients 8

Sofosbuvir Plus Ribavirin Demonstrates Significant Efficacy in Multiple HCV Genotype 2/3 Populations 11

Daclatasvir Plus Sofosbuvir with or without Ribavirin Yields 100% SVR24 Rate in Genotype 1 Patients Who Fail Telaprevir or Boceprevir 14

Addition of TG4040 Vaccine to Peginterferon/Ribavirin Increases Sustained Virologic Response Rate at 24 Weeks in Genotype 1 Hepatitis C Infection 16

Commentary
Ira M. Jacobson, MD 17

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Simeprevir Plus Peginterferon/Ribavirin Is Associated with a High SVR12 Rate in Treatment-Naive Patients with Genotype 1 Hepatitis C Virus Infection

Simeprevir is an investigational hepatitis virus (HCV) NS3/4A protease inhibitor that showed potent antiviral activity against multiple genotypes in preclinical studies and allows once-daily dosing. Two international, phase IIb, randomized, double-blind, placebo-controlled studies in patients with genotype 1 HCV demonstrated the efficacy and safety of simeprevir in combination with peginterferon/ribavirin in treatment-naive patients (PILLAR trial)[1] and treatment-experienced patients (ASPIRE trial).[2] In both trials, the addition of simeprevir to peginterferon/ribavirin was associated with high sustained virologic response (SVR) rates with little additional toxicity over peginterferon/ribavirin alone.

Based on these findings, 2 randomized, double-blind, placebo-controlled phase III trials, QUEST-1 and QUEST-2, were undertaken to evaluate the efficacy and safety of simeprevir plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1 infection.[3,4] Results of both trials were presented at the 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013).

QUEST-1: Simeprevir Plus Peginterferon/Ribavirin

Results of QUEST-1 were presented by Ira M. Jacobson MD, Chief of the Division of Gastroenterology and Hepatology and Vincent Astor Distinguished Professor of Medicine at the Joan Sanford I. Weill Medical College of Cornell University in New York City. Simeprevir 150 mg once daily plus peginterferon/ribavirin (n=264) was compared with placebo plus peginterferon/ribavirin (n=130) in treatment-naive patients with HCV genotype 1 infection. Patients were stratified by HCV genotype subtype and the interleukin-28B (*IL-28B)* genotype.

Patients received simeprevir or placebo for the first 12 weeks of peginterferon/ribavirin therapy. 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.

Patient characteristics were well balanced between arms. Approximately 56% of patients were male. Patients were predominately white, with a median age of 48 years, 29% had the *IL-28B* CC genotype, and approximately 56% had genotype 1a infection. Cirrhosis was present in approximately 12% of patients.

The addition of simeprevir to peginterferon/ribavirin was associated with a significant improvement in efficacy over peginterferon/ribavirin alone, with SVR at Week 12 (SVR12) rates of 80% and 50%, respectively ($P<.001$). Responses to therapy also occurred more rapidly in patients treated with simeprevir; the rapid virologic response (RVR) rate was 80% versus 12% with placebo, and 85% of patients treated with simeprevir were able to receive the shorter 24-week therapy. The SVR12 rate among those patients was 91%. The SVR12 rate among the patients not eligible for shortened therapy was 21%.

Subgroup analyses demonstrated a benefit with simeprevir across patient groups, including by *IL-28B* genotype, METAVIR score, and HCV genotype subtype; the only exception was patients with the Q80K polymorphism at baseline, in whom the difference from placebo was not significant. However, among the patients with Q80K who attained RVR, the SVR12 rate was 74%. Among patients with liver cirrhosis, SVR12 rates were 58% and 29%, respectively, in the simeprevir and control arms.

The addition of simeprevir to peginterferon/ribavirin also was associated with a reduction in the incidence of on-treatment failure compared with peginterferon/ribavirin alone (9% vs 34%) and viral relapse (9% vs 21%). In 92% of evaluable cases (35 of 38), emergent mutations in the NS3 protease domain were detected in patients not attaining SVR. These mutations were primarily R155K (alone or with other substitutions) in genotype 1a and D168V in genotype 1b.

Patients treated with simeprevir reported significant improvements from baseline in fatigue and degree of impairment in productivity and activity, the findings of which were reported in detail in another presentation.

Simeprevir was generally well tolerated. The rate of discontinuation due to adverse events was 3% in both arms. The incidence of grade 3/4 adverse events was 23% in the simeprevir plus peginterferon/ribavirin arm and 29% in the peginterferon/ribavirin only arm. The most common adverse events in the simeprevir and control arms were fatigue (40% and 38%, respectively), headache (31% and 37%, respectively), and pruritus (21% and 11%, respectively). Simeprevir was associated with transient, mild elevations in bilirubin levels, although these were not accom-

ABSTRACT SUMMARY 12-Week Regimen of Sofosbuvir Plus Peginterferon/Ribavirin Is Associated with a 90% SVR12 Rate

In the previously published phase II ATOMIC trial, administration of sofosbuvir in combination with peginterferon alfa-2a and ribavirin in treatment-naive patients with genotype 1 HCV infection was associated with an SVR rate of 87–89% at post-treatment Week 24 (SVR24) after a treatment period of 12–24 weeks.[1] High SVR24 rates also were observed in patients with genotype 4 (9 of 11 patients; 82%) and genotype 6 (5 of 5; 100%).

Based on these outcomes, the open-label, single-arm NEUTRINO trial was conducted to further evaluate the efficacy and safety of this 3-drug regimen in patients with previously untreated HCV infection. Results of the NEUTRINO trial were presented at EASL 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.

The NEUTRINO study enrolled 327 treatment-naive patients with genotype 1, 4, 5, or 6 HCV infection.[2] All patients received sofosbuvir (400 mg once daily), peginterferon alfa (180 mg weekly), and ribavirin (1,000–1,200 mg daily) for a treatment duration of 12 weeks. The inclusion criteria were broad, defining no upper limit for age or BMI. Opioid replacement therapy was allowed. Hematologic inclusion criteria were a platelet count above 90,000/mm^3 and a neutrophil count above 1,500 cells/mm^3.

Dr. Lawitz noted that the patient population accurately reflected the US HCV population, with a mean age of 52 years and a median BMI of 29 kg/m^2. Sixty-seven percent of patients were male and 17% were black. The most prevalent HCV genotype was genotype 1 (89%). The *IL-28B* CC genotype was present in 29% of patients, and 17% of patients had evidence of cirrhosis.

The primary endpoint was SVR12, defined as HCV RNA below the limit of quantification (<25 IU/mL) at post-treatment Week 12. the SVR12 rate with triple therapy containing sofosbuvir was 90%, representing a substantial improvement over the calculated historical control rate of 60% with peginterferon/ribavirin alone (*P*<.001). SVR12 rates were high across all genotypes, including 89% for genotype 1, 96% for genotype 4, and 100% for genotypes 5 and 6. The SVR12 rate among patients with *IL-28B* genotype CC was 98% and was 92% in patients without cirrhosis and 80% in patients with cirrhosis. Dr. Lawitz noted that 80% was the highest SVR rate reported thus far in a population of patients with cirrhosis.

All patients attained HCV RNA below the limit of quantification by Week 6. Of the 28 treatment failures, all were relapses. No sofosbuvir resistance was detected in these patients as assessed by S282T resistance mutations or by phenotypic analysis.

Grade 3/4 adverse events were reported in 15% of patients ,and 5 (2%) patients discontinued treatment early due to adverse events. The safety profile of the regimen was as expected for peginterferon/ribavirin, with common adverse events, including fatigue, headache, nausea, and insomnia. There did not appear to be any additive toxicity with the inclusion of sofosbuvir in the otherwise standard regimen.

The investigators concluded that peginterferon/ribvarin plus sofosbuvir offers a short, effective therapy for patients with HCV genotype 1, 4, 5, or 6 infection.

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ABSTRACT SUMMARY High SVR Rate with Daclatasvir, Asunaprevir, and BMS-791325 in Treatment-Naive Patients with Genotype 1 HCV

Updated interim findings of a peginterferon/ribavirin-free triple therapy regimen look promising, with the regimen producing high SVR rates. The randomized, open-label, phase II trial evaluated a regimen consisting of 3 investigational direct-acting antivirals (DAA)—the NS5A inhibitor daclatasvir, the protease inhibitor asunaprevir, and the non-nucleoside NS5B inhibitor BMS-791325—in treatment-naive patients with genotype 1 HCV infection and without cirrhosis.[1]

The study, presented at EASL 2013 by Gregory T. Everson, MD, Professor and Director of Hepatology and Liver Transplantation at the University of Colorado Health Sciences in Denver, enrolled 32 patients who were randomly assigned to receive daclatasvir 60 mg once daily, asunaprevir 200 mg twice daily, and BMS-791325 75 mg twice daily for 24 weeks or 12 weeks. After the regimen demonstrated an acceptable safety profile, 34 additional patients were enrolled and randomly assigned to the same regimens and treatment durations, although the BMS-791325 dose was increased from 75 mg to 150 mg.

Of the 66 enrolled patients, 74% had genotype 1a infection, 79% were white;,and 30% had the *IL-28B* CC genotype. In a previous report on the efficacy and safety of arms 1 and 2, the daclatasvir, asunaprevir, and BMS-791325 regimen was associated with significant efficacy, with SVR4 and SVR12 rates exceeding 90%.[2] At EASL 2013, Dr. Everson provided an updated analysis from all 4 groups.

The primary endpoint, which was the SVR12 rate, was high in all evaluable groups although data on longer-term follow-up are pending in some of the treatment arms. The SVR rate in patients receiving 75 mg bid of BMS-791325 for either 24 or 12 weeks of therapy was 94%. SVR24 rates for 24 and 12 weeks were 88% and 94%, respectively, and the SVR36 rate in patients receiving 12 weeks of BMS-791325 was 88%.

The SVR12 rate in patients receiving 150 mg bid of BMS-791325 for 12 weeks was 89%. Data on SVR are pending for the treatment arm that received 24 weeks of treatment.

No cases of viral breakthrough were reported during treatment in patients receiving 75 mg bid of BMS-791325. No cases of post-treatment relapse were reported. In the 150-mg groups, virologic failure was reported during or after treatment in 3 (9%) of 34 patients receiving 150 mg bid of BMS-791325.

The single treatment-related serious adverse event was a case of cerebral vasoconstriction during peginterferon/ribavirin treatment intensification that had been initiated due to viral breakthrough. Otherwise adverse events were generally mild to moderate in severity. The most common adverse events across all treatment groups were headache (27%), asthenia (17%), diarrhea (17%), and nausea (14%). No grade 3/4 liver enzyme elevations or elevations in bilirubin levels were reported. One grade 3 headache that resolved during treatment and 1 grade 3 instance of lymphopenia in a patient with influenza were reported.

The findings, thus, suggest that the combination of daclatasvir, asunaprevir, and BMS-791325 can deliver high SVR rates as a peginterferon/ribavirin-free regimen with good tolerability. Based on the demonstrated activity and safety profile, a phase III trial is planned to evaluate these agents as a fixed-dose combination.

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panied by elevations in aminotransferases or alkaline phosphatase levels.

QUEST-2: Simeprevir Plus Peginterferon (Alfa-2a or Alfa-2b) plus Ribavirin

Results of the QUEST-2 trial were presented by Michael Manns, MD, Professor and Chairman of the Department of Gastroenterology, Hepatology, and Endocrinology at the Medical School of Hannover in Hannover, Germany. Patients were randomly assigned 2:1 to receive either simeprevir (150 mg once daily) plus peginterferon (alfa-2a or alfa-2b) for 12 weeks followed by peginterferon/ribavirin alone for 12 weeks or placebo plus peginterferon (alfa-2a or alfa-2b) and ribavirin for 12 weeks followed by peginterferon/ribavirin alone for an additional 36 weeks.[3] 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 *IL-28B* genotype.

More than 90% of the patient population of QUEST-2 was white. The median age was 46–47 years, and the median body mass index (BMI) was 26 kg/m^2. Thirty percent of patients in the simeprevir arm and 31% in the placebo-controlled arm had the *IL-28B* CC genotype, and 58% in both groups had genotype 1b disease. Cirrhosis was present in 7% of patients in the simeprevir arm and 11% in the placebo arm. The baseline HCV RNA level was 6.5 log.

The SVR12 rate was significantly higher in patients receiving simeprevir plus peginterferon/ribavirin than in patients receiving peginterferon/ribavirin alone (81% vs 50%; *P*<.001). Moreover, 91% of patients treated with simeprevir received the shorter 24-week therapy based on response-guided therapy. The SVR12 rate among these patients was 86%. Of the remaining 9% of patients in the simeprevir arm who did not meet the early stopping criteria, the SVR12 rate was 32%.

The significant superiority of simeprevir to placebo was observed regardless of the type of interferon used and across all key subgroups, including gender, viral load, genotype subtype, *IL-28B* genotype, and METAVIR score. Dr. Manns reviewed SVR12 rates across key subgroups. An analysis according to *IL-28B* genotype showed higher SVR12 rates in the simeprevir arm than in the placebo arm in all 3 genotypes, including CC (96% vs 81%), CT (80% vs 41%), and TT (58% vs 19%). There was no significant difference in response to simeprevir-containing therapy based on subtype (1a or 1b). SVR12 rates were also higher with simeprevir versus placebo in patients with mild liver disease (METAVIR score F0–F2: 85% vs 51%), in patients with F3 fibrosis (67% vs 53%), and in patients with cirrhosis (65% vs 40%).

Simeprevir plus peginterferon/ribavirin therapy also was more effective than placebo plus peginterferon/ribavirin as assessed by rates of on-treatment failure (7% vs 32%) and relapse (13% vs 24%).

Rates of adverse events were similar between arms; the incidence of serious adverse events with simeprevir and placebo was 2.3% and 1.5%, respectively. The most frequently reported adverse events, occurring at a similar rate in both arms, were headache, pyrexia, fatigue, and influenza-like illness. Two adverse events reported more frequently with simeprevir than placebo were rash (24% vs 11%) and photosensitivity (4% vs 1%). The incidence of anemia was similar between treatment arms. Simeprevir was associated with mild elevations in bilirubin levels that increased over time, leading to differences in mean hemoglobin levels between treatment arms at Week 24, although levels returned to baseline thereafter.

Patient-reported outcomes showed comparable treatment effects on fatigue, productivity and activity impairment, and absenteeism, with some improvements in the simeprevir arm reflecting a higher response rate.

Clinical trials evaluating the optimal use of simeprevir are ongoing, including the QUEST-1 and QUEST-2 trials in treatment-naive patients and the PROMISE trial in treatment-experienced patients. The COSMOS trial is evaluating a combination of simeprevir and sofosbuvir with or without ribavirin in treatment-naive patients and nonresponders.[5] Interim results of COSMOS, reported at the 20th Conference on Retroviruses and Opportunistic Infections, which took place March 3–6, 2013 in Atlanta, Georgia, suggest that 12 or 24 weeks of simeprevir plus sofosbuvir with or without ribavirin is generally well tolerated and achieves high suppression of HCV RNA by Week 4 of therapy.

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Addition of Simeprevir to Peginterferon/Ribavirin Is Associated with Faster Resolution of Fatigue in Treatment-Naive Patients

Fatigue is a significant issue in patients with chronic HCV infection. The infection itself is associated with increased fatigue, and HCV therapy with peginterferon/ribavirin is also associated with worsened fatigue.[1] In addition, HCV infection is associated with impairments in health-related quality of life (HRQoL) that are exacerbated by peginterferon/ribavirin.[2,3]

At EASL 2013, Jane Scott, MD, Director of Patient Reported Outcomes at Janssen Global Services in High Wycombe, United Kingdom, presented 2 reports on the effects of adding simeprevir to peginterferon/ribavirin on fatigue and HRQoL in patients with genotype 1 chronic HCV infection in 2 phase II trials: the PILLAR trial[4] in treatment-naive patients and the ASPIRE trial[5] in treatment-experienced patients.

In addition to reporting on the effects of fatigue with simeprevir, Dr. Scott and coinvestigators provided data on the reliability and validity of the Fatigue Severity Scale (FSS) and the EuroQOL 5 dimensions questionnaire (EQ-5D) in patients with HCV infection.

The FSS is a 9-item questionnaire that is measured on a 1–7 scale in which higher numbers indicate worse fatigue. The EQ-5D measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a visual analogue scale that rates health on the day of presentation, resulting in a HRQoL value ranging from 0–100, with 100 indicating perfect health. Based on their analysis, the investigators concluded that these scales provided valid measures for assessing fatigue in patients with chronic HCV and may be useful in other HCV-focused clinical trials.

PILLAR was an international, randomized, double-blind, placebo-controlled phase IIb trial that evaluated the addition of simeprevir (75 or 150 mg once daily) to peginterferon/ribavirin for 12 or 24 weeks in 386 treatment-naive patients with genotype 1 HCV infection.[4] In the simeprevir-containing arms, response-guided therapy was used to determine the duration of peginterferon/ribavirin therapy. Patients with an HCV RNA viral load of less than 25 IU/mL at Week 4 and undetectable HCV RNA at Weeks 12, 16, and 20 received treatment for 24 weeks. All other patients received peginterferon/ribavirin for 48 weeks. Post-therapy follow-up was continued until Week 72 for all patients. Patient characteristics were balanced between arms. The patient population was primarily white, with a median age of 46.5 years, and 55% were male.

The ASPIRE trial was an international, randomized, double-blind, placebo-controlled phase IIb trial that evaluated the addition of simeprevir (100 or 150 mg once daily) to peginterferon/ribavirin for 12, 24, or 48 weeks in 462 treatment-experienced patients with genotype 1 HCV infection.[5] The total duration of peginterferon/ribavirin therapy was 48 weeks in all arms. Post-therapy follow-up was continued until Week 72 for all patients. Patient characteristics also were balanced between arms. The patient population was primarily white (93%), with a median age of 50 years, and 67% were male.

The addition of simeprevir to peginterferon/ribavirin was associated with an improvement in SVR rates over peginterferon/ribavirin alone in both trials. In treatment-naive patients, SVR24 rates were 75–82% in the simeprevir 75-mg arms, 81–86% in the simeprevir 150-mg arms, and 65% in the control arm.[6] In treatment-experienced patients, SVR24 rates were 61–70% in the simeprevir 100-mg arms, 67–80% in the simeprevir 150-mg arms, and 23% in the control arm.[7]

Patient-reported fatigue during the 72-week follow-up period was included as a secondary endpoint for both trials. At baseline, fatigue was assessed in 63–65% of treatment-naive patients and 97% of treatment-experienced patients and thereafter assessed at Weeks 4, 12, 24, 36, 48, 60, and 72. In both trials, the mean FSS score at baseline was higher among enrolled patients compared with historical reports of scores in healthy controls, indicating the presence of clinically important fatigue before the start of treatment.

In both trials, the mean FSS score increased to a similar extent during treatment, indicating a similar degree of worsening fatigue during treatment. However, fatigue resolved more quickly in treatment-naive patients who were receiving simeprevir compared with patients receiving peginterferon/ribavirin alone. The mean FSS score returned to baseline after Week 24 in patients treated with simeprevir, whereas FSS scores did not return to baseline until after Week 48 in patients receiving standard peginterferon/ribavirin therapy. The shorter duration of fatigue in patients receiving simeprevir in comparison with patients receiving peginterferon/ribvarin resulted in a significant overall reduction in fatigue over the entire 72-week follow-up period ($P<.001$). In treatment-experienced patients, FSS scores remained stable from Weeks 12 to Week 48, returning to levels comparable to or below baseline by Weeks 60–72. There were no significant

ABSTRACT SUMMARY 12-Week Interferon-Free Direct-Acting Antiviral Regimens Are Feasible in Patients with Genotype 1 HCV Infection

Results of the AVIATOR study, which compared various combinations of investigational DAAs with or without ribavirin for varying treatment durations in patients with genotype 1 HCV infection, were presented at EASL 2013 by Kris V. Kowdley, MD, Clinical Professor of Medicine at the University of Washington in Seattle. The study enrolled patients with genotype 1 HCV infection without cirrhosis who were treatment-naive or had a prior null response to peginterferon/ribavirin. The treatment regimen studied consisted of the protease inhibitor ABT-450, given at a dosage of 100–200 mg once daily, plus 100 mg of ritonavir in combination with 1 or 2 other DAAs. Other DAAs included the NS5A inhibitor ABT-267, administered at a dosage of 25 mg once daily, and/or the non-nucleoside NS5B inhibitor ABT-333, administered at a dosage of 400 mg twice daily with or without ribavirin. Treatment durations of 8, 12, and 24 weeks were evaluated.

Dr. Kowdley presented data on outcomes among patients who received all 3 DAAs plus ribavirin for 12 or 24 weeks. Of the 247 patients in these arms, 55% were male, 10.5% were black, and the mean age was 51 years. Most (81%) patients had non-CC *IL-28B* genotypes, 66% had genotype 1a infection, and 37% of patients had at least METAVIR stage 2 fibrosis.

The 12-week regimen consisting of 3 DAAs plus ribavirin was associated with an SVR12 rate of 98% in treatment-naive patients and 93% in prior null responders. SVR4 rates were 99% and 93%, respectively. SVR4 rates were similarly high among patients receiving 24 weeks of 3 DAAs plus ribavirin, at 96% in treatment-naive patients and 98% in prior null responders.

In a combined analysis of the 12-week and 24-week arms, responses to 3 DAAs plus ribavirin were similar across key patient subgroups, including *IL-28B* genotype (CC vs non-CC), HCV genotype subtype, baseline HCV RNA (<7 $\log_{10}$ vs ≥7 $\log_{10}$ IU/mL), and degree of fibrosis (F0–F1 vs ≥F2).

Four (1.6%) patients discontinued treatment due to treatment-related adverse events. Of the 7 (2.8%) patients with serious adverse events, 1 case of arthralgia was considered possibly treatment-related. The most common moderate-to-severe treatment-related adverse events were asthenia and fatigue. Grade 3/4 laboratory abnormalities, which all resolved with continued treatment, included 6 (3%) cases of elevations in bilirubin levels and 1 case (0.6%) of an elevation in alanine transaminase level.

Based on the efficacy and safety findings from this trial, a phase III trial is underway to evaluate the efficacy and safety of a 12-week regimen of 3 DAAs with or without ribavirin in treatment-naive and treatment-experienced patients without cirrhosis. A separate phase III trial is evaluating the 3-DAA regimen with ribavirin for 12 or 24 weeks in patients with cirrhosis.

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ABSTRACT SUMMARY Short-Course Peginterferon/Ribavirin Plus 2 Direct-Acting Antiviral Agents in Treatment-Naive Patients with Genotype 1 and *IL-28B* CC

The *IL-28B* CC genotype is associated with a high likelihood of response and rapid responses to interferon-containing therapy.[1] Therefore, there has been interest in evaluating shorter-course therapies (<12 weeks) in these patients. Alexander J. Thompson, MD, PhD, a researcher in the Duke Clinical Research Institute and Division of Gastroenterology at Duke University in Durham, North Carolina, presented results of a study that shortened the course of peginterferon/ribavirin by adding 2 investigational DAAs to the regimen, the protease inhibitors GS-5885 and GS-9541.[2]

The 4-drug combination was administered to noncirrhotic, treatment-naive patients with HCV *IL-28B* CC genotype 1 infection for 6 or 12 weeks. Patients were stratified according to baseline viral load.

A total of 244 patients were randomly assigned to receive 30 mg of GS-5885 once daily plus GS-9541 200 mg once daily plus peginterferon/ribavirin (n=123) or peginterferon/ribavirin alone (n=121). Patients in the experimental arm who had a very rapid virologic response (vRVR), defined as an HCV RNA viral load below the lower limit of quantification (<25 IU/mL) at Week 2, were re-randomized to a treatment duration of 6 weeks or 12 weeks. Patients also were stratified by viral load at the second randomization.

A vRVR was achieved in 113 (92%) of the 123 patients in the experimental arm and were assigned to 6 weeks (53 patients) or 12 weeks (60 patients) of therapy. In comparison, an RVR, defined as a HCV RNA level below the lower limit of quantification at Week 4, was achieved in 43% of patients in the peginterferon/ribavirin arm.

The SVR12 rates were 89% with the 4-drug regimen (including 79% with 6 weeks of therapy and 98% with 12 weeks of therapy) compared with 73% with peginterferon/ribavirin. There were 9 relapses in the experimental arm in patients receiving 6 weeks of therapy and no relapses in the 12-week experimental arm. No differences were observed in the response rate based on HCV subtype in either arm.

Aplastic anemia and pancytopenia developed in 1 patient in the 4-drug arm. Because 3 cases of pancytopenia have been observed in trials of quadruple therapy regimens involving 2 DAAs plus peginterferon and ribavirin, the 4-drug regimen was discontinued. This early discontinuation did not affect patients in the 6-week treatment cohort but did affect 8 patients in the 12-week cohort, although all 8 of these patients received at least 10 weeks of treatment.

Otherwise, adverse events were expected for patients receiving peginterferon/ribavirin. Frequently reported adverse events included headache (40%), fatigue (29–39%), and nausea (37%). Elevations in bilirubin levels occurred in 3 patients while on therapy.

Dr. Thompson concluded that, although he did not expect this particular regimen to move forward in development, the findings warrant further investigation of short-duration therapy for patients with the HCV *IL-28B* CC genotype.

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differences in FSS score between groups over the study period.

In both trials, HRQoL also decreased to a similar extent from baseline to Week 24 across treatment groups. However, HRQoL also improved more rapidly among treatment-naive patients who were receiving simeprevir compared with patients who were receiving peginterferon/ribavirin alone. In the simeprevir groups, EQ-5D values increased after Week 24, approaching baseline levels by Week 48. In the control group, improvements in HRQoL occurred more gradually, returning to baseline ranges by Week 72. In treatment-experienced patients, HRQoL improved to levels comparable to or above baseline by Week 72 in all groups.

Dr. Scott concluded that the addition of simeprevir to peginterferon/ribavirin was associated with an increase in SVR rates without significantly increasing fatigue or impairing HRQoL over changes observed with peginterferon/ribavirin alone in treatment-naive patients and in treatment-experienced patients. Moreover, in treatment-naive patients, the shorter treatment duration associated with higher SVR rates resulted in a shortening of the time of fatigue and HRQoL impairments.

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Sofosbuvir Plus Ribavirin Demonstrates Significant Efficacy in Multiple HCV Genotype 2/3 Populations

Sofosbuvir is an orally administered nucleotide analog that inhibits the HCV-specific NS5B polymerase. Sofosbuvir has demonstrated potent antiviral activity against all identified HCV genotypes and has a high barrier to resistance.[1] In a phase II study in patients with HCV genotype 2 or 3 infection, a 12-week regimen of sofosbuvir and ribavirin was associated with SVR in 10 (100%) of 10 treatment-naive patients and 17 (68%) of 25 treatment-experienced patients.[2,3] Sofosbuvir also demonstrated an acceptable safety profile.

Several presentations provided updates on phase III trials of sofosbuvir/ribavirin in patients with genotypes 2/3 at EASL 2013. Featured were findings from the FISSION trial[4] in treatment-naive patients, the FUSION trial[5] in treatment-experienced patients, and the POSITRON trial[6] in patients who were not candidates for interferon therapy.

FISSION: Treatment-Naive Patients with HCV Genotypes 2/3

The final results of the FISSION trial were presented by Edward Gane, MD, Deputy Director of the New Zealand Liver Transplant Unit at Auckland City Hospital in New Zealand. FISSION compared 12 weeks of an all-oral regimen of sofosbuvir/ribavirin with 24 weeks of peginterferon/ribavirin in treatment-naive patients with HCV genotypes 2/3.[1] The trial enrolled 499 patients who were randomly assigned to 12 weeks of sofosbuvir (400 mg daily) plus ribavirin (1,000–1,200 mg daily) or 24 weeks of peginterferon (180 mg weekly) plus ribavirin (800 mg daily). Patients were stratified by HCV genotype, HCV RNA level (< or ≥106 IU/mL), and presence of cirrhosis.

In this noninferiority study, the primary endpoint was SVR12, which was defined as the proportion of patients with plasma HCV RNA below the level of quantification at 12 weeks post-treatment (based on a lower limit of detection of 25 IU/mL). Secondary endpoints included safety, viral kinetics, drug resistance, and HRQoL.

Patient characteristics were similar between the 2 treatment arms. The mean age of patients was 48 years, 87% were white, 66% were male, and 43% had the *IL-28B* CC genotype. The majority of patients (72%) had HCV genotype 3 infection, and 20% had compensated cirrhosis.

The study met its primary endpoint, with an SVR12 rate of 67% in both treatment arms. An analysis by genotype showed that SVR12 rates were significantly higher in patients with genotype 2 HCV receiving sofosbuvir/ribavirin than those receiving peginterferon plus ribavirin (97% vs 78%), but this improvement was not seen in patients with genotype 3 HCV infection compared with the placebo group (56% vs 63%).

Among patients with genotype 2 HCV infection plus cirrhosis, SVR12 rates with sofosbuvir/ribavirin were 91% compared with SVR12 rates of 62% with peginterferon/ribavirin. SVR12 rates among patients with genotype 3 infection and cirrhosis were 34% in those receiving sofosbuvir/ribavirin and 30% in those receiving peginterferon/ribavirin.

Sofosbuvir/ribavirin appeared to induce a more rapid response than peginterferon/ribavirin; at Week 4, the proportion of patients with HCV RNA levels below the limit of quantification was 99% and 67%, respectively. End-of-treatment response rates were 99% in both groups. No resistance was detected in any of the patients who failed sofosbuvir/ribavirin, all of whom relapsed except for a single patient who attained a response at Week 4 and whose relapse was associated with nonadherence to therapy.

The adverse event profile of sofosbuvir/ribavirin was similar to that reported with ribavirin alone and was associated with fewer adverse events than peginterferon/ribavirin, including lower rates of fatigue (36% vs 56%), headache (25% vs 44%), nausea (18% vs 28%), insomnia (12% vs 28%), and depression (6% vs 17%).

Overall rates of grade 3 or higher adverse events were also lower in patients receiving sofosbuvir/ribavirin than peginterferon/ribavirin (7% vs 19%), as were rates of hematologic adverse events (anemia [1% vs 4%], neutropenia [0% vs 15%], and thrombocytopenia [0% vs 7%]).

FUSION: Treatment-Experienced Patients with HCV Genotype 2/3 Infection

Final results of the phase III FUSION trial, which compared outcomes of sofosbuvir/ribavirin in treatment-experienced patients with HCV genotype 2/3 infection at 12 and 16 weeks werepresented by David Nelson, MD, Professor of Medicine in Molecular Genetics and Microbiology in the Division of Gastroenterology, Hepatology, and Nutrition at the University of Florida in Gainesville.[2] The trial enrolled 201 patients who had failed prior interferon-based therapy. Patients were randomly assigned to receive sofosbuvir (400 mg daily) and ribavirin (1,000–1,200 mg)

ABSTRACT SUMMARY Addition of Faldaprevir to Peginterferon/Ribavirin Yields High Response Rates in Treatment-Naive Patients with HCV Genotype 1

The final results of the randomized, double-blind, placebo-controlled phase III STARTVerso1 trial suggest that the response rate of peginterferon/ribavirin in treatment-naive patients with HCV genotype 1 can be improved with addition of the novel NS3/4A protease inhibitor faldaprevir. The findings were presented at EASL 2013 by Peter Ferenci, MD, Professor of Medicine in the Department of Gastroenterology and Hepatology at the Medical University of Vienna in Austria.[1]

The study enrolled 652 patients who were randomly assigned 1:2:2 to receive 24 weeks of peginterferon alfa-2a/ribavirin plus faldaprevir 120 mg once daily for 12 or 24 weeks, faldaprevir 240 mg once daily for 12 weeks, or placebo for 24 weeks. Patients in the faldaprevir-containing arms with an HCV RNA viral load of less than 25 IU/mL at Week 4 and an undetectable HCV RNA viral load at Week 8 stopped all treatment at Week 24. All other patients received peginterferon/ribavirin for 48 weeks. Patients were stratified based on HCV genotype 1 subtype and race.

Of the 652 enrolled patients, the mean age was 48 years, 52% were male; 78% were white, 20% were Asian, 17% had grade 3 or greater fibrosis, 39% had the *IL-28B* CC genotype, and 66% had genotype 1b.

The primary endpoint, the SVR12 rate after the planned end of treatment was significantly higher in patients receiving triple therapy with faldaprevir and faldaprevir monotherapy (79% and 80%, respectively) compared with placebo (52%; *P*<.0001 for both comparisons after adjusting for genotype and race). Among patients with the *IL-28B* CC genotype, triple therapy with faldaprevir and faldaprevir monotherapy were associated with SVR12 rates of 90% and 95%, respectively, compared with 63% with peginterferon/ribavirin alone. The SVR12 rates among patients with non-CC *IL-28B* genotypes were 71% in both faldaprevir arms and 47% in the peginterferon/ribavirin only arm.

Overall, 88% of patients receiving a faldaprevir-containing regimen were able to stop treatment at Week 24. Among patients with an early treatment response, SVR12 rates were 86% with faldaprevir 120 mg plus peginteferon/ribavirin, 89% with faldaprevir monotherapy, and 90% with peginterferon/ribavirin alone.

Outcomes were similar across all 3 treatment arms, including discontinuation rates (4–5%) and serious adverse event rates (6–7%). The incidence of grade 3 rash was less than 1% in each arm, and there were no reports of grade 4 rash. Anemia (hemoglobin ≤8.5 g/dL) was reported in 2–3% of patients across treatment arms.

Overall, the addition of faldaprevir to peginterferon/ribavirin appeared to significantly increase SVR12 rates in previously untreated patients with HCV genotype 1, and allowed a 24-week course of therapy in nearly 90% of patients.

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for 12 weeks followed by 4 weeks of placebo or else active treatment for 16 weeks. Patients were stratified by presence of cirrhosis and HCV genotype.

The enrolled patient population was primarily white (87%) and male (70%). Sixty-three percent had genotype 3 infection, and 30% had the *IL-28B* CC genotype. Cirrhosis was detected in approximately 34% of patients.

The SVR rates at study completion were 50% in patients receiving 12 weeks of therapy and 73% in those receiving 16 weeks of therapy (*P*<.001). Each treatment arm demonstrated superiority over historical controls. An analysis by genotype showed that the longer duration of therapy was particularly beneficial in patients with genotype 3 HCV infection. The SVR rates at 12 and 16 weeks of therapy were 30% and 62%, respectively. In patients with genotype 2, only a numerical trend toward better outcomes with 16 weeks of therapy was seen: SVR rates for 12 and 16 weeks of therapy were 86% and 94%, respectively, in these patients.

No difference in outcomes was seen between treatment groups in patients with genotype 2 HCV infection and without cirrhosis. In patients with genotype 2 infection and cirrhosis, a numerical improvement in the SVR rate was seen from 12 to 16 weeks of therapy (60% vs 78%), although Dr. Nelson cautioned that patient numbers for this analysis were small.

In patients with genotype 3 HCV infection, the longer duration of therapy was associated with greater improvement in SVR rates in both cirrhotic and noncirrhotic patients. The longer duration of therapy was of particular benefit in patients with genotype 3 infection and cirrhosis: The SVR rate was 19% with 12 weeks of therapy and 37% with 16 weeks of therapy.

Viral suppression was rapid. HCV RNA was below the limit of quantification in more than 80% of patients by Week 2 and 100% of patients by Week 4 and at the end of treatment. Relapse also occurred rapidly, with 85% of relapses occurring by Week 4. Overall, 73 patients had disease relapse; no S282T mutations were detected, and there were no phenotypic changes that could account for the resistance.

A safety analysis showed no new adverse events. Again, the most common adverse events were typical of those seen with ribavirin use and included fatigue (44%), headache (27%), insomnia (24%), and nausea (21%). Increasing the duration of therapy from 12 to 16 weeks did not appear to affect the safety profile. Moreover, no patients discontinued treatment due to adverse events.

ABSTRACT SUMMARY Predictive Factors for Serious Adverse Events with Triple Therapy in Patients with Advanced Liver Disease

The currently available HCV protease inhibitors telaprevir and boceprevir have significantly increased cure rates in patients with HCV infection. However, as the French Compassionate Use of Protease Inhibitors in Cirrhotics (CUPIC) cohort study demonstrated, these agents also increase the risk of severe adverse events in patients with advanced liver disease.[1] The ability to identify patients at greater risk for such severe safety issues could be valuable in the treatment selection process.

Results of a study identifying predictive factors associated with the development of serious adverse events in patients who are receiving protease inhibitor–containing triple therapy for treatment of advanced liver disease were presented by Karoline Rutter, MD, a researcher at the Abteilung Clinic for Gastroenterology and Hepatology at the Medical University of Vienna in Austria.[2] The researchers evaluated outcomes among 191 Austrian patients with HCV genotype 1 who received triple therapy with boceprevir or telaprevir and peginterferon/ribavirin. The researchers compared the incidence of adverse events between 131 patients with advanced liver disease (fibrosis stage 3–4) and 60 patients with mild liver disease (fibrosis stage 0–2). Baseline laboratory parameters were similar between the 2 groups except that patients with advanced fibrosis had lower platelet counts and serum albumin levels.

Overall, an infection-associated serious adverse event developed in 10% of patients. Such infections were more common in patients with more severe liver disease. Patients with cirrhosis accounted for 8 of 11 severe infections among patients treated with telaprevir and 7 of 9 severe infections among patients treated with boceprevir. Sepsis developed in 4 patients treated with telaprevir, 1 of whom died, and in 3 patients treated with boceprevir, 2 of whom died.

Predictive factors that were significantly associated with risk of severe infection included a platelet count of less than 100,000/mm^3, a serum albumin level of less than 35 g/dL, and significant portal hypertension, defined as a pretreatment hepatovenous pressure gradient of 10 mmHg or greater.

Overall, 20% of patients discontinued treatment due to adverse events that were most commonly due to infections (8%). There were no differences in discontinuation due to adverse events based on degree of fibrosis.

SVR rates according to degree of fibrosis decreased from 65% with fibrosis stage 0–2 to 47% with stage 3 and 28% in patients with cirrhosis (24% with boceprevir and 33% with telaprevir). Dr. Rutter noted that responses to lead-in therapy in patients with fibrosis stage 3–4 identified patients with the highest likelihood of SVR. Among patients treated with boceprevir, the SVR rates were 90% among patients with an HCV RNA of greater than 1 log at Week 4 and 42% among other patients.

Dr. Rutter concluded that, although triple therapy with telaprevir or boceprevir plus peginterferon and ribavirin is feasible in patients with advanced liver disease, proper patient selection and close monitoring are crucial. Moreover, responses to the lead-in period provided valuable information on the likelihood of attaining an SVR.

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POSITRON: Interferon-Ineligible, Intolerant, or Unwilling Patients with HCV Genotypes 2/3

Results of the phase III POSITRON trial, which evaluated the use of sofosbuvir/ribavirin in patients with HCV genotypes 2/3 who were lacking other treatment options, were presented by Ira M. Jacobson, MD, Chief of the Division of Gastroenterology and Hepatology and Vincent Astor Distinguished Professor of Medicine at the Joan Sanford I. Weill Medical College of Cornell University in New York City. The trial enrolled 278 patients who were unwilling to receive interferon (47%), ineligible for peginterferon therapy because of medical or psychiatric conditions (44%), or intolerant to peginterferon (9%).[3] Patients were stratified based on the presence of cirrhosis and randomly assigned 3:1 to sofosbuvir (400 mg once daily) plus ribavirin (1,000–1,200 mg daily; n=207) or placebo (n=71) for 12 weeks. After completion of the study, patients in the placebo group were eligible for open-label treatment.

Patient characteristics were well balanced between the study arms. The mean patient age was 51 years, the majority of patients were white, and 45% had the *IL-28B* CC genotype. Cirrhosis was present in 16% of patients in the sofosbuvir/ribavirin arm.

The primary endpoint—the SVR12 rate—was significantly higher

in the sofosbuvir/ribavirin group than the placebo group (78% vs 0%; *P*<.001). SVR12 rates by genotype were 93% for genotype 2 and 61% for genotype 3 HCV infection. Overall, SVR12 rates associated with sofosbuvir were higher in noncirrhotic than cirrhotic patients.

Responses to sofosbuvir/ribavirin occurred rapidly; HCV RNA was below the limit of quantification in 91% of patients by Week 2 and 99% of patients by Week 4. At Week 12, HCV RNA was undetectable in 100% of patients. No virologic breakthrough occurred on-treatment.

Of the 42 patients with virologic failure due to relapse, 40 were evaluated for resistance mutations. As in the FUSION trial, there were no reports of resistance to sofosbuvir, as indicated by the examination for the presence of S282T mutations or phenotypic analysis.

The safety profile of sofosbuvir/ribavirin was similar to that observed in other trials, with the occurrence of the expected adverse events associated with ribavirin use. Adverse events occurring more frequently among patients receiving sofosbuvir/ribavirin compared with placebo were fatigue, nausea, headache, and insomnia.

Findings from the FISSION, FUSION, and POSITRON trials indicate that sofosbuvir/ribavirin may be effective in patients with genotype 2 or 3 HCV infection. The regimen was more effective in patients with genotype 2 HCV infection and patients without cirrhosis.

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Daclatasvir Plus Sofosbuvir with or without Ribavirin Yields 100% SVR24 Rate in Genotype 1 Patients Who Fail Telaprevir or Boceprevir

A 3-drug regimen consisting of a protease inhibitor (telaprevir or boceprevir) in combination with peginterferon/ribavirin is effective in many patients with genotype 1 HCV infection and is now considered the standard of care in these patients. However, there are patients in whom this approach is not as likely to yield SVR. These include patients with the *IL-28B* CT or TT genotypes patients with a prior nonresponse to peginterferon/ribavirin, and patients with a poor rate of virologic decline during lead-in therapy. For this subset of patients who fail to attain response to telaprevir- or boceprevir-containing therapy, there are no treatment options available. An approach being evaluated in these patients is a combination regimen that includes the investigational NS5A replication complex inhibitor daclatasvir and the NS5B polymerase inhibitor sofosbuvir administered with or without ribavirin.

Daclatasvir and sofosbuvir have both demonstrated antiviral activity against multiple HCV genotypes, and each is dosed orally once daily. Both daclatasvir and sofosbuvir have been extensively evaluated in clinical trials and have demonstrated good tolerability.

The randomized, open-label, parallel-group, phase IIa trial AI-444040 evaluated the efficacy and safety of daclatasvir plus sofosbuvir with or without ribavirin in various HCV patient populations, including patients with difficult-to-treat HCV infection. The combination of daclatasvir and sofosbuvir with or without ribavirin for 12 or 24 weeks has been associated with an SVR rate nearing 100% in treatment-naive patients with genotype 1 infection.[1]

In the current analysis, Mark S. Sulkowski, MD, Professor of Medicine and Medical Director of the Viral Hepatitis Center at Johns Hopkins University in Baltimore, Maryland, presented findings at EASL 2013 from the AI-444040 study on patients with genotype 1 infection with virologic failure following telaprevir or boceprevir plus peginterferon/ribavirin.[2] Eligible patients could have had a lack of response on therapy, viral breakthrough during therapy, or virologic relapse after the end of treatment. The study excluded patients who discontinued telaprevir or boceprevir due to adverse events.

A total of 41 patients were randomly assigned to daclatasvir 60 mg once daily plus sofosbuvir 400 mg once daily with or without ribavirin for a total of 24 weeks. The median age was 57–59 years; patients primarily had HCV genotype 1a, and 98% of patients had a non-CC *IL-28B* genotype. The majority of patients had a METAVIR fibrosis score of F2 or greater, although patients with cirrhosis were not eligible. In the majority of cases, treatment failure was due to nonresponse or viral breakthrough rather than virologic relapse. Moreover, nearly half of the patients (45–48%) had NS3 polymorphisms conferring resistance to telaprevir and boceprevir at baseline.

All 41 patients attained SVR4 and 40 of 41 patients (98%) attained an SVR12. The single patient in whom an SVR12 was considered not achieved had failed to report to the study center for evaluation. However, the patient did present for the post-treatment Week 24 evaluation and had undetectable HCV RNA at that time. The SVR24 rate among the 21 evaluable patients was 100%. No virologic failures or relapses have been reported in this trial.

An analysis of outcomes according to baseline polymorphisms showed no difference in the kinetics of virologic suppression over the first 14 days based on existing protease inhibitor resistance.

One serious adverse event occurred in a single patient who was hospitalized with aplastic anemia in the setting of furosemide use. All other adverse events were mild to moderate. There were no reports of hemoglobin greater than 9 g/dL. The most common adverse events included fatigue, (which was more common in patients receiving ribavirin), headache, arthralgia, and alopecia. No other grade 3 or 4 hematologic abnormalities or hepatic abnormalities were reported.

Dr. Sulkowski concluded that this proof-of-concept study indicated that an oral, once-daily regimen of daclatasvir plus sofosbuvir with or without ribavirin could induce an SVR in patients with HCV genotype 1 infection who had demonstrated virologic failure on or after a course of treatment with telaprevir or boceprevir plus peginterferon/ribavirin.

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ABSTRACT SUMMARY Novel HS3/4A Protease Inhibitor MK-5172 Yields a High SVR Rate in Combination with Peginterferon/Ribavirin

MK-5172 is an investigational HCV NS3/4A protease inhibitor that demonstrated a high barrier to resistance in preclinical studies. Michael Manns, MD, Professor and Chairman of the Department of Gastroenterology, Hepatology, and Endocrinology at the Medical School of Hannover in Germany, presented updated interim results of a phase II dose-ranging study of MK-5172 in combination with peginterferon alfa-2b and ribavirin in patients with previously untreated HCV genotype 1 infection without cirrhosis.[1]

Patients were randomly assigned in 2 sequential cohorts to receive peginterferon/ribavirin and either MK-5172 100 mg, 200 mg, 400 mg, or 800 mg once daily, or else boceprevir for 24–48 weeks depending on HCV RNA levels at Week 4. Of the 332 enrolled patients, 13% were black, 60% had genotype 1a infection, and 27% of patients had the *IL-28B* CC genotype.

RvRs were observed in 84–91% of patients in the first MK-5172 cohort, allowing a shorter duration of therapy. In the combined cohort, MK-5172 plus peginterferon/ribavirin was associated with an SVR24 rate of 86% in the 100-mg arm, 92% in the 200-mg arm, and 54% in the boceprevir-containing arm.

Higher doses of MK-5172 (400 mg/day or 800 mg/day) were associated with new elevations in transaminase levels, which were managed with MK-5172 dose reductions to 100 mg once daily. In the majority of cases, transaminase levels normalized by Week 16 with continued MK-5172 administration at the 100-mg dose. The incidence rates of rash were similar between patients receiving the MK-5172–containing regimens and patients receiving the boceprevir-containing regimen (20% vs 27%), whereas the incidence of anemia was lower for patients receiving the MK-5172 regimens compared with patients receiving the boceprevir regimen (18% vs 27%). Clinical trials will further evaluate the efficacy and safety of MK-5172 administered at 100 mg once daily.

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Addition of TG4040 Vaccine to Peginterferon/Ribavirin Increases Sustained Virologic Response Rate at 24 Weeks in Genotype 1 Hepatitis C Infection

Immunotherapy is another approach under investigation in the treatment of HCV infection. The investigational therapeutic vaccine TG4040, a recombinant vaccinia poxvirus containing sequences that encode the NS3, NS4, and NS5B proteins from the genotype 1b HCV, was shown to boost the SVR rate in patients with genotype 1 HCV infection who were receiving peginterferon/ribavirin therapy. The vaccine was designed to activate HCV-specific T cells, which would then migrate to the liver and mount an immune response against infected cells, increasing the efficacy of HCV therapy.

After a phase I study demonstrated the acceptable safety profile and activity of TG4040, a randomized, open-label phase II study was initiated. It evaluated TG4040 in combination with peginterferon alfa-2a and ribavirin in treatment-naive patients with HCV genotype 1 infection.[1]

A total of 153 patients were randomly assigned 2:2:1 to receive 13 injections of TG4040 starting 12 weeks before peginterferon/ribavirin (TG4040 pretreatment; n=59), 6 injections of TG4040 starting 4 weeks after peginterferon/ribavirin (peginterferon lead-in; n=63), or peginterferon/ribavirin alone (control arm; n=31).

Patient characteristics were well balanced among arms. Overall, 55% of patients were male, 97% were white, the mean age was 41–44 years, 78% had genotype 1b infection, and 25% had the *IL-28B* CC genotype.

Initial results showed that pretreatment vaccination was associated with a significant improvement over peginterferon/ribvarin alone in the primary endpoint, which was complete early virologic response (cEVR).[2] The cEVR was defined as HCV RNA viral load below the 10 IU/mL limit of detection at 12 weeks after starting peginterferon/ribavirin. The proportion of patients attaining a cEVR was significantly higher in the TG4040 pretreatment arm than the control arm (64% vs 30%; *P*=.003). The cEVR rate in the peginterferon lead-in arm was 46%.

At EASL 2013, Heiner Wedemeyer, MD, Associate Professor in the Department of Gastroenterology, Hepatology, and Endocrinology at Hannover Medical School in Germany, presented updated results of the study. SVR rates and laboratory data on the immune-stimulating effects of the vaccine were reported. The trend toward higher virologic response rates with TG4040 pretreatment was maintained. SVR24 rates were 58% with TG4040 pretreatment, 51% with peginterferon lead-in, and 48% in the control arm.

Laboratory analyses of peripheral blood mononuclear cells isolated from patients in the TG4040 pretreatment arm showed an induction of TG4040-specific T-cell responses in 71% of patients and NS3-specific responses in 46%. The intensity of HCV-specific T-cell responses declined during peginterferon/ribavirin treatment, which Dr. Wedemeyer noted would be expected during interferon-based therapy. In some cases, antigen-specific immune responses increased again after the completion of interferon therapy.

Analyses of isolated serum samples detected total and neutralizing antibodies against the TG4040 vaccine vector (the poxvirus strain MVA) in all vaccinated patients. Although titers of MVA-specific neutralizing antibodies were highest in the TG4040 pretreatment arm than in the peginterferon lead-in arm, there was no significant association between the presence of neutralizing antibodies and virologic responses.

Adverse events were as expected for interferon-based therapy. The most common adverse events associated with TG4040 were mild-to-moderate injection site reactions, fatigue, influenza-like symptoms, and headache. Serious adverse reactions occurred in 19 patients, although none were considered TG4040-related. Serious hematologic adverse events developed in 4 patients receiving TG4040 and peginterferon/ribavirin. These serious hematologic events included 3 cases of severe thrombocytopenia and 1 case of aplastic anemia. Blood cell counts returned to normal ranges by 4 months post-treatment.

Dr. Wedemeyer concluded that proof-of-concept for viral vector-based immunotherapy has been established and that immunotherapy warrants further exploration in combination with interferon-free regimens.

References

1. Wedemeyer H, Janczewska E, Wlodzimierz M, et al. Phase II HCVac study of TG4040 immunotherapuetic in combination with pegIFNa2a and ribavirin in genotype 1 CHC treatment naive patients: SVR24 final results. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 62.
2. Wedemeyer H, Janczewska E, Wlodzimierz M, et al. Significant improvement of complete EVR in HCVac phase II clinical trial when adding TG4040 therapeutic vaccine to PegIFNa2a and ribavirin. Presented at the 47th Annual Meeting of the European Association for the Study of the Liver; April 18–22, 2012; Barcelona, Spain. Abstract 1403.

ABSTRACT SUMMARY Twice-Daily Telaprevir Dosing Is Associated with Higher Adherence Versus Every-8-Hour Dosing

The protease inhibitor telaprevir is approved for every-8-hour dosing in combination with peginterferon/ribavirin. Findings of the randomized, open-label, phase III OPTIMIZE trial comparing the efficacy and tolerability of a twice-daily regimen of telaprevir plus peginterferon/ribavirin with standard every-8-hour dosing in treatment-naive patients with genotype 1 HCV demonstrated an association between better adherence and telaprevir twice-daily dosing.[1] Higher adherence was associated with a near doubling of the likelihood of attaining SVR12. These findings were presented at EASL 2013 by William Sievert, MD, Clinician-Scientist at Monash University in Melbourne, Victoria, Australia.

A total of 740 patients were randomly assigned to telaprevir 1,125 mg twice daily plus peginterferon/ribavirin (n=369) or telaprevir 750 mg every 8 hours plus peginterferon/ribavirin (n=371) for 12 weeks. Patients with an RVR, received an additional 12 weeks of peginterferon/ribavirin; all other patients received an additional 36 weeks of peginterferon/ribavirin. Adherence was measured using a patient-reported electronic diary and pill count. Adherence data were available for 95% of the enrolled patients.

Overall, twice-daily telaprevir dosing was associated with a significant improvement in adherence over every-8-hour dosing as assessed by pill count (mean adherence, 99% vs 98%; *P*=.02) and by electronic diary (mean reported adherence, 95% vs 92%; *P*<.0001). Greater telaprevir adherence was associated with a higher likelihood of attaining SVR12. Among all patients treated with telaprevir, the SVR12 rate was 79% among those with high telaprevir adherence (≥95%) and 69% in patients with lower adherence (<95%). In a multivariate analysis, higher telaprevir adherence was associated with a nearly 2-fold increase in the likelihood of SVR12 (odds ratio, 1.86; 95% confidence interval, 1.29–2.69; *P*=.0008).

Reference

1. Sievert W, Buti M, Agarwal K, et al. Adherence with telaprevir bid versus every 8 hour dosing in treatment-naïve HCV-infected patients: results from the phase III OPTIMIZE study. Presented at the 48th Annual Meeting of the European Association for the Study of the Liver; April 24–28, 2013; Amsterdam, the Netherlands. Abstract 905.

Commentary

Ira M. Jacobson, MD

The findings from clinical trials of various treatment regimens for hepatitis C virus (HCV) infection presented at the 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013) included phase III data that may lead to regulatory approval of 3 new direct-acting antiviral (DAA) agents. Of greatest importance, because of their long-term implications, were findings from new or updated studies that demonstrated the curability of HCV infection without interferon across a broad spectrum of patient populations. The findings provided an increasingly firm foundation for a profound paradigm shift in HCV therapy that was being suggested at previous international meetings.

Final results of 3 phase III trials of 2 new protease inhibitors, simeprevir and faldaprevir, were presented at EASL 2013. Each is administered once daily and, when combined with peginterferon and ribavirin, confers a high sustained virologic response (SVR) rate with a good safety profile.

The QUEST-1 and QUEST-2 study findings confirmed the efficacy and safety of simeprevir in treatment-naive patients with genotype 1 HCV infection, demonstrated in earlier phase II studies. The SVR rates with 12 weeks of simeprevir combined with peginterferon and ribavirin followed by peginterferon and ribavirin alone were 80–81% versus 50% with peginterferon and ribavirin alone. Eighty-five percent to 91% of patients in these trials qualified for shortening the duration of therapy per response-guided–therapy criteria. Of patients who met the response-guided–therapy criteria, 86–91% had SVR. Rates of hemoglobin decline and rash with simeprevir were comparable to those observed with peginterferon and ribavirin alone.

Hyperbilirubinemia without concomitant elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels occurred more frequently with simeprevir, an observation previously shown to be related to interactions with transporters. Quality of life improved more quickly after simeprevir-based therapy than peginterferon and ribavirin therapy because patients were, for the most part, able to stop medication after 24 weeks instead of 48 weeks.

Similar results were obtained with the protease inhibitor faldaprevir in treatment-naive patients with genotype 1 HCV infection. Overall SVR rates were 79–80% with faldaprevir and 50% with peginterferon/ribavirin alone. Eighty-seven to 89% of patients met response-guided–treatment criteria and 86–89% of these patients had SVR. As with simeprevir, the safety profile of faldaprevir was favorable. Higher rates of hyperbilirubinemia unaccompanied by signs of hepatotoxicity (ie, ALT/AST level elevations) occurred with faldaprevir, owing to interactions with UDP-glucuronyl transferase and transporters.

The potential addition of these 2 protease inhibitors to the treatment armamentarium for HCV infection is exciting because they enhance efficacy when given with peginterferon and ribavirin to at least the same degree as currently available protease inhibitors with less frequent dosing and fewer adverse effects. The studies lay a clear foundation for the exploration of these drugs in interferon-free combination regimens.

Also presented at this year's EASL meeting were final results of the first phase III trials of an all-oral antiviral regimen for HCV infection. Presentations included results of 3 trials of sofosbuvir, a potent HCV nucleotide polymerase inhibitor, and ribavirin in either treatment-naive or treatment-experienced patients with HCV genotype 2 or 3. The findings indicate that 12 weeks of sofosbuvir plus ribavirin is extraordinarily effective in patients with HCV genotype 2 infection and also effective, but to a lesser degree, in patients with HCV genotype 3 infection, with the lowest response rates being seen in patients with genotype 3 HCV infection and cirrhosis. The adverse effects of this regimen appear to be attributable to known effects of ribavirin: eg, fatigue, insomnia, and anemia.

In treatment-experienced patients, 16 weeks of therapy was superior to 12 weeks, especially in patients with genotype 3 HCV infection. Additional studies on the extension of duration up to 24 weeks of sofosbuvir plus ribavirin in patients with genotype 3 HCV infection are needed as well as studies that examine the addition to the regimen of another antiviral agent—with or without ribavirin—to assess whether shorter durations of therapy can result in significantly higher SVR rates.

The NEUTRINO study findings brought a new dimension to interferon-based therapy by demonstrating SVR in 90% of patients infected with HCV genotypes 1, 4, 5, and 6 treated for 12 weeks with triple therapy containing sofosbuvir, peginterferon and ribavirin. SVR was achieved in 80% of patients with cirrhosis. This interferon-based regimen combines the highest rates of efficacy and shortened treatment duration with interferon-based therapy shown to date. Assuming that this regimen is approved, clinicians may consider it in patients for whom therapy is presently being deferred. Even patients who were hitherto unwilling to take interferon may be amenable to this regimen. Notably, in the 4 phase III trials of sofosbuvir, all treatment failures were due to post-treatment relapse, not on-treatment virologic failure, except for treatment failure in 1 patient with virologic breakthrough attributed to nonadherence. Samples from patients who failed to have SVR showed no evidence of genotypic or phenotypic resistance.

In the QUANTUM study of sofosbuvir and another polymerase inhibitor, PSI-938, in treatment-naive patients with genotype 1 HCV infection, the single most interesting feature was that patients who had failed 12 weeks of sofosbuvir and ribavirin—accounting for almost 50% of patients receiving the regimen—did very well on retreatment with 24 weeks of the same regimen; an SVR rate of 70% was achieved. This finding further underscores the absence of emergent resistance in patients who fail sofosbuvir-based regimens, contrary to other classes of antiviral agents that have lower barriers to resistance, whereby virologic failure or relapse is often accompanied by the appearance of resistance variants. Development of PSI-938 was suspended because of an association with hepatotoxicity.

Although it had been suggested in earlier studies that patients with a history of poor responsiveness to interferon were going to have problems responding to interferon-free regimens, findings reported at EASL 2013 suggested that oral antiviral regimens could essentially "level the playing field" between treatment-naive patients and treatment-experienced patients who had not responded to interferon-based therapy. The combination of ledipasvir (GS-5885), another NS5A inhibitor, and sofosbuvir along with ribavirin yielded SVR in 9 of 9 null responders to peginterferon/ribavrin therapy. Even more dramatically, the NS5A inhibitor daclatasvir plus sofosbuvir, with or without ribavirin, in 41 noncirrhotic patients who had failed protease inhibitor therapy yielded SVR in 100%. (One patient with missing data at follow-up Week 12 had SVR24.)

In another study of a regimen not containing a component with a high-barrier resistance, ABT-450/r (a protease inhibitor boosted by ritonavir), ABT-267 (an NS5A inhibitor), ABT-333 (a non-nucleotide polymerase inhibitor), and ribavirin for 12 weeks yielded SVR24 rates of 96% and 93% in treatment-naïve patients and null responders, respectively. The efficacy of a regimen lacking a nucleotide polymerase inhibitor was also suggested by a combination of asunaprevir (a protease inhibitor), daclatasvir, and BMS-791235 (a non-nucleotide polymerase inhibitor), which yielded SVR rates in treatment naive-patients in the 90% range across 4 treatment arms evaluating 12 or 24 weeks of therapy and 2 doses of BMS-791235.

The findings on an immunotherapeutic strategy were interesting in that there was a signal of impact on viral response and demonstrable HCV-specific T-cell responses. The results could set the foundation for potential studies of immunotherapy in combination with interferon-free regimens. Given the extraordinary rates of response that are being reported with DAAs, the role of immunotherapy is unclear.

The studies reported at EASL 2013 illustrate how far we have come from the days when some questioned whether HCV infection was curable without interferon. We have now leaped from proof-of-concept for this proposition to increasingly compelling evidence that most patients will be successfully treated in the future with interferon-free therapy.


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