A SPECIAL MEETING REVIEW EDITION

Advances in the Treatment of Hepatitis C Virus Infection From EASL 2015

The 50th Annual Meeting of the European Association for the Study of the Liver • April 22-26, 2015 • Vienna, Austria

Special Reporting on:

- Daclatasvir, Sofosbuvir, and Ribavirin Combination for HCV Patients With Advanced Cirrhosis or Posttransplant Recurrence: Phase 3 ALLY-1 Study
- Efficacy and Safety of Grazoprevir and Elbasvir in Hepatitis C Genotype 1–Infected Patients With Child-Pugh Class B Cirrhosis (C-SALT Part A)
- Ledipasvir/Sofosbuvir With Ribavirin Is Safe and Efficacious in Decompensated and Post Liver Transplantation Patients With HCV Infection: Preliminary Results of the Prospective SOLAR 2 Trial
- Retreatment of Patients Who Failed 8 or 12 Weeks of Ledipasvir/Sofosbuvir-Based Regimens With Ledipasvir/Sofosbuvir for 24 Weeks
- Sofosbuvir + Peginterferon/Ribavirin for 12 Weeks Vs Sofosbuvir + Ribavirin for 16 or 24 Weeks in Genotype 3 HCV Infected Patients and Treatment-Experienced Cirrhotic Patients With Genotype 2 HCV: The BOSON Study
- Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER
- C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in Cirrhotic and Noncirrhotic, Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection for Durations of 4, 6 or 8 Weeks and Genotype 3 Infection for Durations of 8 or 12 Weeks

PLUS Meeting Abstract Summaries

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INDICATION
HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

Please see Brief Summary of full Prescribing Information adjacent to this ad.
HARVONI is the only HCV treatment offering an 8-week course of therapy.

- Overall SVR12 was 94% (n=202/215) in subjects receiving HARVONI for 8 weeks.
- In treatment-naïve subjects taking HARVONI for 12 weeks, 96% (n=208/216) achieved SVR12 in the ION-3 trial and 99% (n=210/213) achieved SVR12 in the ION-1 trial.
- The recommended treatment duration for treatment-naïve patients is 12 weeks.
- HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL.

**Study Designs**

- ION-1: A randomized, open-label trial evaluating HARVONI with or without ribavirin (RBV) in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks, and stratified by presence or absence of cirrhosis and HCV genotype (1a vs. 1b).
- ION-3: A randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks, and stratified by HCV genotype (1a vs. 1b).

**Adverse Reactions**

- Most common (≥10%, all grades) adverse reactions were fatigue and headache.
- The most common (≥1%, all grades) laboratory adverse reactions were increases in transaminases, bilirubin, creatinine, and neutrophils.

**Drug Interactions**

- Rifampin and St. John’s wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.

**Related Products Not Recommended**

- HARVONI is not recommended for use with other products containing sofosbuvir (SOVALDI).
HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of Full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS: Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradyarrhythmia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradyarrhythmia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone’s long half-life for patients discontinuing amiodarone just prior to starting HCV treatment, it is recommended to start amiodarone 48 hours before starting HARVONI. Heart rate monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which time heart rate monitoring or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradyarrhythmia should be immediately evaluated immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to P-gp Inducers: The safety of increased ledipasvir and sofosbuvir concentrations and may lead to a reduced effect of HARVONI. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John’s wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended. Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as well as predicted drug interactions that may occur with HARVONI. This list includes potentially significant interactions but is not all inclusive. An alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:

• Acid Reducing Agents: Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration.

• Antibiotics: Separate HARVONI and antibiotic administration by 4 hours.

• H2-receptor antagonists: Doses comparable to famotidine 20 mg twice daily or omeprazole 40 mg twice daily or lansoprazole 30 mg may be administered simultaneously with or 12 hours apart from HARVONI.

Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

• HARVONI for 8 weeks: fatigue (16%); headache (1%); nausea (6%); diarrhea (4%); and insomnia (3%)

• HARVONI for 12 weeks: fatigue (13%); headache (14%); nausea (7%); diarrhea (3%); and insomnia (5%)

• HARVONI for 24 weeks: fatigue (18%); headache (17%); nausea (14%); diarrhea (7%); and insomnia (3%)

Adverse reactions assessed as causally related by the investigator): The most common adverse reactions (>10%; all grades) were fatigue and headache.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: HARVONI is Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk but had no effect on nursing pups. It is not known if HARVONI and its metabolites are secreted in human breast milk. The developmental and health benefits of breastfeeding should be considered along with the potential benefit of HARVONI and any potential adverse effects on the nursing child from the drug or from the underlying maternal condition.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) or end stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis has not been established in patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.


Daclatasvir, Sofosbuvir, and Ribavirin Combination for HCV Patients With Advanced Cirrhosis or Posttransplant Recurrence: Phase 3 ALLY-1 Study

The phase 3 ALLY trials are investigating the combination of daclatasvir and sofosbuvir with or without ribavirin in patient populations representing an urgent medical need. Daclatasvir is a panegytopyc inhibitor of the nonstructural NS5A protein of the hepatitis C virus (HCV).1 A recent study demonstrated that daclatasvir blocks viral RNA synthesis as well as virion assembly and secretion, causing a rapid decline in extracellular HCV titers.2 Daclatasvir has received approval by the European Medicines Agency and is under regulatory review in the United States. Sofosbuvir is a nucleotide analog that acts as a panegytopyc inhibitor of HCV NS5B polymerase and has been approved in the United States, Europe, and Canada.3

Dr Fred Poordad and colleagues presented findings from the phase 3 ALLY-1 trial.4 The study recruited 53 patients with HCV recurrence after liver transplant and 60 patients with advanced cirrhosis. They received daclatasvir (60 mg daily), sofosbuvir (400 mg daily), and ribavirin for 12 weeks. Ribavirin was initially dosed at 600 mg daily, but could be adjusted to 1000 mg daily depending on the patient’s hemoglobin level and creatinine clearance rate. Although the study enrolled all HCV genotypes, assessment of the primary endpoint—sustained virologic response at 12 weeks (SVR12)—included only genotype 1a and 1b patients. Patients with advanced cirrhosis and treatment-experienced patients were enrolled. Previous treatment could include direct-acting antiviral agents, with the exception of NS5A inhibitors. Enrolled patients had Child-Pugh class A, B, or C liver disease and Model for End-Stage Liver Disease (MELD) scores of 40 or lower. Patients with liver cancer were permitted to enter the study. Patients who had undergone liver transplant could initiate treatment at a minimum of 3 months after the procedure. Cirrhotic patients who underwent liver transplant during the study could receive an additional 12 weeks of treatment after transplant.

Approximately two-thirds of the enrolled patients were male, and the median age was 59 years (range: 19-82 years). Nearly all patients (96%) were white. Most patients (59%) had received previous treatment. Among the patients with advanced cirrhosis, 57% were genotype 1a and 18% were genotype 1b. In the posttransplant arm, 58% were genotype 1a and 19% were genotype 1b. No genotype 5 patients were enrolled in the study. Approximately two-thirds of patients in each arm had the intercellin-28B (IL28B) non-CC genotype. In the advanced cirrhosis arm, the majority of patients had cirrhosis of Child-Pugh class B (53%) or C (27%). Among the Child-Pugh class C patients, more than 80% had a MELD score of 16 or higher.

**ABSTRACT SUMMARY C-SURFER: Grazoprevir Plus Elbasvir in Treatment-Naive and Treatment-Experienced Patients With Hepatitis C Virus Genotype 1 Infection and Chronic Kidney Disease**

In patients with stage 4 or 5 chronic kidney disease, HCV infection is associated with an increased risk of death and failure of kidney transplant. These patients have limited treatment options. The phase 2/3 C-SURFER trial evaluated the 12-week combination course of grazoprevir and elbasvir in HCV genotype 1 patients with stage 4 or 5 chronic kidney disease (Abstract LRP02). The study randomized 224 patients to immediate treatment with grazoprevir (100 mg daily) and elbasvir (50 mg daily) for 12 weeks or a deferred treatment (MELD) course, which consisted of placebo followed by active dosing. Patients could be treatment-naive or treatment-experienced. Approximately 58% were genotype 1a. Among the 116 patients who remained in the study, 99% achieved a SVR12. One noncirrhotic patient relapsed at follow-up week 12. Serious AEs occurred in 16% (14/116) in the immediate treatment arm and 17 patients (15%) in the deferred treatment arm. An AEs led to treatment discontinuation in no patients in the active treatment arm and 4% of patients in the placebo group. The most common adverse events were headache, nausea, and fatigue.

with HCV genotype 1; the SVR12 rates were 82% for the advanced arm and 95% for the posttransplant arm. Regression analysis revealed no differences in outcome based on sex, age, IL28B status, or HCV RNA levels in the advanced cirrhosis patients with HCV genotype 1. Failure to achieve SVR12 was attributed to relapse in all but 1 patient (with advanced cirrhosis). Patients who relapsed received treatment with the same regimen for a longer duration.

In the advanced cirrhosis arm, SVR12 rates by HCV genotype ranged from 76% for genotype 1a to 100% for genotypes 1b and 4 (Figure 1). In the posttransplant cohort, SVR12 rates were 90% or greater for every genotype represented. In the advanced cirrhosis arm, patients with Child-Pugh class A or B showed SVR12 rates of 92% and 94%, respectively, whereas only 56% of patients with Child-Pugh class C achieved SVR12. Albumin levels below 2.8 g/dL correlated with the greatest reduction in SVR12. Four cirrhotic patients underwent liver transplant while on study treatment. Following liver transplant, 2 of the patients received the study treatment, 1 patient received the study treatment but discontinued ribavirin, and 1 patient was not treated after transplant. All of the patients achieved SVR12.

Comparison of MELD scores at baseline vs after 12 weeks of treatment showed that patients who had Child-Pugh class C at baseline experienced a greater decrease in MELD score compared with patients who were Child-Pugh class A or B (Figure 2). Among the 13 patients with virologic failures at the end of study treatment, baseline NS5A resistance-associated variants (RAVs) had been identified in 4 of 10 patients in the advanced cirrhosis cohort and 6 of 3 patients in the posttransplant cohort. In all 13 patients, however, NS5A RAVs were identified after virologic failure.

No deaths occurred during the study. Serious adverse events (AEs) were observed in 17% of advanced cirrhosis patients and 9% of posttransplant patients, but none of the events were considered related to the study treatment. Only 1 patient in each cohort discontinued all study medications due to an AE. The most common AEs in the advanced cirrhosis or posttransplant cohort were headache (20% and 36%, respectively), fatigue (18% and 28%), anemia (20% and 19%), diarrhea (8% and 19%), nausea (17% and 6%), and arthralgia (2% and 13%). Hemoglobin levels fell below 9 g/dL in 8% of advanced cirrhosis patients and 4% of posttransplant patients. Five percent of patients in the advanced cirrhosis cohort had elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST). In all cases, however, the elevation was transient and resolved without intervention. Bilirubin levels greater than 2.5 times the upper limit of normal were observed in 15% of patients in the advanced cirrhosis cohort.

References


**Figure 2. Changes in MELD score according to Child-Pugh class in the phase 3 ALLY-1 trial of daclatasvir, sofosbuvir, and ribavirin. “The patient did not achieve a sustained virologic response at week 12. MELD: Model for End-Stage Liver Disease. Adapted from Poordad F et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY-1 study [EASL abstract LOB]. J Hepatol. 2015;62(1):suppl.1.”**
Efficacy and Safety of Grazoprevir and Elbasvir in Hepatitis C Genotype 1–Infected Patients With Child-Pugh Class B Cirrhosis (C-SALT Part A)

The combination of grazoprevir (MK-5172) and elbasvir (MK-8742) is being investigated in several HCV patient populations. These drugs inhibit HCV NS3/4A protease and NS5A, respectively, and have demonstrated activity against most HCV genotypes.1-3 Moreover, these drugs retain in vitro activity against HCV variants that arise after exposure to first-generation drugs against the same HCV targets. Despite the recent advances in HCV treatment, patients with advanced cirrhosis represent an unmet medical need.

The phase 2, open-label C-SALT study enrolled 10 noncirrhotic patients, to which 30 cirrhotic patients, the remaining patients had cirrhosis and/or fibrosing cholestatic hepatitis. Among the remaining patients had cirrhosis and/or fibrosing cholestatic hepatitis. Among the remaining patients had cirrhosis and/or fibrosing cholestatic hepatitis.

In the intent-to-treat population, SVR12 was achieved by 90% of the cirrhotic patients who had undetectable HCV RNA. One patient exhibited a HCV RNA level of 212 IU/mL at treatment week 4, yet subsequently achieved SVR12. These 6 patients continued to show undetectable HCV RNA when tested at follow-up weeks 4, 8, and 12. Among the 24 patients with undetectable HCV RNA at treatment week 4, all 24 patients continued to demonstrate undetectable HCV RNA through treatment weeks 8 and 12. By follow-up week 12, however, 2 patients had relapsed (8.3%), and 1 patient had died (4.2%). Therefore, early response to treatment did not predict SVR12. No virologic failures were observed in the noncirrhotic patients, and no breakthrough or rebound were observed in the cirrhotic or noncirrhotic cohorts. Both of the patients who relapsed had Child-Pugh scores of 8 or 9.

From baseline to follow-up week 12, MELD scores decreased in 11 patients; this decrease was primarily attributed to a reduced bilirubin level in 10 of the patients. The MELD score remained unchanged in 11 patients, and it increased in 6 patients, 1 of whom showed symptoms suggesting hepatotoxicity. Subgroup analyses yielded large confidence intervals. Although statistical analysis did not demonstrate a difference in outcomes based on prior response to treatment, Dr Jacobson noted that all 6 patients with a prior null response to pegylated interferon plus ribavirin achieved SVR12 (Figure 3).

Of the 2 cirrhotic patients who demonstrated virologic relapse, the only RAV observed at baseline was Q80S in the NS5A region (in 1 patient). However, at follow-up week 12, both patients had clinically significant RAVs in both the NS3 and NS5A coding regions. This observation was observed within the presence of baseline NS5 or NS5A RAVs and SVR12. Pharmacokinetic analysis suggested a slightly higher exposure to grazoprevir in cirrhotic patients receiving 50 mg daily compared with noncirrhotic patients receiving 100 mg daily, with a 24-hour serum concentration (C24h) ratio of 1:71 (95% CI, 0.87-3.33). Elbasvir pharmacokinetics were similar in the 2 patient populations (C24h, 1:84; 95% CI, 0.67-1.60).

Treatment with grazoprevir and elbasvir was generally well tolerated. AEs occurred with similar frequency in the 2 treatment cohorts. The most common AE was fatigue (30% in both arms). Arthralgia occurred in 16.7%

**ABSTRACT SUMMARY**

**The Association of Sofosbuvir and Daclatasvir for Treating Severe Recurrence of HCV Infection After Liver Transplantation: Results From a Large French Prospective Multicenter ANRS C023 CUPILT Cohort**

The French National AIDS Research Agency C023 CUPILT study is assessing the efficacy and safety of sofosbuvir and daclatasvir regimens in patients with recurrent HCV infection following liver transplant. Data from 130 patients (genotype 1, 65 patients without previous treatment for HCV infection) were included in the current analysis (Abstract G15). Treatment was selected by the investigator. Among the 14 patients who received 12 weeks of treatment, 11 received sofosbuvir (400 mg daily) plus daclatasvir (60 mg daily), and 3 received sofosbuvir (400 mg daily) (dosage based on renal function). Of the 116 patients treated for 24 weeks, 64 received the ribavirin-free regimen, and 52 received the 2 direct-acting antiviral agents plus ribavirin. The mean total bilirubin levels were 23.6 ± 30.3 μmol/L for patients treated without ribavirin vs 42.7 ± 57.3 μmol/L for patients treated with ribavirin (P=0.02). The mean baseline MELD scores were 11 ± 5 and 13 ± 5, respectively (P=0.03). Approximately 50% to 60% of patients had F0 to F3 fibrosis; the remaining patients had cirrhosis and/or fibrosing cholestatic hepatitis. Among patients treated for 12 weeks, SVR12 rates and relapse rates were similar in patients treated with or without ribavirin, with creatinine clearance falling from 88.7 ± 26.1 mL/min at the end of treatment (P=0.001).
of patients with cirrhosis vs 20.0% without, and nausea was observed in 10.0% vs 20.0%, respectively. Serious AEs were reported in 13.3% and 0%, respectively, but all events were considered unrelated to study treatment. Only one patient in the cirrhosis arm died. Grade 3/4 bilirubin elevation was observed in 13.3% of cirrhotic patients. No patients discontinued treatment due to an AE. No AST or ALT elevations were observed in either arm.

References

Outcomes after 12 vs 24 weeks of treatment for genotype 1 patients with Child-Turcotte-Pugh class B or C cirrhosis were analyzed separately for pretransplant and posttransplant patients. The longer duration of therapy was associated with higher SVR12 rates among the pretransplant Child-Turcotte-Pugh class B patients (96% with 24 weeks vs 87% with 12 weeks). In contrast, the shorter duration was better in pretransplant Child-Turcotte-Pugh class C patients (89% with 12 weeks vs 72% with 24 weeks). SVR12 was higher with 24 weeks of treatment of both sets of posttransplant patients. Posttransplant Child-Turcotte-Pugh class B patients achieved a SVR12 rate of 95% with 12 weeks vs 100% with 24 weeks. Among the posttransplant Child-Turcotte-Pugh class C patients, SVR12 was 50% with 12 weeks vs 75% with 24 weeks.

Comparison of laboratory parameters at baseline vs follow-up week 4 showed improvements for both compensated and decompensated patients. Median total albumin levels increased for the compensated cohort and for the decompensated cohort (P<0.001 for both). Median bilirubin levels decreased for the compensated and decompensated cohorts (P<0.001 for both). In contrast, the shorter duration was better in pretransplant Child-Turcotte-Pugh class B patients (96% with 24 weeks vs 87% with 12 weeks). The rate of grade 3/4 AEs ranged from 0% to 5%, as serious AEs among Child-Turcotte-Pugh B patients (96% with 24 weeks vs 72% with 24 weeks).

AEs of any grade were observed in more than 90% of patients in both cohorts. The rate of grade 3/4 AEs ranged from 19% (with 12 weeks of treatment in the F0 to F3 or Child-Turcotte-Pugh A group) to 30% (with 24 weeks of treatment in the Child-Turcotte-Pugh B or C group). Among the F0 to F3 or Child-Turcotte-Pugh A patients, serious AEs were observed in 14% of patients with 12 weeks of treatment and 15% of patients with 24 weeks. The rate of serious AEs among Child-Turcotte-Pugh B or C patients was 28%, regardless of the treatment duration. Treatment-related serious AEs ranged from 0% to 5%, as did the rate of treatment discontinuation due to an AE. No deaths were considered treatment-related.

Results


References


ADVANCES IN THE TREATMENT OF HEPATITIS C VIRUS INFECTION FROM EASL 2015

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Figure 4. SVR12 rates in a preliminary analysis of the SOLAR-2 trial evaluating ledipasvir/sofosbuvir with ribavirin (LDV/SOF + RBV) in post-liver transplant patients with HCV. The error bars represent the 2-sided exact 90% confidence intervals. CPT, Child-Turcotte-Pugh; SVR12, sustained virologic response at week 12; HCV, hepatitis C virus. Adapted from Manns M et al. Ledipasvir/sofosbuvir in patients with cirrhosis and selected drug resistance. In: Gastroenterology. 2016;150(6):1349-1360.
Retreatment of Patients Who Failed 8 or 12 Weeks of Ledipasvir/Sofosbuvir-Based Regimens With Ledipasvir/ Sofosbuvir for 24 Weeks

Shorter treatment regimens with direct-acting antiviral agents have yielded high SVR12 rates. Patients who failed these shorter regimens may benefit from retreatment with the same drugs given for a longer time. Dr. Eric Lawitz and colleagues presented efficacy and safety results from an open-label, single-arm, phase 2 trial that enrolled patients who had experienced virologic failure after 8 or 12 weeks of ledipasvir/sofosbuvir in phase 2 or 3 trials and retreated them with the same 2-drug combination given once daily for 24 weeks.1 Patients were recruited from the ION-1, ION-2, ION-3, LONESTAR, and TRILOGY-1 studies.2,3 Two additional arms of the trial are investigating the combination of ledipasvir and sofosbuvir plus ribavirin in patients who had previously failed a sofosbuvir-based regimen.4 The 41 enrolled patients had a median age of 58 years (range, 35-71 years), 83% were male, and 24% were black. Most patients (83%) had HCV genotype 1a infection. The mean HCV RNA level was 6.2 log10 IU/mL (range, 4.5-7.4 log10 IU/mL). Among the 19 patients with cirrhosis, 79% had baseline NSSA RAVs. Prior HCV treatment duration was 8 weeks for 30 patients and 12 weeks for 11 patients. NSSA RAVs were present in 63% of patients who had received 8 weeks of treatment and in all patients treated for 12 weeks. Undetectable levels of HCV RNA were reported in 95% of patients after 4 weeks of treatment and in all patients after 8 weeks. One patient experienced a virologic breakthrough at week 16. After cessation of treatment, several patients relapsed. The SVR4 rate was 73%, and the SVR12 rate was 71%. Analysis of patient subgroups showed little numerical difference in SVR12 rates for noncirrhotic vs cirrhotic patients (68% vs 74%; Figure 5). However, SVR12 rates were 80% in patients with 8 weeks of prior treatment vs 46% among those with 12 weeks of prior treatment. The presence of NSSA RAVs at baseline reduced the SVR12 rate to 60% from their absence. These 2 latter outcomes are related to the earlier exposure to the NS5A RAVs. Patients who had previously received 12 weeks of treatment had more NSSA RAVs at baseline. Further analysis showed a decrease in SVR12 rates with increasing numbers of baseline RAVs. SVR12 rates among patients with 0, 1, or at least 2 baseline NSSA RAVs were 100%, 69%, and 50%, respectively. Specific baseline RAVs also impacted viral clearance, with SVR12 rates of 100% for patients with Q53R (n=4) or M28T (n=1), 80% for patients with L15M (n=3), and 53% for patients with Y93H/N mutations (n=6). Although no patients had NSSB RAVs at baseline, NSSB RAVs were detected in 33% of patients who experienced virologic failure (n=12). RAVs included S282T in 2 patients, L159F in 1 patient, and both were considered unrelated to study treatment. No patient discontinued treatment due to an AE, and no deaths occurred. Grade 3 laboratory abnormalities were reported in 2 patients (5%), but no clinical consequences were noted. The most common treatment-emergent AEs were headache (15%), fatigue (10%), and insomnia (7%). The majority of AEs were mild to moderate in severity. In the phase 3 ION-1, ION-2, and ION-3 studies, the combination of sofosbuvir and simeprevir yielded high SVR12 rates (93%, or higher in patients with HCV genotype 1 infection. Both agents have demonstrated in vitro activity against genotypes 1 and 4, and these data account for approximately 14% of chronic HCV infections worldwide (Gower E et al.) Regimens containing 3 drugs (sav/sof/TW1) have expanded treatment options for patients with these less common HCV genotypes, an open-label study investigated the efficacy and safety of 12 weeks of daily treatment with sofosbuvir (400 mg) and ledipasvir (90 mg) in patients with HCV genotypes 4 and 5 (Abstract O506). The 45 enrolled patients had a median age of approximately 57 years, and more than half were female. Half of the patients were treatment-experienced; among them, 36% had cirrhotic HCV rates were 93% in genotype 4 patients and 95% in genotype 5 patients. All treatment failures were due to relapse. No significant differences emerged for treatment-naive or treatment-experienced patients with cirrhotic vs noncirrhotic patients. The 2-drug combination was generally well tolerated, with 1 serious AE reported. No treatment modifications or interruptions were attributable to an AE. No grade 3/4 laboratory abnormalities were observed, and no patients exhibited hemoglobin levels below 10 g/dL.

References
4. Wyles DL, Peddiasri P, Yang J, et al. Retreatment of patients who failed prior Ledipasvir/sofosbuvir-based regimens with all oral fixed-dose combination Ledipasvir/sofosbuvir plus ribavirin in genotype 1b treatment-experienced patients with prior NS5A RAVs. J Hepatol. 2015;62(1):suppl.1. 5. Ellerbroek PL, King D, Dieterich DT, et al. Sofosbuvir and ledipasvir for 12 weeks in patients with hepatitis C genotype 5 infection: descriptive analysis of data from phase 2 and 3 trials. Hepatology. 2015;61(1 suppl):S45-S57. To download a copy, visit the Hepatology website (hepatology.ahajournals.org). 6. King D, Dieterich DT, Dieterich SM. ADVANCES IN THE TREATMENT OF HEPATITIS C VIRUS INFECTION FROM EASL 2015. 7. Sulkowski MS, Poordad F, Sanchez LA, et al. Ledipasvir/sofosbuvir for 24 weeks in patients with HCV genotype 3 infection compared with other genotypes. In genotype 3 patients, the combination of sofosbuvir plus ribavirin administered for 24 weeks yielded SVR12 rates of 68% in patients with cirrhosis and 90% without.1 In genotype 2 patients, 12 weeks of the same drug combination yielded SVR12 rates of 82% and 94% in patients with and without cirrhosis, respectively. In a small phase 2 study, 12 weeks of sofosbuvir plus pegylated interferon and ribavirin demonstrated efficacy in treatment-experienced patients with HCV genotype 2 and 3 infections, with similar SVR12 rates observed in patients with or without cirrhosis.2 8. Dr. Graham Foster and colleagues presented results of the multicenter, open-label BOSON study, which examined the efficacy and safety of sofosbuvir and ribavirin with or without pegylated interferon in patients with HCV genotype 2 or 3 infection.3 The study enrolled 592 patients at 80 sites in the United States, the United Kingdom, Australia, Canada, and New Zealand. In addition to evaluating the safety and tolerability of the drug combination, the trials aimed to document the emergence of viral resistance to sofosbuvir in patients who had failed to achieve radiologic responses to previous treatment. The study randomized 196 patients to receive 16 weeks of treatment with sofosbuvir (400 mg daily) plus ribavirin (1200 mg daily). 199 patients receive 24 weeks of the same drug combination, and 197 patients receive sofosbuvir (400 mg daily), pegylated interferon (180 µg once per week), and ribavirin (1200 mg daily) for 12 weeks. All patients with genotype 2 infection were treatment-experienced and cirrhotic. The genotype 3 group included cirrhotic or noncirrhotic patients who were treatment-naive or retreated. Of the 92 patients who were patients, 37% had cirrhosis. The mean body mass index was 28 kg/m2 (range, 18-55 kg/m2). Thirty-eight percent of the patients had the IL28B CC genotype, and 92% of patients had HCV genotype 3. The mean baseline HCV RNA level was 6.3 log10 IU/mL (range, 3.3-7.6 log10 IU/mL). Slightly more than half of patients had failed prior treatment with pegylated interferon and ribavirin, and 37% had cirrhosis. The
Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER

I. Stanislas Pol and colleagues presented the first results from the French National AIDS Research Agency CO22 cohort of the HEPATHER study.1 The study is designed to include 10,000 hepatitis B and 15,000 hepatitis C patients, who will be followed for 10 years to obtain real-world clinical data. The CO22 cohort includes HCV genotype 1 patients treated with the combination of daily sofosbuvir and daclatasvir for either 12 or 24 weeks. Although many studies have been conducted on sofosbuvir combinations, there is a lack of real-world data pertaining to the combination of sofosbuvir and daclatasvir.

Data from the CO22 cohort were available for 409 patients treated before July 1, 2014, of whom 317 had received treatment with sofosbuvir (400 mg) and daclatasvir (60 mg) alone and 92 had received the same combination plus ribavirin (1000-1200 mg daily). Patients had a median age of 59 years, and two-thirds were male. Approximately half of the patients had HCV genotype 1a infection. The mean body mass index was 25 kg/m². Most patients (78%) had cirrhosis, including 9% with decompensated cirrhosis. Diabetes was present in 18% of patients, and hypertension in 31%. Four-thirds of patients had received prior treatment with pegylated interferon and ribavirin, with or without a first-generation protease inhibitor. Patients had a mean MELD score of 9 ± 5. A total bilirubin level below 21 μmol/L was detected in 74% of patients. Hemoglobin levels below 13 g/dL were reported in 19%.

SVR2 rates were available for 237 patients treated with sofosbuvir and daclatasvir alone. SVR12 rates were 84.9% after 12 weeks of treatment vs 93.4% after 24 weeks. However, the majority of analyses were performed on data available after 4 weeks of follow-up (SVR4) derived from 409 patients (Table 1). Sofosbuvir and daclatasvir yielded SVR4 rates of 85.2% with 12 weeks of treatment vs 95.1% with 24 weeks. With the addition of ribavirin, SVR4 rates were 100% with 12 weeks vs 98.7% with 24 weeks. Among patients with cirrhosis, the addition of ribavirin improved SVR4. Without ribavirin, a mean platelet count was 198 cells/mm³ (range, 54-537 cells/mm³). Treatment with sofosbuvir and ribavirin yielded SVR12 rates of 72% for 16 weeks and 85% for 24 weeks (P=.0013). Figure 6. The addition of pegylated interferon to sofosbuvir and ribavirin in a 12-week treatment regimen yielded the highest SVR12 rate (93%). A significant increase in comparison to the 24-week interferon-free regimen (85%; P=.023). For patients with HCV genotype 2 infection, no significant differences in outcomes were apparent. SVR12 rates were 87% for 16 weeks of sofosbuvir and ribavirin, 100% for 24 weeks of sofosbuvir and ribavirin, and 94% for 12 weeks of sofosbuvir and ribavirin plus interferon.

For patients with genotype 3 infection, the SVR12 rate for the same treatment were, respectively, 71%, 84%, and 93%. Among patients with genotype 3 infection, the interferon-containing regimen consistently yielded the highest SVR12 rates for patients without cirrhosis, with cirrhosis, without prior HCV treatment, and with prior HCV treatment.

The lowest SVR12 rate observed after treatment with sofosbuvir, pegylated interferon, and ribavirin was 88% for patients with genotype 3 infection and cirrhosis. Further analysis of genotype 3 subpopulations based on the combined factors of treatment history and cirrhosis status showed that the best results were consistently achieved with the addition of pegylated interferon for 12 weeks (Figure 7). SVR12 rates with this regimen ranged from a high of 96% for treatment-naive patients without cirrhosis to a low of 86% for treatment-experienced, cirrhotic patients. Resistance analysis was performed by means of deep sequencing in 78 of 88 patients with virologic failure. No 5227T mutation was observed in any samples, and no consistent variants or resistance patterns emerged.

The inclusion of pegylated interferon to sofosbuvir and ribavirin was generally well tolerated in this challenging patient population. AEs of any grade were observed in 82% of patients in the 3 arms. Grade 3/4 AEs were observed in 4% to 8% of patients, and serious AEs were observed in 4% in daily sofosbuvir and ribavirin alone and in 6% of patients. Few patients (<1% to 2%) discontinued treatment due to an AE, and no patients died during the study. Laboratory abnormalities occurred in 15% of patients in both interferon-free arms and in 38% in the interferon-containing arm.

The most common AEs of any grade in patients treated with sofosbuvir were fatigue (46%), headache (30%), insomnia (25%), and nausea (25%).

References


With the success of direct-acting antiviral agents demonstrated in several populations of HCV patients, these drugs are now being investigated in patients with decompensated cirrhosis and less common genotypes. To determine the optimal direct-acting antiviral regimen in these patients, a study was conducted in which patients with HCV genotype 1 or 3 and decompensated cirrhosis were treated for 12 weeks with sofosbuvir plus either daclatasvir or ledipasvir, with or without ribavirin, as selected by the physician (Abstract 0002). Of the 465 patients available for analysis, 50.3% had genotype 1, and 40.5% had genotype 3. The mean age was 55.6 years (range, 29-81 years), and 72.5% were male. Nearly half of the patients were treatment-experienced, 10.1% had undergone liver transplant, and 5.7% were HIV-positive. For genotype 1 patients, SVR12 rates were 86% for sofosbuvir and ledipasvir with ribavirin, 81% for sofosbuvir and ledipasvir alone, 82% for sofosbuvir and daclatasvir with ribavirin, and 60% for sofosbuvir and daclatasvir alone. For genotype 3 patients, the SVR12 rates were 59% for sofosbuvir and ledipasvir with ribavirin, 42% for sofosbuvir and ledipasvir alone, 70% for sofosbuvir and daclatasvir with ribavirin, and 71% for sofosbuvir and daclatasvir alone. SVR12 rates were reduced overall in genotype 3 patients compared with genotype 1 patients. The combination of sofosbuvir and daclatasvir with or without ribavirin, was superior to sofosbuvir and ledipasvir, with or without ribavirin (P<.05) among genotype 3 patients. Among the 173 reports of serious AEs, 78.9% were attributed to liver disease and/or HCV therapy. Fourteen patients (3.6%) died during treatment. A MELD score decrease of 2 points was more common in patients older than 65 years (32%) than in patients who were younger than 65 years (14%).

Data from Poordad F et al: C-SWIFT: grazoprevir/elbasvir + sofosbuvir in cirrhotic and noncirrhotic, treatment-naive patients with hepatitis C virus genotype 1 infection for durations of 4, 6 or 8 weeks and genotype 3 infection for durations of 8 or 12 weeks. [EASL abstract O006]. J Hepatol. 2015.63(2):suppl.1. Table 2. Treatment Arms in the C-SWIFT Trial of Grazoprevir, Elbasvir, and Sofosbuvir in Patients With HCV Genotype 1 or 3.

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**C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in Cirrhotic and Noncirrhotic, Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection for Durations of 4, 6 or 8 Weeks and Genotype 3 Infection for Durations of 8 or 12 Weeks.**

Grazoprevir, elbasvir, and sofosbuvir are 3 highly potent direct-acting antiviral agents with different mechanisms of action and efficacy against a range of HCV genotypes. Shorter duration of therapy may be possible with coadministration of these 3 drugs. Dr Fred Poordad and colleagues presented results of the open-label, phase 2 C-SWIFT study, which enrolled patients with HCV genotype 1 or 3, with or without cirrhosis, to receive a daily fixed-dose tablet of grazoprevir (100 mg) and elbasvir (50 mg), plus daily sofosbuvir (400 mg). The study enrolled treatment-naive adults with chronic HCV genotype 1 or 3, a minimum baseline hemoglobin level of 9.5 g/dL, and AST and ALT levels below 350 IU/L. Patients with HIV or hepatitis B virus were excluded. Treatment duration varied from 4 weeks to 12 weeks in the 7 arms, based on HCV genotype and the presence of cirrhosis (Table 2). The genotype 1 cohort included 4 arms. Treatment consisted of 4 or 6 weeks of therapy for noncirrhotic patients and 6 or 8 weeks of therapy for cirrhotic patients. The genotype 3 cohort included 3 arms. Treatment duration was 8 or 12 weeks for noncirrhotic patients and 12 weeks for those with cirrhosis. The trial included 102 patients with genotype 1 and 41 with genotype 3. Patient characteristics were generally well balanced among the 7 arms. Patients had a median age of approximately 52 years (range, 42-57 years). Less than half of the patients (37%) had cirrhosis. Mean baseline viral load ranged from 1.66 x 10^6 IU/mL to 3.69 x 10^6 IU/mL. For genotype 1 patients, SVR12 rates for noncirrhotic patients were 93% with 4 weeks of treatment and 87% with 6 weeks (Figure 8). SVR12 rates for cirrhotic patients were 80% with 6 weeks of treatment vs 94.0% with 24 weeks. With ribavirin, SVR4 rose to 100% and 98.9%, respectively. All patients without cirrhosis achieved SVR4, regardless of treatment duration and use of ribavirin. Treatment-naive patients had similar SVR4 rates after 12 or 24 weeks of treatment without ribavirin (87.1% vs 88.7%). The rates increased with the addition of ribavirin (100% for both durations). For treatment-experienced patients, however, SVR4 rates in the absence of ribavirin increased from 82.6% with 12 weeks of treatment to 96.7% with 24 weeks of treatment.

The addition of ribavirin yielded SVR4 rates of 100% after 12 weeks of treatment and 98.5% after 24 weeks. For the entire study population, treatment factors that influenced the likelihood of achieving SVR4 included the addition of ribavirin (P=0.06) and extending treatment to 24 weeks (P=0.015). Unexpectedly, a lower HCV viral load was associated with a reduced likelihood of achieving SVR4 (P=0.04). Independent risk factors for failure to achieve SVR4, as identified by a logistic regression analysis, included absence of ribavirin (odds ratio [OR], 6.4; P=0.057) and shorter duration of treatment (OR, 3.2; P=0.0085). The presence of cirrhosis was associated with an OR of 9 (P=0.0022), reflecting the fact that all of the patients who failed to achieve SVR4 had cirrhosis. In the subset of patients with cirrhosis, failure to achieve SVR4 was again associated with the absence of ribavirin (OR, 6.3; P=0.007) and shorter duration of treatment (OR, 4.3; P=0.008).

Reference
P  resentations at the 2015 Euro-
  pean Association for the Study of the Liver (EASL) International Liver Congress provided important data on new all-oral, interferon-free regimens in diverse patient populations. The phase 3 ALLY-1 trial, which evaluated ledipasvir and sofosbuvir in decompensated and post–liver transplant patients with HCV, demonstrated high rates of response in this sick patient population. After 12 weeks of treatment, SVR12 rates were 98% for posttransplant patients with Child-Turcotte-Pugh class A and 85% for patients with Child-Turcotte-Pugh class B or C before or after transplant.

In the 24-week treatment arm, SVR12 rates were 98% and 88%, respectively. As reported separately in a poster, effi-
  cacy in HCV patients with advanced cirrhosis, those with the HCV genotypes 1a, 4, or 8, and those with fibrosing cholestatic hepatitis following 12 or 24 weeks of treatment, which is a promising development. The placebo-controlled, phase 3 C-EDGE trial evaluated a 12-week course of grazoprevir and elbasvir (with-
  out ribavirin). Stefan Zeuzem, MD, presented results for treatment-naive patients with genotype 1 (n=385), 4 (n=26), or 6 (n=13). The placebo arm included 105 patients who received placebo for 12 weeks before treatment began with grazoprevir and elbasvir. The placebo phase enabled investigation of adverse events. In the treatment arm, 12 weeks of grazoprevir and elbasvir given immediately were well tolerated, and adverse events were minimal. The grazoprevir/elbasvir regimen was highly efficacious. The overall SVR12 rate was 95%. According to genotype, the SVR12 rates were: genotype 1a (99% in genotype 1b, 100% in genotype 4, and 80% in genotype 6).

In the 24-week treatment arm, SVR12 rates were 98% and 88%, respectively. As reported separately in a poster, efficacy in HCV patients with advanced cirrhosis, those with the HCV genotypes 1a, 4, or 8, and those with fibrosing cholestatic hepatitis following 12 or 24 weeks of treatment, which is a promising development. The placebo-controlled, phase 3 C-EDGE trial evaluated a 12-week course of grazoprevir and elbasvir (without ribavirin). Stefan Zeuzem, MD, presented results for treatment-naive patients with genotype 1 (n=385), 4 (n=26), or 6 (n=13). The placebo arm included 105 patients who received placebo for 12 weeks before treatment began with grazoprevir and elbasvir. The placebo phase enabled investigation of adverse events. In the treatment arm, 12 weeks of grazoprevir and elbasvir given immediately were well tolerated, and adverse events were minimal. The grazoprevir/elbasvir regimen was highly efficacious. The overall SVR12 rate was 95%. According to genotype, the SVR12 rates were: genotype 1a (99% in genotype 1b, 100% in genotype 4, and 80% in genotype 6).

ABSTRACT SUMMARY Safety of Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir for Treating HCV GT1 Infection in Patients With Severe Renal Impairment or End-Stage Renal Disease: The RUBY-1 Study

The phase 3b RUBY-1 study evaluated patients with stage 4 or 5 chronic kidney disease and HCV genotype 1 infection (Abstract LO1). Patients with HCV genotype 1a or 1b infection received the coformulation of daily ombitasvir (25 mg), paritaprevir (50 mg), and ritonavir (100 mg) plus dasabuvir (200 mg) for 12 weeks. Ribavirin (200 mg qd) was administered only to genotype 1a patients. Treatment was given for 12 weeks. Preliminary results were presented for 20 patients. Fourteen patients had completed the first 12 weeks of treatment, and the remaining 6 were continuing treatment. More than half of patients (60%) were on dialysis. By the end of treatment week 4, all but 1 patient showed 250 g/wk of RVR (and this patient’s viral load was undetectable by week 6). All of the 11 patients who presented with nephrotic syndrome. HCV RNA levels were followed every 4 weeks. Two patients reached discontinuation due to a serious AE (bleeding in a patient with a history of upper gastrointestinal bleed). The phase 3b RUBY-1 study evaluated patients with stage 4 or 5 chronic kidney disease and HCV genotype 1 infection (Abstract LO1). Patients with HCV genotype 1a or 1b infection received the coformulation of daily ombitasvir (25 mg), paritaprevir (50 mg), and ritonavir (100 mg) plus dasabuvir (200 mg) for 12 weeks. Ribavirin (200 mg qd) was administered only to genotype 1a patients. Treatment was given for 12 weeks. Preliminary results were presented for 20 patients. Fourteen patients had completed the first 12 weeks of treatment, and the remaining 6 were continuing treatment. More than half of patients (60%) were on dialysis. By the end of treatment week 4, all but 1 patient showed 250 g/wk of RVR (and this patient’s viral load was undetectable by week 6). All of the 11 patients who presented with nephrotic syndrome. HCV RNA levels were followed every 4 weeks. Two patients reached discontinuation due to a serious AE (bleeding in a patient with a history of upper gastrointestinal bleed).
The study showed that an impressive 71% of patients with genotype 1 were cured after retreatment. Another interesting finding from this study involved NSSA RAVs. Some patients have RAVs at baseline that prevent the development after an ineffective course of treatment with a regimen involving an NSSA inhibitor such as ledipasvir. Among patients in the retreatment arm who had developed a NSSA RAV, among patients who failed the 8-week regimen, 19 of 30 developed a NSSA RAV. Eleven of 30 did not. It appears that in some patients who failed therapy, the duration of treatment with ledipasvir was too short to lead to an NSSA RAV (at least one that could be detected). On the other hand, all 11 patients who failed 12 weeks of treatment developed a NSSA RAV. Among the 11 patients in the 8-week arm who did not have the NSSA RAV, 100% were cured with the longer 24-week course of therapy. Among the 50 patients who developed the NSSA RAV to the setting of treatment failure, the cure rate was only 60% (18 of 30). Therefore, the presence of the NS5A RAV could be used to potentially identify patients who would benefit from retreatment with the same regimen for a longer period.

The analysis by Lawitz also identified development of a NSSB RAV to sofosbuvir in patients who failed the 24-week regimen. Previously, this mutation was linked to treatment failure in few patients. In this study, among the 12 patients who failed treatment, 4 developed a NSSB RAV. This implication of finding is unknown.

Xavier Form, MD, presented results from C-SALVAGE, a study that examined a regimen consisting of grazoprevir and elbasvir in patients who had failed therapy with 8 or 12 weeks of ledipasvir and sofosbuvir in previous trials.

There were several previously involved patients who had failed a previous antiviral regimen and then were retreated. Our group used the term "antiviral refractory" for those patients who had failed treatment with or without cirrhosis. Treatment for these patients currently varies greatly and is determined in each case. In this study, the treatment durations varied.

Noncirrhotic genotype 1 patients received 4 or 6 weeks of therapy, and genetic genotype 1 patients received therapy for 6 or 8 weeks. Among genotype 1 noncirrhotic patients, none of the patients received 8 or 12 weeks of therapy, and the cirrhotic group received 12 weeks.

In noncirrhotic genotype 1 patients who received 6 weeks of therapy, the cure rate was 33%. In noncirrhotic genotype 1 patients who received 6 weeks of therapy, the cure rate was 100%. For noncirrhotic genotype 3 patients, 8 weeks of treatment yielded a cure rate of 93%. The cure rate was 100% for noncirrhotic patients who received 12 weeks of treatment. Among the cirrhotic genotype 3 patients, 8 weeks of treatment were difficult to achieve, and four patients failed to achieve cure. Three-quarters of the patients were receiving dialysis. Patients could be treatment-naive or treatment-experienced, and approximately 7% had cirrhosis. The study evaluated a 12-week regimen of grazoprevir/elbasvir. Among the 116 patients who remained in the study, 115 were cure, for a modified analysis SVR12 rate of 99%. Six patients discontinued treatment for reasons deemed unrelated to drugs, including 1 who died. In this regard, considering the patients who withdrew (intention-to-treat analysis), the SVR12 rate was 94%. The robust response seen in this study is a promising development for the future.

Three conclusions can be drawn from these data. First, very short courses of therapy (approximately 4 weeks) did not seem to be effective even with potent agents from all 3 classes of direct-acting antiviral agents. Second, combinations of potent agents might be able to shift treatment away from cirrhotic patients, who now often still require 24-week treatment courses. Third, a shorter course of triple therapy with high-potency, pan- genotypic agents (agents with efficacy in multiple genotypes) was associated with higher efficacy in genotype 3 patients than with regimens currently available.

One drawback to the recently approved therapies is that they cannot be used in patients dialysis dependent. Patients who had ledipasvir/sofosbuvir combination is contraindicated in patients with a glomerular filtration rate of less than 30 ml/min/meter. Ombramivir, paritaprevir, and ritonavir can be used in patients with a glomerular filtration rate of less than 30 ml/min/meter, but only in those with underlying dialysis. HCV is common among patients with end-stage renal disease, so it is an important concern. The study included only patients, reflecting the fact that few patients failed treatment with ledipasvir/sofosbuvir in the first place.