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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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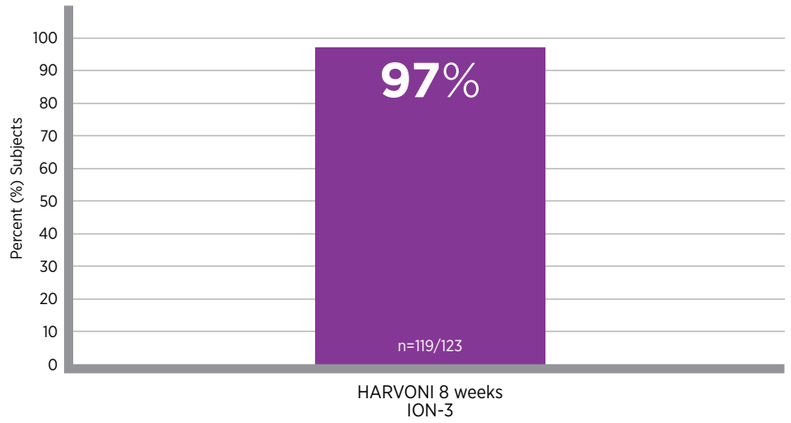
HARVONI is the only HCV treatment offering an 8-week course of therapy[1]

% SVR12 among treatment-naïve HCV GT 1 subjects without cirrhosis who had baseline HCV RNA <6 million IU/mL[1]



- Overall SVR12 was 94% (n=202/215) in subjects receiving HARVONI for 8 weeks[1,a]
- 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[1,a]
- The recommended treatment duration for treatment-naïve patients is 12 weeks[1]
- HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL[1]

Study Designs

ION-1[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 1:1:1:1 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[1]: a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 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).

[a]SVR12 was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment.[1] Achieving SVR is considered a virologic cure.[2]

RBV was not shown to increase the response rates observed with HARVONI in ION-1 or ION-3. Therefore, the HARVONI + RBV arms are not presented.[1]

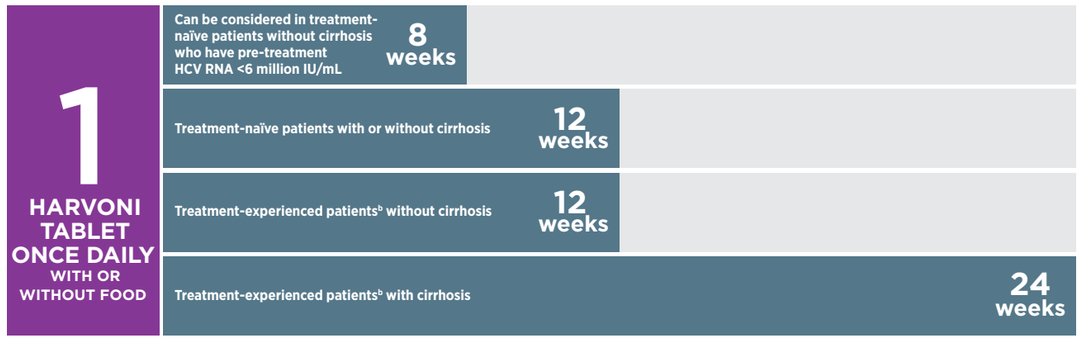
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Risk of Serious Symptomatic Bradycardia when Coadministered with Amiodarone:** Amiodarone is not recommended for use with HARVONI due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** 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 is the only once-daily single-tablet regimen for HCV GT 1 patients[1]

Recommended treatment duration[1]



[b]Treatment-experienced patients who failed treatment with either peginterferon (Peg-IFN) alfa + ribavirin (RBV) or an HCV protease inhibitor + Peg-IFN + RBV.[1]

- HARVONI is interferon- and RBV-free for GT 1 treatment-naïve and treatment-experienced patients with or without cirrhosis, regardless of GT 1a or 1b subtype[1]
- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]
- Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups[1]
- No dose adjustments are required based on advanced age, mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment. The safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis[1]
- No dose recommendations can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite[1]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue and headache.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

Visit harvoni.com/hcp

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets
EVERY REASON TO CURE

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 bradycardia, 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 bradycardia 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 HARVONI: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient 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 bradycardia should seek medical evaluation 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: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir (SOVALDI®) is not recommended.

ADVERSE REACTIONS:

The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials in subjects with genotype 1 CHC with compensated liver disease (with and without cirrhosis) who received HARVONI for 8 (N=215), 12 (N=539) and 24 (N=326) weeks. Adverse events led to permanent treatment discontinuation in 0%, <1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively.

Adverse Reactions (adverse events assessed as causally related by the investigator): The most common adverse reactions (≥10%; all grades) were fatigue and headache. Adverse reactions (all grades; majority Grade 1) observed in ≥5% of subjects by treatment duration were:

- *HARVONI for 8 weeks:* fatigue (16%); headache (11%); 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 (9%); diarrhea (7%); and insomnia (6%)

Direct comparison across trials should not be made due to differing trial designs.

Laboratory Abnormalities: ***Bilirubin Elevations:*** Bilirubin elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Lipase Elevations:*** Transient, asymptomatic lipase elevations of greater than 3x ULN were observed in <1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. ***Creatine Kinase:*** Creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Postmarketing Experience

Cardiac Disorders: Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. 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 individual agents, or are 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.
  - *Antacids:* Separate HARVONI and antacid administration by 4 hours.
  - *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI.

Brief Summary (cont.)

  - *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
- **Antiarrhythmics (amiodarone; digoxin)** *Amiodarone:* Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HIV Antiretrovirals**
  - *Regimens containing tenofovir disoproxil fumarate (DF) and an HIV protease inhibitor/ritonavir (emtricitabine/tenofovir DF plus atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir):* The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.
  - *Efavirenz/emtricitabine/tenofovir DF:* Monitor for tenofovir-associated adverse reactions. Refer to VIREAD, TRUVADA or ATRIPLA prescribing information for renal monitoring recommendations.
  - *Elvitegravir/cobicistat/emtricitabine/tenofovir DF:* The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.
  - *Tipranavir/ritonavir:* Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.
- **HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs individually: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, tenofovir DF or verapamil.

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 mother's clinical need for 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 have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for 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 Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

References: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. March 2015.
2. US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013.

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 pangenotypic 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 pangenotypic 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 1 patients. Treatment-naive 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 interleukin-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.

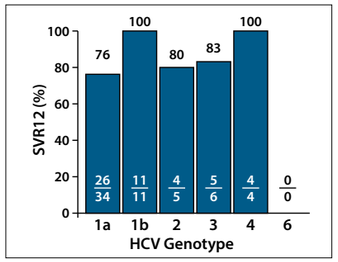


Figure 1. SVR12 among patients with advanced cirrhosis in the phase 3 ALLY-1 trial of daclatasvir, sofosbuvir, and ribavirin. HCV, hepatitis C virus; SVR12, sustained virologic response at week 12. Adapted from Poordad F et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY-1 study [EASL abstract LO8]. *J Hepatol*. 2015;62(1)(suppl).[4]

The SVR12 rate was 83% for the advanced cirrhosis arm and 94% for the posttransplant arm. The outcome was similar for the subset of patients with HCV genotype 1; the SVR12 rates were 82% for the advanced cirrhosis 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 0 of 3 patients in the posttransplant cohort. In all 13 patients, however, NS5A RAVs were identified after virologic failure.

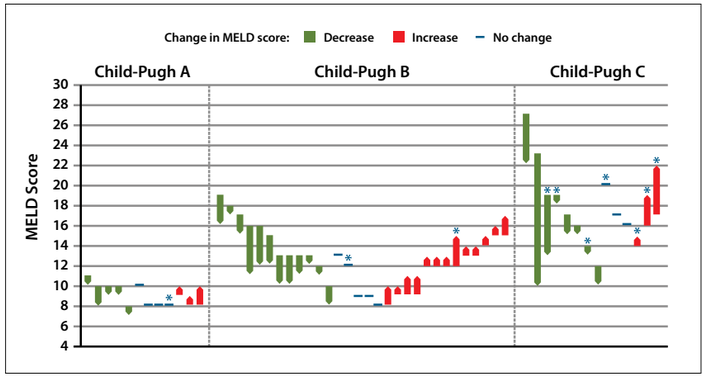


Figure 2. Changes in MELD score according to Child-Pugh class in the phase 3 ALLY-1 trial of daclatasvir, sofosbuvir, and ribavirin. *The patient did not achieve a sustained virologic response at week 12. MELD, Model for End-Stage Liver Disease. Adapted from Poordad F et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY-1 study [EASL abstract LO8]. *J Hepatol*. 2015;62(1)(suppl).[4]

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 (15% 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.

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 a 12-week course of grazoprevir and elbasvir in HCV genotype 1 patients with stage 4 or 5 chronic kidney disease (Abstract LP02). 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 course, which consisted of placebo followed by active dosing. Patients could be treatment-naive or treatment-experienced. Approximately 7% had cirrhosis. 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 patients (14%) in the immediate treatment arm and 17 patients (15%) in the deferred treatment arm. An AE led to treatment discontinuation in no patients in the active treatment group and 4% of patients in the placebo group. The most common AEs in the active treatment arm were headache, nausea, and fatigue.

References

1. Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. *Nature*. 2010;465(7294):96-100.
2. Guedj J, Dahari H, Rong L, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. *Proc Natl Acad Sci U S A*. 2013;110(10):3991-3996.
3. Sofia MJ, Bao D, Chang W, et al. Discovery of a β-d-2'-deoxy-2'-α-fluoro-2'-β-C-methyluridine nucleotide prodrug (PSI-7977) for the treatment of hepatitis C virus. *J Med Chem*. 2010;53(19):7202-7218.
4. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: phase 3 ALLY-1 study [EASL abstract LO8]. *J Hepatol*. 2015;62(1)(suppl).

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. The 2 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 RAVs 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 investigated the efficacy, safety, and pharmacokinetics of grazoprevir and elbasvir without ribavirin in patients with HCV genotype 1 infection and Child-Pugh class B cirrhosis.[4] In addition to the 30 cirrhotic patients, the study enrolled 10 noncirrhotic patients, primarily for pharmacokinetic analyses. All patients received daily treatment with elbasvir (50 mg) for 12 weeks, plus grazoprevir dosed at 50 mg for those with cirrhosis or 100 mg for those without. Plasma samples were collected in a subset of Child-Pugh class B and noncirrhotic patients at treatment week 4. MELD and Child-Pugh scores were assessed at baseline, the end of treatment, and follow-up week 12.

Slightly more than half of patients were male, and the mean age was approximately 59 years. More than 90% of patients were white. Of the 30 patients with Child-Pugh grade B cirrhosis, 90% had HCV genotype 1a. Nearly two-thirds were treatment-naive. The most common Child-Pugh score was 7 (in 70%), followed by 8 (23%) and 9 (7%). The mean MELD score was 9.9.

In the intent-to-treat population, SVR12 was achieved by 90% of the cirrhotic patients and 100% of the noncirrhotic patients. By the end of the 12-week treatment period, 100% of the cirrhotic patients had undetectable HCV RNA. At the fourth week of follow-up, 1 patient had relapsed, and 1 patient had died of progressive liver failure. One patient relapsed at follow-up week 8.

It is of great interest to determine whether early response to treatment with a direct-acting antiviral agent predicts SVR12. Therefore, HCV RNA levels were examined at 4-week intervals. At treatment week 4, 6 patients still had evidence of HCV infection, with HCV RNA levels greater than 15 IU/mL. By treatment week 8, 83% of these patients had undetectable HCV RNA. By treatment week 12, all patients 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 breakthroughs or rebounds 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 Q30R in the NS5A sequence (in 1 patient). However, at follow-up week 12, both patients had clinically significant RAVs in both the NS3 and NS5A coding regions. No correlation was observed between the presence of baseline NS3 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 (C_{24}) ratio of 1.71 (95% CI, 0.87-3.33). Elbasvir pharmacokinetics were similar in the 2 patient populations (C_{24}, 1.04; 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%

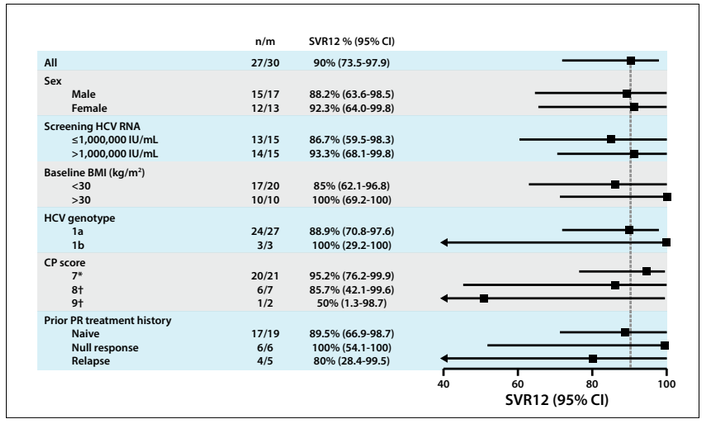


Figure 3. SVR12 rates according to subgroup analysis in part A of the C-SALT study of grazoprevir and elbasvir in patients with HCV genotype 1 and CP class B cirrhosis. BMI, body mass index; CP, Child-Pugh; HCV, hepatitis C virus; SVR12, sustained virologic response at week 12. Adapted from Jacobson IM et al. Efficacy and safety of grazoprevir and elbasvir in hepatitis C genotype 1–infected patients with Child-Pugh class B cirrhosis (C-SALT Part A) [EASL abstract O008]. *J Hepatol*. 2015;62(1)(suppl).[4]

ABSTRACT SUMMARY The Association of Sofosbuvir and Daclatasvir for Treating Severe Recurrence of HCV Infection After Liver Transplantation: Results From a Large French Prospective Multicentric ANRS CO23 CUPILT Cohort

The prospective French National AIDS Research Agency CO23 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 with HCV infection (and without HIV 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 patients also received ribavirin (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*=.02). The mean baseline MELD scores were 11 ± 5 and 13 ± 5, respectively (*P*=.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 were 100% without ribavirin and 67% with ribavirin. The 24-week regimen was associated with a SVR12 of 97% without ribavirin and 96% with ribavirin. One patient who experienced a virologic breakthrough at week 12 had no *NS5A* or *NS5B* mutations at baseline but exhibited the Q30R mutation in the *NS5A* gene at treatment failure. Treatment yielded overall improvements in mean total bilirubin levels, mean albumin levels, and mean platelet counts. Overall, 23% of patients experienced a serious AE. A significant decrease in renal function was observed for treatment with or without ribavirin, with creatinine clearance falling from 72.7 ± 29.0 mL/min at baseline to 68.7 ± 26.1 mL/min at the end of treatment (*P*<.0001).

ABSTRACT SUMMARY The Phase 3 C-EDGE Treatment-Naïve (TN) Study of a 12-Week Oral Regimen of Grazoprevir (GZR, MK-5172)/Elbasvir (EBR, MK-8742) in Patients With Chronic HCV Genotype (GT) 1, 4, or 6 Infection

The C-EDGE treatment-naive study evaluated the safety and efficacy of the fixed-dose combination of grazoprevir (100 mg) plus elbasvir (50 mg) once daily for 12 weeks in treatment-naive patients with HCV genotype 1, 4, or 6 (Abstract G07; Zeuzem S et al. *Ann Intern Med*. 2015; Epub ahead of print). The international, randomized, blinded, placebo-controlled, parallel-group trial enrolled cirrhotic patients and excluded those with decompensated liver disease. After stratification based on HCV genotype and fibrosis stage, patients were randomized 3:1 to receive either immediate treatment or placebo followed by open-label treatment. The 421 enrolled patients included 194 women and 157 nonwhite patients. Most patients (91%) had genotype 1 infection. Cirrhosis was present in 22%. Baseline platelet counts were less than 100 × 10^3/µL in 8.1% of patients. Among the 316 patients who received immediate treatment, 95% achieved SVR12. SVR12 rates for HCV genotypes 1a, 1b, 4, and 6 were 92%, 99%, 100%, and 80%, respectively. Cirrhotic patients achieved a SVR12 rate of 97.1%. One virologic breakthrough occurred at treatment week 8, and 12 patients relapsed; these patients had baseline NS5A RAVs, as well as emergent NS3 or NS5A variants. The combination of grazoprevir and elbasvir was generally well tolerated in cirrhotic and noncirrhotic patients. The most common AEs of any grade in the treatment vs placebo arms were headache (17% vs 18%, respectively), fatigue (16% vs 17%), nausea (9% vs 8%), and arthralgia (6% for each). No serious AEs were considered treatment-related. In the active treatment group, 3 patients (1%) discontinued treatment due to an AE.

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. 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.

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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

Patients with chronic HCV infection and decompensated cirrhosis have a poor prognosis and limited treatment options.[1,2] In the United States and Europe, HCV infection is the leading indication for liver transplant.[3,4] Dr Michael Manns and colleagues presented preliminary results from the international SOLAR-2 (GS-US-337-0124) trial, which investigated the safety and efficacy of 12 or 24 weeks of treatment with ledipasvir, which inhibits NS5A, and sofosbuvir plus ribavirin in patients with HCV genotype 1 or 4 infection and decompensated cirrhosis, and patients with recurrent genotype 1 or 4 infection before or after liver transplant.[5]

Main inclusion criteria included creatinine clearance of at least 40 mL/min and a platelet count of greater than $30 \times 10^3/\mu L$. A 3-month interval was required from the time of liver transplant, and no patients with hepatocellular carcinoma were included. The most important exclusion criterion was a Child-Turcotte-Pugh score of 13 or higher. Patients received a single daily tablet of ledipasvir (90 mg) and sofosbuvir (400 mg). Ribavirin dosing was weight-based for patients with METAVIR stage F0 to F3 fibrosis or Child-Turcotte-Pugh class A cirrhosis. In patients with Child-Turcotte-Pugh class B or C cirrhosis, ribavirin was initiated at 600 mg with subsequent dose escalation as appropriate. The primary endpoint was SVR12 in the intent-to-treat population, defined as a HCV RNA of less than 15 IU/mL. For this analysis, data from posttransplant patients with METAVIR stage F0 to F3 and Child-Turcotte-Pugh class A patients were combined.

SOLAR-2 enrolled 329 patients at 34 sites in 12 countries. The study included 168 posttransplant patients with METAVIR stage F0 to F3 or Child-Turcotte-Pugh class A cirrhosis and 160 patients with decompensated cirrhosis, of whom 53 were posttransplant. One patient was not treated. For the entire study population, the median age was approximately 59 years (range, 27-79 years). Approximately three-fourths of patients were male, and more than 90% were white. The majority of patients had HCV genotype 1a or 1b infection, and approximately 11% of patients had genotype 4. Approximately three-fourths of patients had failed prior treatment for their HCV infection.

The incidence of ascites was higher in the Child-Turcotte-Pugh class B or C cohort (72%) than the combined F0 to F3 and Child-Turcotte-Pugh class A cohort (2.5%), as was the rate of encephalopathy (41% vs 0%, respectively). Patients in the Child-Turcotte-Pugh class B or C cohort also had a higher median level of total bilirubin (2.3 mg/dL vs 0.8 mg/dL) and a lower median platelet count ($79 \times 10^3/\mu L$ vs $138 \times 10^3/\mu L$).

For the combined cohort of posttransplant patients with F0 to F3 or Child-Turcotte-Pugh class A, SVR12 was 95% with 12 weeks of treatment and 98% with 24 weeks of treatment (Figure 4). For the cohort of pretransplant and posttransplant patients with decompensated cirrhosis, SVR12 was 85% with 12 weeks of treatment and 88% with 24 weeks. In both cohorts, patients with genotype 1 infection had similar rates of SVR12 for either 12 or 24 weeks of treatment. For patients in the F0 to F3 plus Child-Turcotte-Pugh class A cohort, SVR12 was 96% with 12 weeks of treatment vs 98% with 24 weeks. SVR12 rates in the Child-Turcotte-Pugh class B or C cohort were 88% with 12 weeks of treatment vs 89% with 24 weeks. Among patients with compensated liver disease and genotype 4 infection, SVR12 was 91% for 12 weeks of treatment and 100% for 24 weeks. For patients with decompensated liver disease and genotype 4 infection, 12 weeks of treatment yielded a SVR12 of only 57%, compared with 86% for 24 weeks. Eleven patients in the study had fibrosing cholestatic hepatitis; results for these patients, reported separately, showed a SVR12 of 100%.[6]

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 (85% with 12 weeks vs 72% with 24 weeks). SVR12 was higher with 24 weeks of treatment among 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 ($P<.001$ for both). Median total bilirubin levels decreased for the compensated and decompensated cohorts ($P<.001$ for both). From baseline to follow-up week 4, MELD scores improved in the majority of patients with available data. The MELD score was unchanged in 18 patients and increased in 22 patients. A challenge with the latter patients is determining when antiviral therapy may no longer be effective. In the same time frame, 35% of patients with a baseline Child-Turcotte-Pugh class of B saw an improvement to class A, and nearly half of patients with Child-Turcotte-Pugh class C improved to class B.

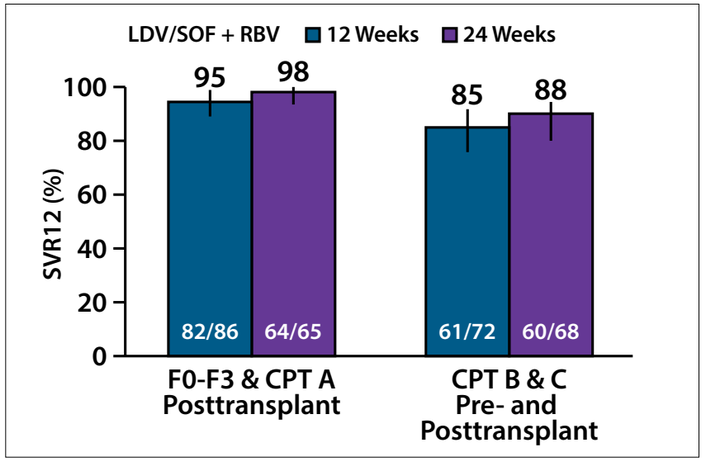

Figure 4. SVR12 rates in a preliminary analysis of the SOLAR-2 trial evaluating ledipasvir/sofosbuvir with ribavirin (LDV/SOF + RBV) in post–liver transplant patients with HCV. The error bars represent the 2-sided exact 90% confidence intervals. CPT, Child-Turcotte-Pugh; SVR12, sustained virologic response at week 12; HCV, hepatitis C virus. Adapted from Manns M et al. Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: preliminary results of the prospective SOLAR 2 trial [EASL abstract G02]. *J Hepatol.* 2015;62(1)(suppl).[5]

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.

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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 fail 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.[2-5] 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.[6]

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 $\log_{10}$ IU/mL (range, 4.5-7.4 $\log_{10}$ IU/mL). Among the 19 patients with cirrhosis, 79% had baseline NS5A RAVs. Prior HCV treatment duration was 8 weeks for 30 patients and 12 weeks for 11 patients. NS5A RAVs were present in 63% of patients who had received 8 weeks of treatment and in all patients treated for 12 weeks.

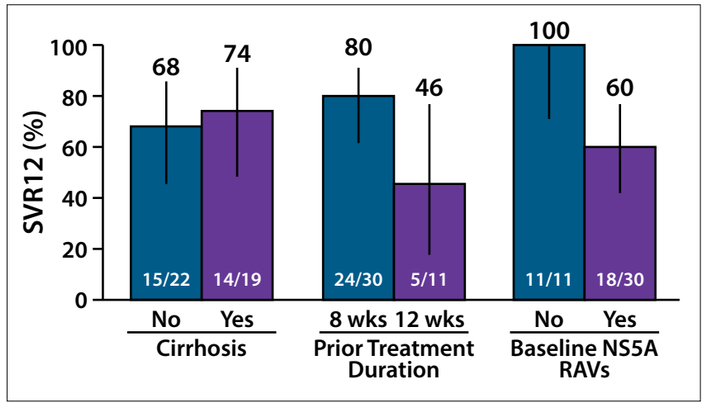

Figure 5. SVR12 in a trial evaluating retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with an additional course of ledipasvir/sofosbuvir. RAV, resistance-associated variants; SVR12, sustained virologic response at week 12. Adapted from Lawitz E et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks [EASL abstract O005]. *J Hepatol.* 2015;62(1)(suppl).[1]

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 experienced relapse. 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 NS5A RAVs at baseline reduced the SVR12 rate to 60% from 100% in their absence. These 2 latter outcomes are related because patients who had previously received 12 weeks of treatment had more NS5A 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 NS5A RAVs were 100%, 69%, and 50%, respectively. Specific baseline RAVs also impacted viral clearance, with SVR12 rates of 100% for patients with Q30R (n=4) or M28T (n=1), 80% for patients with L31M (n=5), and 33% for patients with Y93H/N mutations (n=6). Although no patients had NS5B RAVs at baseline, NS5B variants were detected in 33% of patients who experienced virologic failure (n=12). RAVs included S282T in 2 patients, L159F in 1 patient, and both mutations in 1 patient.

AEs occurred in 20 patients (49%). Two serious AEs were observed, 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.

ABSTRACT SUMMARY Ledipasvir/Sofosbuvir Treatment Results in High SVR Rates in Patients With Chronic Genotype 4 and 5 HCV Infection

In the phase 3 ION-1, ION-2, and ION-3 studies, the combination of sofosbuvir and ledipasvir yielded SVR12 rates of 93% or higher in patients with HCV genotype 1 infection. Both agents have demonstrated in vitro activity against genotypes 4 and 5, and these genotypes account for approximately 14% of chronic HCV infections worldwide (Gower E et al. *J Hepatol.* 2014;61[1 suppl]:S45-S57). To expand treatment options for patients with these less common HCV genotypes, an open-label study investigated the safety and efficacy of 12 weeks of daily treatment with sofosbuvir (400 mg) and ledipasvir (90 mg) in patients with HCV genotypes 4 and 5 (Abstract O056). The 85 enrolled patients had a median age of approximately 57 years, and more than half were male. Half of the patients were treatment-experienced; among them, 36% had cirrhosis. SVR12 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 vs treatment-experienced patients or for 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.

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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

Interferon-free regimens have yielded lower SVR rates for 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 or 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]

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 combinations, the trial aimed to document the emergence of viral resistance to sofosbuvir in patients who had failed to achieve SVR.

The study randomized 196 patients to receive 16 weeks of treatment with sofosbuvir (400 mg daily) plus ribavirin (1200 mg daily), 199 patients to receive 24 weeks of the same drug combination, and 197 patients to 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 treatment-experienced. No patients with decompensated cirrhosis were included. Patients were stratified based on cirrhosis, HCV genotype, and prior HCV treatment. All patients had platelet counts of at least 60,000 cells/mm^3 at screening. Across the entire study group, patients had a mean age of 50 years (range, 19-73 years). Two-thirds of patients were male, and 13% were Asian. The mean body mass index was 28 kg/m^2 (range, 18-55 kg/m^2). Thirty-eight percent of patients had the *IL28B* CC genotype, and 92% of patients had HCV genotype 3. The mean baseline HCV RNA level was 6.3 $\log_{10}$ IU/mL (range, 3.3-7.6 $\log_{10}$ IU/mL). Slightly more than half of patients had failed prior treatment with pegylated interferon and ribavirin, and 37% had cirrhosis. The

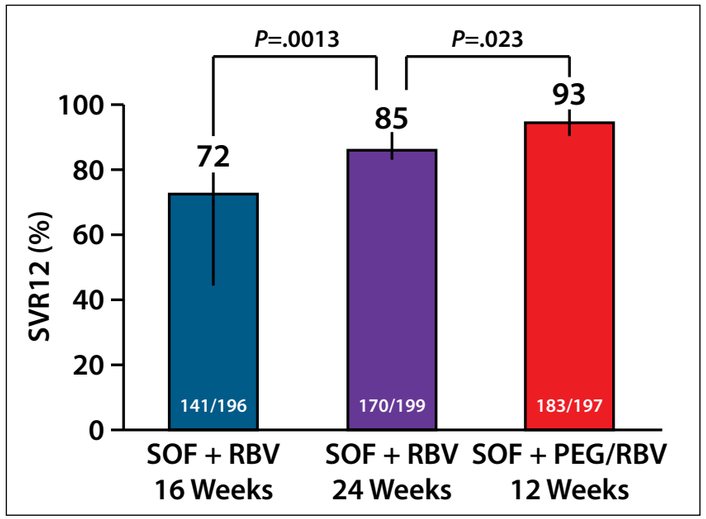

Figure 6. SVR12 in the BOSON trial, which compared sofosbuvir plus peginterferon/ribavirin (SOF + PEG/RBV vs sofosbuvir plus ribavirin (SOF + RBV) in HCV genotype 3 patients and treatment-experienced cirrhotic patients with HCV genotype 2. Error bars show the 95% confidence intervals. HCV, hepatitis C virus; SVR12, sustained virologic response at week 12. Adapted from Foster GR et al. 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 [EASL abstract LO5]. *J Hepatol*. 2015;62(1)(suppl).[3]

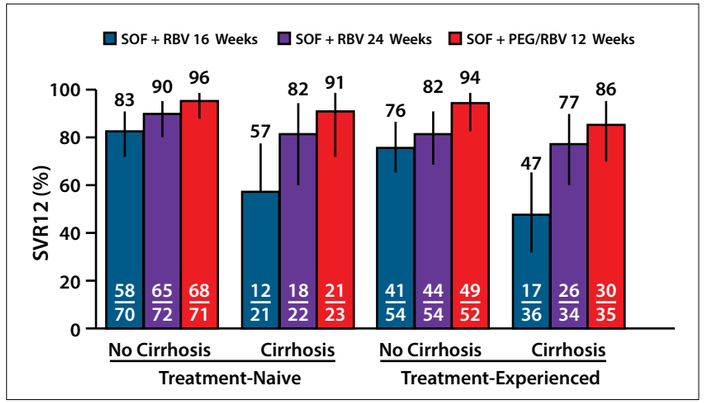

Figure 7. SVR12 by treatment history and cirrhosis status in the BOSON trial, which compared sofosbuvir plus peginterferon/ribavirin (SOF + PEG/RBV) vs sofosbuvir plus ribavirin (SOF + RBV) in HCV genotype 3 patients and treatment-experienced cirrhotic patients with HCV genotype 2. Error bars show the 95% confidence intervals. SVR12, sustained virologic response at week 12. Adapted from Foster GR et al. 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 [EASL abstract LO5]. *J Hepatol*. 2015;62(1)(suppl).[3]

mean platelet count was 198 cells/mm^3 (range, 54-537 cells/mm^3).

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 rates for the same treatments 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 also showed that the best results were consistently achieved with the addition of peginterferon 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 S282T mutation was observed in any samples, and no consistent variants or resistance patterns emerged.

The inclusion of pegylated interferon with sofosbuvir and ribavirin was generally well tolerated in this challenging patient population. AEs of any grade were observed in 94% to 99% 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% to 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 important laboratory abnormality was the decline in hemoglobin levels seen among patients receiving the interferon-containing regimen; hemoglobin fell below 10 g/dL in 24 patients (12%) and below 8.5 g/dL in 2 patients (1%).

The most common AEs of any grade in the interferon-containing arm were fatigue (46%), headache (36%), insomnia (25%), and nausea (25%).

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2. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology*. 2015;61(3):769-775.
3. Foster GR, Pianko S, Cooper C, et al. 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 [EASL abstract LO5]. *J Hepatol*. 2015;62(1)(suppl).

Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER

Dr 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/m^2. Most patients (78%) had cirrhosis, including 9% with decompensated cirrhosis. Diabetes was present in 18% of patients, and hypertension in 31%. Three-fourths 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%.

SVR12 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,

Table 1. SVR Rates in the HEPATHER Trial of Daclatasvir and Sofosbuvir in Patients With HCV Genotype 1

	Daclatasvir and Sofosbuvir (n=317)		Daclatasvir, Sofosbuvir, and Ribavirin (n=92)	
	12 Weeks	24 Weeks	12 Weeks	24 Weeks
SVR4, n (%)	46/54 (85.2)	250/263 (95.1)	12/12 (100)	79/80 (98.7)
SVR12, n (%)	45/53 (84.9)	172/184 (93.4)	11/11 (100)	61/62 (98.4)
SVR4 in patients with cirrhosis, n (%)	26/34 (76.5)	203/216 (94.0)	9/9 (100)	59/60 (98.3)
SVR4 in patients without cirrhosis, n (%)	20/20 (100)	47/47 (100)	3/3 (100)	18/18 (100)
SVR4 in treatment-naive patients, n (%)	27/31 (87.1)	47/53 (88.7)	4/4 (100)	14/14 (100)
SVR4 in treatment-experienced patients, n (%)	19/23 (82.6)	203/210 (96.7)	8/8 (100)	65/66 (98.5)
SVR4 in patients who had received a prior protease inhibitor and peginterferon/ribavirin, n (%)	4/5 (80.0)	128/132 (97.0)	4/4 (100)	32/32 (100)
SVR4 in patients who had received prior peginterferon/ribavirin, n (%)	15/18 (83.3)	75/78 (96.1)	4/4 (100)	33/34 (97.1)

HCV, hepatitis C virus; SVR4, sustained virologic response at week 4; SVR12, sustained virologic response at week 12.

Data from Pol S et al. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS CO22 HEPATHER [EASL abstract LO3]. *J Hepatol*. 2015;62(1)(suppl).[1]

ABSTRACT SUMMARY **Treatment of Decompensated HCV Cirrhosis in Patients With Diverse Genotypes: 12 Weeks Sofosbuvir and NS5A Inhibitors With/Without Ribavirin Is Effective in HCV Genotypes 1 and 3**

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 O002). 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 175 reports of serious AEs, 78.9% were attributed to liver disease and/or HCV therapy. Fourteen patients (3.0%) 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%).

SVR4 was 76.5% with 12 weeks of treatment vs 94.0% with 24 weeks. With ribavirin, SVR4 rose to 100% and 98.3%, 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 ($P=.036$) and extending treatment to 24 weeks ($P=.015$). Unexpectedly, a lower HCV viral load was associated with a reduced likelihood of achieving SVR4 ($P=.04$). Independent risk factors for failure to achieve SVR4, as identified by a logistic regression analysis, included absence of ribavirin (odds ratio [OR], 6.4; $P=.057$) and shorter duration of treatment (OR, 3.2; $P=.0085$). The presence of cirrhosis was associated with an OR of 9 ($P=.0022$), 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; $P=.057$) and shorter duration of treatment (OR, 4.3; $P=.008$).

Reference

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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).[1] 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 1.66×10^6 IU/mL to 3.69×10^6 IU/mL.

For genotype 1 patients, SVR12 rates for noncirrhotic patients were 33% with 4 weeks of treatment and 87% with 6 weeks (Figure 8). SVR12 rates for cirrhotic patients were 80% with 6 weeks of treatment and 94% with 8 weeks. All patients had undetectable HCV RNA after 2 weeks of treatment, and all virologic failures were caused by relapse. An analysis was conducted to identify RAVs known to confer a 5-fold reduction in potency for any of the direct-acting antiviral agents. The majority of patients had no RAVs at baseline or at virologic failure. One patient (3.3%) had a NS5A RAV at baseline. At virologic failure, 1 patient (3%) had a NS3 RAV, and 9 patients (30%) had a NS5A RAV.

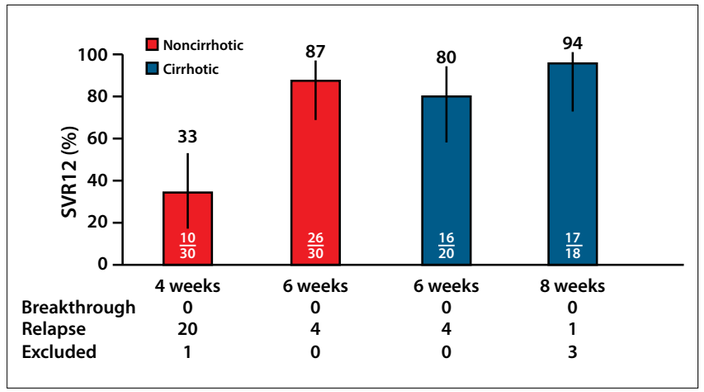

Figure 8. SVR12 rates in the C-SWIFT trial for patients with HCV genotype 1, who received grazoprevir/elbasvir plus sofosbuvir. HCV, hepatitis C virus; SVR12, sustained virologic response at week 12. Error bars show the 95% confidence intervals. Adapted from Poordad F et al. C-SWIFT: grazoprevir/elbasvir + 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;62(1)(suppl).[1]

In the genotype 3 group, SVR12 rates in noncirrhotic patients were 93% after 8 weeks of treatment and 100% after 12 weeks. The cirrhotic patients achieved a SVR12 rate of 91% after 12 weeks of treatment. One patient who discontinued treatment early was omitted from the analysis. Virologic failure, which occurred in 2 patients, was attributed to relapse. One of these patients relapsed after 8 weeks of treatment and had wild-type HCV RNA at baseline and at relapse. The other patient who relapsed after 12 weeks of treatment had the NS3 Q168R mutation at baseline as well as after treatment

Table 2. Treatment Arms in the C-SWIFT Trial of Grazoprevir, Elbasvir, and Sofosbuvir in Patients With HCV Genotype 1 or 3

Cirrhosis Status	Treatment Duration	n
Noncirrhotic	4 weeks	31
Noncirrhotic	6 weeks	30
Cirrhotic	6 weeks	20
Cirrhotic	8 weeks	21
Noncirrhotic	8 weeks	15
Noncirrhotic	12 weeks	14
Cirrhotic	12 weeks	12

HCV, hepatitis C virus.

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;62(1)(suppl).[1]

failure; in addition, the NS5A Y93H mutation was identified at the time of relapse. All of the genotype 3 patients had undetectable HCV RNA at the end of treatment. Subgroup analysis according to baseline viral load, hepatic fibrosis status, sex, or *IL28B* genotype did not yield any definitive correlation with the ability to achieve SVR12.

The 3-drug combination was generally well tolerated. The most common AEs of any grade were headache, fatigue, and nausea. In the entire study group, 2 serious AEs were observed. No patients died. One patient discontinued treatment due to an AE.

Reference

1. Poordad F, Lawitz E, Gutierrez JA, 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;62(1)(suppl).

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

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Presentations at the 2015 European Association for the Study of the Liver (EASL) International Liver Congress provided important data on new all-oral, interferon-free regimens in certain patient subgroups, such as those with advanced liver disease or renal failure, who were largely omitted from previous trials of combination therapy. Studies corroborated earlier findings for previously approved therapies for hepatitis C virus (HCV) in these populations and provided data for additional regimens. Among the new treatments for HCV, there were many studies with an emerging combination, grazoprevir (a NS3/4A protease inhibitor) and elbasvir (a NS5A inhibitor). This combination had previously been evaluated in the C-WORTHY phase 2 trial.[1] Based on the latest data, this regimen will likely be approved and added to the armamentarium in 2016.

Important Patient Subpopulations

Previous studies have shown that sofosbuvir, ledipasvir, and ribavirin are effective in HCV patients with advanced liver disease and in the posttransplant setting.[2,3] Data have also shown that paritaprevir, ombitasvir, dasabuvir, and ribavirin are effective in patients after transplant.[4] Several studies at the 2015 EASL meeting evaluated novel treatment regimens in these patient populations. The phase 3 ALLY-1 trial, presented by Fred Poordad, MD, examined a 12-week course of daclatasvir, a NS5A inhibitor; sofosbuvir, a polymerase inhibitor; and ribavirin.[5] This study included patients with advanced liver disease (n=60) and posttransplant recurrence of HCV (n=53). Patients with Child-Pugh classifications of A, B, or C were enrolled. The study included not only patients with genotype 1 (the population most often included in other trials), but also genotype 3.

The regimen of daclatasvir and sofosbuvir plus ribavirin was highly effective and reasonably well tolerated in this otherwise challenging patient population. For genotype 1 patients, the rates of sustained virologic response at week 12 (SVR12) were 82% in the advanced liver disease group and 95% in the posttransplant group. Although the 82% SVR12 in the advanced liver disease group is slightly lower than in previous reports with other therapies,[3] it still represents a robust response in this very sick population.

The SVR12 rate was 92% among advanced cirrhotic patients with a Child-Pugh class A score. The Child-Pugh class B patients had an excellent SVR12 rate of 94%. Among the 16 patients with Child-Pugh class C, the SVR12 rate was 56%. The Child-Pugh class C patients tolerated the treatment reasonably well, but it is notable that their SVR12 rate was much lower. It seems that the earlier patients are treated, the better the chance of attaining SVR.

Patients with HCV genotype 3, particularly those with cirrhosis, are the most difficult to treat with all-oral regimens consisting of direct-acting antiviral agents.[6-8] The ALLY-1 study is among the first to include genotype 3 patients with advanced cirrhosis and patients who had undergone transplant; the SVR12 rates were 83% and 91%, respectively. These are also robust numbers for an otherwise sick population, although it should be noted that only 17 genotype 3 patients were included.

In a real-life analysis, Graham Foster, FRCP, PhD, evaluated a 12-week course of sofosbuvir and a NS5A inhibitor with or without ribavirin in HCV patients with decompensated cirrhosis.[9] Enrolled patients included subjects with Child-Pugh class B or C, and the genotypes were diverse. The nonrandomized study found that the regimens were effective in patients with genotypes 1 and 3. The analysis included 467 patients who were treated with sofosbuvir and ledipasvir, with or without ribavirin, or sofosbuvir and daclatasvir, with or without ribavirin. Most patients received ribavirin. Among genotype 1 patients who received sofosbuvir, ledipasvir, and ribavirin, the real-life cure rate was 86%, which is similar to outcomes for this combination in the SOLAR-1 trial.[3] Among genotype 1 patients who received sofosbuvir, daclatasvir, and ribavirin, the cure rate was 82%, similar to what was shown with this combination in the ALLY-1 trial.[5]

The real-life cure rates among patients with genotype 3 were lower: 59% with sofosbuvir, ledipasvir, and ribavirin and 70% with sofosbuvir, daclatasvir, and ribavirin. In this real-life analysis, cure rates were lower for the genotype 3 patients than what was shown in the ALLY-3 trial.[10] Although these regimens show some efficacy in the genotype 3 population, they are not ideal.

The C-SALT study is evaluating grazoprevir and elbasvir without ribavirin in patients with HCV genotype 1, 4, or 6 and Child-Pugh B classification. There are no posttransplant patients enrolled. Ira Jacobson, MD, presented results for genotype 1 patients (part A).[11] Among 30 patients, 1 was lost to follow-up and 2 relapsed. The overall SVR12 was 90%. Virologic failure occurred in 2 patients with cirrhosis. This small study showed that this new regimen demonstrated efficacy in this patient population.

Michael Manns, MD, presented preliminary results from the SOLAR-2 trial, which evaluated ledipasvir and sofosbuvir with ribavirin in decompensated and post–liver transplant patients.[12] This study is the European equivalent of the SOLAR-1 trial.[3] The SOLAR-2 trial included several patient subgroups: those with decompensated cirrhosis, those with HCV recurrence after liver transplantation, and those who developed a relatively uncommon catastrophic posttransplant event related to HCV recurrence called *fibrosing cholestatic hepatitis*. Fibrosing cholestatic hepatitis is a life-threatening condition that most often presents within the first few months after liver transplant in patients with HCV.

Results were similar to those in the SOLAR-1 trial, in which decompensated patients achieved SVR12 rates of 87% with 12 weeks of treatment and 89% with 24 weeks.[3] Among the post–liver transplant patients in SOLAR-1, SVR12 rates for patients with F0 to F3 fibrosis were 96% with the 12-week regimen and 98% with the 24-week regimen.[2] Patients with Child-Turcotte-Pugh class A cirrhosis achieved SVR rates of 96% for both treatment durations. SVR12 rates for patients with Child-Turcotte-Pugh class B were lower, at 85% with 12 weeks of therapy and 83% with 24 weeks.[2] In SOLAR-2, the combination of sofosbuvir and ledipasvir plus ribavirin was again safe and efficacious in this sick patient population. After 12 weeks of treatment, SVR12 rates were 95% 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, efficacy was 100% among the 11 patients with fibrosing cholestatic hepatitis after 12 or 24 weeks of treatment, which is a promising development.[13]

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).[14] 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 92% in 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-I Study

The phase 3b RUBY-1 study enrolled 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 (150 mg), and ritonavir (100 mg), plus twice daily dasabuvir (250 mg). Ribavirin (200 mg daily) 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 on treatment. More than half of patients (65%) were on dialysis. By the end of treatment week 4, all but 1 patient had undetectable viral RNA (and this patient's viral load was undetectable by week 6). All of the 11 patients who reached posttreatment week 4 had undetectable HCV RNA. Two patients reached posttreatment week 12, and both had undetectable HCV RNA. Treatment was generally well tolerated. No patient experienced a treatment-related serious AE or discontinued treatment due to an AE. No clinically significant changes in markers of liver function or kidney function were observed.

C-EDGE also assessed the impact of baseline NS5A resistance associated-variants (RAVs) on response rates. Among the patients who have baseline NS5A resistance, the SVR12 rate was 58% compared with 99% among patients without a baseline mutation. Potency, defined as the robustness of resistance to a direct-acting antiviral agent from a baseline variant (NS5A in this case), was also determined and examined in regard to effect on response. Variants were described as conferring less than or greater than 5-fold loss of potency to the NS5A inhibitor. In the study presented by Zeuzem, cure rates were low. Only 22% of HCV genotype 1a patients with a baseline NS5A RAV with greater than 5-fold decrease in potency achieved SVR. This important finding may impact clinical practice by establishing a protocol to assess for the presence and potency of baseline NS5A RAVs in patients with genotype 1a before treatment is initiated.

Results for treatment-experienced patients in the C-EDGE trial were also presented.[15] In this population, ribavirin was included for some patients. Among patients who received grazoprevir and elbasvir for 12 weeks, SVR12 was 94% with ribavirin and 92% without. Treatment for 16 weeks yielded SVR12 rates of 97% with ribavirin and 92% without.

Fred Poordad, MD, presented results from the phase 2 C-SWIFT study.[16] This important trial evaluated the use of high-potency agents from all 3 classes of direct-acting antiviral agents now used for HCV therapy: a protease inhibitor (grazoprevir), a NS5A inhibitor (elbasvir), and a polymerase inhibitor (sofosbuvir). The aim of the study was to determine whether a combination of powerful drugs from each of the different classes could allow truncation of therapy among genotype 1 or 3 patients with and without cirrhosis. Treatment for these patients currently usually lasts 12 to 24 weeks. In this study, the treatment durations varied. Noncirrhotic genotype 1 patients received 4 or 6 weeks of therapy, and cirrhotic genotype 1 patients received therapy for 6 or 8 weeks. Among genotype 3 patients, the noncirrhotic group received 8 or 12 weeks of therapy, and the cirrhotic group received 12 weeks.

In noncirrhotic genotype 1 patients who received 4 weeks of therapy, the cure rate was disappointing (33%). Noncirrhotic genotype 1 patients who received 6 weeks of therapy achieved a better SVR rate of 87%. In comparison, longer courses of therapy have shown cure rates of 97%.[17-23] Among cirrhotic genotype 1 patients, cure rates were 80% for the 6-week course and 94% for the 8-week course. These rates approach but do not exceed those seen with longer courses of therapy.[17,18,24] For noncirrhotic genotype 3 patients, 8 weeks of treatment yielded a SVR12 rate of 93%. The cure rate was 100% for noncirrhotic patients who received 12 weeks of treatment. Among the cirrhotic genotype 3 patients who received 12 weeks of therapy, 91% were cured. These rates are higher than those seen in other studies of similar patients.[6-8]

Three conclusions can be drawn from these data. First, very short courses of therapy—4 weeks—do not appear 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 shorten therapy among cirrhotic patients, who now often still require 24-week treatment courses. Third, a shorter course of triple therapy with high-potency, pangenotypic 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 dialysis patients. The ledipasvir/sofosbuvir combination is contraindicated in patients with a glomerular filtration rate of less than 30 mL/minute. Ombitasvir, paritaprevir, and ritonavir can be used in patients with a glomerular filtration rate of less than 30 mL/minute, but not in those undergoing dialysis. HCV is common among patients with end-stage renal disease, so it is an important concern. RUBY-1 is a phase 3B study evaluating ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with or without ribavirin, in patients with renal failure. Preliminary results for 20 patients were presented by Paul Pockros, MD.[25] The treatment was well tolerated. No patients discontinued therapy, and there were no treatment-related serious adverse events. There were no virologic failures. All 10 patients who reached posttreatment week 4 achieved SVR4.

David Roth, MD, presented results of a study evaluating grazoprevir/elbasvir in renal failure patients.[26] A phase 2/3 study, C-SURFER, included 122 patients with severe renal failure (chronic kidney disease stage 4 or 5). 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 cured, for a modified analysis SVR12 rate of 99%. Six patients discontinued treatment for reasons deemed unrelated to drugs, including 1 who died from cardiovascular disease. When 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 because there are currently no approved regimens for dialysis patients. This regimen will offer hope for these patients when it becomes available.

Retreatment of Patients

There were several studies presented involving patients who had failed a previous antiviral regimen and then were retreated with a different regimen or the same regimen for a longer course. Eric Lawitz, MD, presented preliminary results from a study that enrolled patients who had failed treatment with 8 or 12 weeks of ledipasvir and sofosbuvir in previous trials.[27] Patients received a 24-week course of ledipasvir/sofosbuvir (without ribavirin). The study included only 41 patients, reflecting the fact that few patients fail treatment with ledipasvir/sofosbuvir in the first place. The study showed that an impressive 71% of patients achieved a sustained response after retreatment. Another interesting finding from this study involved NS5A RAVs. Some patients have RAVs at baseline; other patients develop them after an ineffective course of treatment with a regimen involving a NS5A inhibitor such as ledipasvir. Among patients in the retreatment study by Lawitz, 44% had developed a NS5A RAV. Among patients who failed the 8-week regimen, 19 of 30 developed a NS5A 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 NS5A RAV (at least one that could be detected). On the other hand, all 11 patients who failed 12 weeks of treatment developed a NS5A RAV. Among the 11 patients in the 8-week arm who did not have the NS5A RAV, 100% were cured with the longer 24-week course of therapy. Among the 30 patients who developed the NS5A RAV in 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 predict whether a patient will benefit from retreatment with the same regimen for a longer period.

The analysis by Lawitz also identified development of a NS5B RAV to sofosbuvir in patients who failed the 24-week regimen. Previously, this mutation had been identified in very few patients. In this study, among the 12 patients who failed treatment, 4 developed a NS5B RAV. The implications of this finding are unknown.

Xavier Forns, MD, presented results from C-SALVAGE, a study that examined a regimen consisting of grazoprevir, elbasvir, and ribavirin in genotype 1 patients who failed treatment with interferon, ribavirin, and a first-generation protease inhibitor.[28] The regimen of sofosbuvir (a NS5B polymerase inhibitor) and ledipasvir (a NS5A inhibitor) works extremely well in patients who have failed treatment with a protease inhibitor and is approved in this population.[18] It might have been expected that patients who had failed treatment with a protease inhibitor would not benefit from retreatment with a regimen including a protease inhibitor, such as grazoprevir. However, the approach worked well. The regimen was administered for 12 weeks, and the SVR12 rate was 96%.

Disclosure

Dr Flamm has performed research for Gilead, AbbVie, BMS, and Janssen. He is a consultant for Gilead, AbbVie, BMS, Janssen, and Merck.

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