DR. TARIK ASSELAH (Orcid ID : 0000-0002-0024-0595)
DR. JORDAN J FELD (Orcid ID : 0000-0003-2640-2211)

Article type : Original Articles

Handling Editor: Zobair Younossi

# Sofosbuvir/Velpatasvir in Patients With Hepatitis C Virus Genotypes 1-6 and Compensated Cirrhosis or Advanced Fibrosis

**Short title:** Sofosbuvir/Velpatasvir in HCV With Cirrhosis

Tarik Asselah, MD, PhD,[1] Stefan Bourgeois, MD,[2] Stephen Pianko MD, PhD,[3] Stefan Zeuzem, MD,[4] Mark Sulkowski, MD,[5] Graham R. Foster, PhD,[6] Lingling Han, PhD,[7] John McNally, PhD,[7] Anu Osinusi, MD,[7] Diana M. Brainard, MD,[7] G. Mani Subramanian, MD,[7] Edward J. Gane, MD,[8] Jordan J. Feld, MD, MPH,[9] and Alessandra Mangia, MD[10]

From the [1]Department of Hepatology, Hôpital Beaujon, APHP, University Paris-Diderot and INSERM CRI UMR1149, Clichy, France; [2]Campus Stuivenberg, Antwerp, Belgium; [3]Monash Health and Monash University, Clayton, Victoria, Australia; [4]Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, Germany; [5]Johns Hopkins University, Baltimore, Maryland, USA; [6]Queen Mary University London, London, UK; [7]Gilead Sciences, Inc., Foster City, California, United States; [8]Auckland Clinical Studies Ltd, Auckland, New Zealand; [9]Toronto Centre for Liver Disease, Toronto, Canada; and [10]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy

**Financial support:** Funding for this study was provided by Gilead Sciences, Inc.

**Abbreviations:** APRI, AST to Platelet Ratio Index; BMI, body mass index; DAA, directly acting antiviral; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; IQR, interquartile range; LLOQ, lower limit of quantification; PEG-IFN, peginterferon; RAS, resistance-associated substitutions; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; ULN, upper limit of normal; VEL, velpatasvir.

**Address correspondence to**: Tarik Asselah, Department of Hepatology, Hôpital Beaujon, APHP, University Paris-Diderot and INSERM CRI UMR1149, Clichy, France; Email: tarik.asselah@aphp.fr.

**Conflicts of Interest:** Tarik Asselah has been an advisory board/speakers bureau member and investigator for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck & Co., and Roche. Stefan Bourgeois has been a consultant and speaker for Gilead Sciences, Janssen Pharmaceuticals, BristolMyersSquibb, Merck & Co., and AbbVie. Stephen Pianko has been a consultant for Abbvie, Merck & Co., and Gilead Sciences and been on the BristolMyersSquibb speaker bureau. Stefan Zeuzem has been a consultant for Abbvie, BristolMyersSquibb, Gilead Sciences, Janssen Pharmaceuticals, and Merck & Co. Graham Foster has been on speakers bureaus and/or served on advisory boards for the following companies: AbbVie, Gilead Sciences, Janssen Pharmaceuticals, BristolMyersSquibb, Merck & Co., Idenix Pharmaceuticals, Novartis, Arbutus, Alnylam, GlaxoSmithKline, and Roche. The following authors are employees of Gilead Sciences and may hold stock interest in the company: Lingling Han, John McNally, Anu Osinusi, Diana M. Brainard, and G. Mani Subramanian. Edward Gane has been on speakers bureaus and/or

served on advisory boards for the following companies: AbbVie, Gilead Sciences, Janssen Pharmaceuticals, Merck & Co., ALIOS, Idenix Pharmaceuticals, Novira, Arrowhead, Arbutus, Alnylam, GlaxoSmithKline, and Roche. Mark Sulkowski, Jordan Feld, and Alessandra Mangia have no declared conflicts of interest.

**Writing assistance:** Jennifer King, PhD, of August Editorial helped draft the manuscript.

**Author contributions:** Tarik Asselah, John McNally, and Lingling Han conceived and designed the study. Tarik Asselah, Stefan Bourgeois, Stephen Pianko, Stefan Zeuzem, Mark Sulkowski, Graham Foster, Lingling Han, John McNally, Anu Osinusi, Diana Brainard, G. Mani Subramanian, Edward Gane, Jordan Feld, and Alessandra Mangia were involved with data generation, collection, assembly, analysis, and/or interpretation. Tarik Asselah, Stefan Bourgeois, Stephen Pianko, Stefan Zeuzem, Mark Sulkowski, Graham Foster, Lingling Han, John McNally, Edward Gane, Jordan Feld, and Alessandra Mangia were involved with drafting or revising the manuscript. All authors approved the final version of the manuscript.

**Key Points:**

- Patients with chronic hepatitis C virus (HCV) infection and advanced fibrosis or cirrhosis require immediate treatment.
- We analyzed 501 patients from 3 large phase 3 trials (ASTRAL-1, -2, and -3) with compensated cirrhosis (Metavir F3) or advanced fibrosis (F4) who received sofosbuvir-velpatasvir for 12 weeks.
- Overall, 98% of patients (490/501; 95% CI 96-99) achieved sustained virologic response 12 weeks after the end of treatment.
- Sofosbuvir-velpatasvir is highly effective in patients infected with HCV with advanced fibrosis or cirrhosis.

## ABSTRACT

**Background & Aims:** Patients with chronic hepatitis C virus (HCV) infection and advanced fibrosis (Metavir F3) or cirrhosis (Metavir F4) have been identified as a priority group for immediate treatment. We evaluated the safety and efficacy of sofosbuvir-velpatasvir in patients with HCV genotype 1–6 infection and compensated cirrhosis or advanced fibrosis.

**Methods:** This retrospective analysis included 501 patients with compensated cirrhosis or advanced fibrosis (F3/F4), as defined by >0.59 on Fibrotest, >9.5 kPa on Fibroscan, or F3/F4 (Metavir) or F4 (Ishak) on liver biopsy. Patients received sofosbuvir-velpatasvir for 12 weeks. Sustained virological response 12 weeks after treatment (SVR12) was determined.

**Results:** Forty-four percent of patients had cirrhosis. SVR12 was achieved by 98% of patients (490/501; 95% CI, 96%-99%). SVR12 rates were 100% for HCV genotypes 2 (85/85), 4 (60/60), 5 (13/13), and 6 (20/20). SVR12 rates were 98% (167/170) in HCV genotype 1 patients and 95% (145/153) in HCV genotype 3 patients. Among patients with cirrhosis 96% (212/220) achieved SVR12, versus 99% (278/281) for those with advanced fibrosis. SVR12 was 98% (306/311) for treatment-naïve patients and 97% (184/190) for treatment-experienced patients. No patients discontinued treatment due to adverse events. Eight patients reported nine serious adverse events; none was considered related to study procedures or drugs.

**Conclusions:** Sofosbuvir plus velpatasvir is highly effective and safe for treating patients with HCV genotypes 1, 2, 3, 4, 5, or 6 and advanced fibrosis or compensated cirrhosis.


**Keywords:** antiviral agents; direct-acting antivirals; polymerase inhibitor; NS5A inhibitor

## INTRODUCTION

For persons with chronic hepatitis C virus (HCV) infection and advanced liver disease, achieving sustained response to treatment results in substantial decreases in the risks for hepatic decompensation events, hepatocellular carcinoma, liver transplantation, and both all-cause and liver-related mortality.[1-5] Sustained virologic response (SVR) following interferon-based therapy, which has been shown to be durable up to 18 years, halts fibrosis progression and in some patients results in cirrhosis regression.[6] Given the benefits of successful treatment and risks for complications without treatment, patients with advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) have been identified as a priority group for immediate HCV treatment.[7] Historically, with interferon-based regimens, HCV patients with cirrhosis and advanced fibrosis had higher rates of toxicity and lower rates of sustained virologic response.[8] The newer all-oral regimens with directly acting antivirals have reduced toxicity, but the presence of cirrhosis reduces response to several of these regimens, especially in patients infected with genotype 3 HCV.[8-10]

Sofosbuvir, a nucleotide analogue inhibitor of the HCV NS5B polymerase, is approved for treating HCV in combination with several other agents, including NS5A inhibitors, ribavirin, and peginterferon–ribavirin. Velpatasvir (formerly GS-5816, Gilead Sciences) is a second-generation HCV NS5A inhibitor with antiviral activity against HCV replicons in genotypes 1 through 6.[11] The combination of sofosbuvir and velpastavir for treating chronic HCV has been evaluated in several phase 3 studies.[12-14] ASTRAL-1, -2, and -3 each evaluated a once-daily, fixed dose combination regimen of sofosbuvir–velpatasvir for 12 weeks, and collectively the studies encompassed a broad range of HCV populations, including HCV genotypes 1–6. The overall response rate in more than 1,000 patients was high, with 98% achieving sustained virologic response 12 weeks after treatment (SVR12).[12,13]

ASTRAL-1, -2, and -3 each included patients with compensated cirrhosis, but they represented minority populations.

Distinguishing between Metavir F3 and F4 histology in clinical practice is difficult because of the limitations of available methodologies.[15] To encompass patients who receive an F3 score but have undetected cirrhosis, all F3 patients are clinically managed as if they are F4. Patients with advanced fibrosis and compensated cirrhosis are frequently underrepresented in clinical trials. To better define the efficacy and safety of sofosbuvir plus velpatasvir, we conducted a retrospective pooled analysis in patients with HCV genotype 1–6 infection and compensated cirrhosis or advanced fibrosis in the ASTRAL-1, -2, and -3 registrational trials.

## METHODS

### Patients

Participants included a pooled subset of patients with chronic hepatitis C and advanced fibrosis or compensated cirrhosis from the phase III ASTRAL-1, -2, and -3 trials.[12,13] ASTRAL-1 (NCT02201940) was conducted in the United States, Canada, Europe, and Hong Kong. ASTRAL-2 (NCT02220998) was conducted in the United States. And ASTRAL-3 (NCT02201953) was conducted in the United States, Canada, Europe, Australia, and New Zealand. Patients were 18 years of age or older. In this pooled analysis, patients had genotype 1-6 HCV and received a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir orally once daily for 12 weeks. The presence of cirrhosis or advanced fibrosis (F3/F4) was defined as scoring either >0.59 on Fibrotest, >9.5 kPa on Fibroscan,[16] or F3/F4 (Metavir) or F4 (Ishak) on liver biopsy. If scores conflicted, the presence of cirrhosis or advanced fibrosis overruled its absence. Patients with clinical evidence of decompensated cirrhosis (ascites, encephalopathy, or variceal hemorrhage) were excluded

from participation in this study In addition, patients with ALT or AST >10 times the upper limit of normal (ULN), direct bilirubin > 1.5 x ULN, platelets < 50,000 /uL, albumin <3 g/dL, or INR > 1.5 x ULN were excluded.

**Resistance Analyses**

Deep sequencing of HCV NS5A coding region was performed to identify viral sequences with NS5A class resistance associated substitutions (RASs). The RASs evaluated for this report were those that were present in more than 15% of the sequence reads.

**Endpoints and Statistical Analyses**

This exploratory analysis was not designed to evaluate formal statistical hypotheses. We calculated point estimates for rates of SVR12 for the total population and each HCV genotype along with exact two-sided 95% exact confidence intervals (CIs) using the binomial distribution (Clopper-Pearson's method).

***Laboratory Assessments of Liver Disease***

From baseline to posttreatment week 4, median values of platelets, albumin, and total bilirubin were evaluated. Fibrosis was assessed by APRI scores. APRI (*AST to Platelet Ratio Index*) score was calculated as ((AST [IU/L] / AST upper normal limit [IU/L]) / Platelet count [$10^9$/L]) x 100. Liver necroinflammation was assessed by alanine transaminase (ALT) and aspartate transaminase (AST) at baseline and posttreatment week 4. Laboratory assessments were evaluated through posttreatment week 4, and are not available for subsequent posttreatment visits. Assessments were performed in accordance with the safety monitoring schedule which concludes approximately four weeks after the end of treatment.

**Study Oversight**

The studies from which this analysis pooled patient data (ASTRAL-1, -2, and -3 trials) were

approved by the institutional review board or independent ethics committee at each participating study site (appendix) and were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients from each trial provided written informed consent.

## RESULTS

### Baseline Characteristics

Among 501 patients included in this analysis, 73% were male, 84% were white, and 65% had a non-CC *IL-28B* genotype (Table 1). All HCV genotypes were represented, with genotype 1 (34%) and genotype 3 (31%) most common. Thirty-eight percent of patients were treatment experienced, with 33% of all patients having received peginterferon-based therapy. Forty-four percent of all patients had cirrhosis (Table 2). Of the 497 patients who had Fibrotest scoring, 48% had values indicating cirrhosis. Twelve percent of pateints had platelets <100,000/μL and 4% had albumin <3.5 g/dL.

### Efficacy

SVR12 was achieved by 98% of patients (490/501; 95% CI, 96% to 99%) (Table 3 and Figure 1). Patients with cirrhosis had an SVR12 rate of 96% (212/220), and those with advanced fibrosis had an SVR12 rate of 99% (278/281). Response rates were similar among other evaluated subgroups of patients (Table 4). SVR12 was 98% (306/311) for treatment-naïve patients and 97% (184/190) for treatment-experienced patients. Patients with a non-CC *IL-28B* genotype had an SVR rate of 97% (318/327), versus 99% (169/171) for patients with the CC genotype. SVR12 rates were 100% among patients infected with HCV genotypes 2, 4, 5, or 6. SVR12 rates were 98% (167/170) in patients with HCV genotype 1 infection and 95% (145/153) in patients with HCV genotype 3 infection. Patients with HCV genotype 1 and cirrhosis had an SVR12 rate of 99% (72/73), whereas patients with HCV genotype 3 and

cirrhosis had an SVR12 rate of 91% (73/80). Of patients with baseline NS5A resistance-associated substitutions ≥15%, 96% (134/139) achieved SVR12, versus 98% (355/361) of patients without an NS5A resistance-associated substitutions.

No patients had virologic failure on treatment. Of the 10 patients who did not achieve SVR12, all had virologic relapse after the end of treatment. Eight had HCV genotype 3 infection, and 2 had HCV genotype 1 infection (Table 5). Seven of the patients who relapsed had cirrhosis.

***Measures of Liver Function***

From baseline to posttreatment week 4, median values of platelets, albumin, and total bilirubin showed improvement (Table 6). APRI scores, which were a median of 1.13 (IQR=0.68, 2.24) at baseline, had a median change at posttreatment week 4 of -0.68 (IQR=-1.59, -0.35). The maximum APRI change from baseline to posttreatment week 4 was -9.34. At baseline, 31% of patients (154/501) had an APRI score >2.0, versus only 1% (5/426) of patients at posttreatment week 4.

**Safety**

The most common adverse events, occurring in more than 10% of patients, were headache (31%), fatigue (21%), nausea (13%), and nasopharyngitis (11%) (Table 7). No patients discontinued treatment because of an adverse event. Eight patients had serious adverse events. Of the serious adverse events, none was considered related to study procedures or drugs. Three patients had lipase values >5 × ULN, but the increases were asymptomatic. No patients had hemoglobin <10 g/dL or total bilirubin >5 × ULN.

One patient died 112 days after the end of treatment because of complications related to metastatic lung cancer, which was not considered treatment-related. The patient was a 58-year-old white male who had cirrhosis at baseline and achieved SVR12 with study treatment.

## DISCUSSION

In this retrospective analysis of more than 500 patients, sofosbuvir plus velpatasvir was highly effective as a pangenotypic treatment for HCV patients with advanced fibrosis or compensated cirrhosis, a population historically considered difficult to cure and as having higher risks for safety issues. Treatment with sofosbuvir plus velpatasvir for 12 weeks resulted in SVR12 for 98% of patients infected with HCV genotypes 1–6. Furthermore, 190 (38%) of patients were treatment experienced, and 327 (65%) had a non-*CC-IL28 B* genotype. All these factors (advanced fibrosis, prior nonresponse to treatment, non-*CC-IL28 B* genotype) are historically associated with failure to respond to therapy.[17] To date, this analysis is the largest involving an interferon- and ribavirin-free regimen of direct-acting antivirals in patients with HCV and advanced fibrosis or cirrhosis, which represent a priority group for immediate treatment.

In this analysis, 100% of patients with HCV genotypes 2 (85/85), 4 (60/60), 5 (13/13), and 6 (20/20) achieved SVR12. Ninety-eight percent (167/170) of patients with HCV genotype 1 infection and 95% (145/153) of patients with HCV genotype 3 infection achieved SVR12. Among the 8 patients with HCV genotype 3 who did not achieve SVR12, 6 had cirrhosis at baseline. However, slightly more than half (52%, 80/153) of patients with HCV genotype 3 had cirrhosis at baseline, and 91% (73/80) of them achieved SVR12. These are the highest reported SVR rates for HCV genotype 3–infected patients, who have been more challenging to cure even with the newer regimens containing direct-acting antivirals.[18] In comparison, in a study of daclatasvir, sofosbuvir, and ribavirin, SVR12 in patients with HCV genotype 3 and cirrhosis was 86% overall (31/36): 83% (15/18) with 12 weeks of treatment and 89% (16/18) with 16 weeks. Among treatment-experienced patients, 87% (26/30) achieved SVR12.[19] In the proof-of-concept study C-SWIFT, 11/12 (91%) patients HCV

genotype 3 patients with cirrhosis who received sofosbuvir with grazoprevir and elbasvir for 12 weeks achieved SVR12.[8,20]

In our analysis, the most common adverse events were headache, fatigue, nausea, and nasopharyngitis. No patients discontinued treatment because of adverse events. Although 8 patients had serious adverse events, none of these events was considered related to study procedures or drugs. In the era of triple-therapy with telaprevir or boceprevir and peginterferon and ribavirin, several teams reported that serum albumin <3.5 g/dL and platelet count ≤100,000/mm$^3$ were independent predictors of severe complications.[21,22] In this analysis of more than 500 patients, there were 18 patients with serum albumin <3.5 g/dL and 59 patients with platelet count ≤100,000/mm$^3$, yet no patients had severe complications attributed to study drugs.

Median values of platelets, albumin, and total bilirubin showed improvement from baseline to posttreatment week 4. APRI scores had a median change at posttreatment week 4 of -0.68. A cohort study of patients in the United States has reported significant drops in APRI and Fibrosis-4 (FIB4) scores with SVR, and the scores remained low for 10 years posttreatment, suggesting long-term regression of fibrosis.[23]

One limitation of this study is the uneven distribution of HCV genotypes among study participants, where HCV genotypes 5 and 6 each accounted for <5% of patients. However, both of these genotypes account for a small percentage of cases of HCV globally, with HCV genotype 6 responsible for approximately 5% of cases and genotype 5 for fewer than 1%.[24] Additionally, the follow-up period of 4 weeks may be insufficient for capturing the extent of clinically meaningful changes.

In conclusion, sofosbuvir plus velpatasvir is a highly effective and safe pangenotypic treatment for patients with chronic HCV infection and advanced fibrosis or compensated cirrhosis, a population that was previously considered difficult to treat.

**ACKNOWLEDGMENTS**

We thank the patients and their families as well as the study-site personnel. Jennifer King, PhD, of August Editorial helped draft the manuscript.

**References**

1. Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652–657.

2. Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833–844.

3. Dienstag JL, Ghany MG, Morgan TR, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. Hepatology 2011;54:396–405.

4. Meer AJ van der, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.

5. Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329–337.

6. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology 2008;135:821–829.

7. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015.

8. Majumdar A, Kitson MT, Roberts SK. Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. Aliment Pharmacol Ther 2016.

9. Zopf S, Kremer AE, Neurath MF, et al. Advances in hepatitis C therapy: What is the

current state - what comes next? World J Hepatol 2016;8:139–147.

10. Asselah T, Boyer N, Saadoun D, et al. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver Int. 2016;36 Suppl 1:47–57.

11. Cheng G, Yu M, Peng B, et al. GS-5816, a second-generation HCV NS5A inhibitor with potent antiviral activity, broad genotypic coverage and a high resistance barrier. Journal of Hepatology 2013;58(Suppl 1):S484.

12. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015.

13. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608–2617.

14. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628.

15. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012;142:1293–1302.

16. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970–1979.

17. Estrabaud E, Vidaud M, Marcellin P, et al. Genomics and HCV infection: progression of fibrosis and treatment response. J Hepatol 2012;57:1110–1125.

18. Ampuero J, Romero-Gómez M. Hepatitis C Virus: Current and Evolving Treatments for Genotypes 2 and 3. Gastroenterol Clin North Am 2015;44:845–857.

19. Leroy V, Angus P, Bronowicki J-P, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016;63:1430–1441.

20. Poordad F, Lawitz E, Guitierrez 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. J Hepatol 2015;62(Suppl 2):S192–S193.

21. Hézode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013;59:434–441.

22. Gordon SC, Muir AJ, Lim JK, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. J Hepatol 2015;62:286–293.

23. Lu M, Li J, Zhang T, et al. Serum Biomarkers Indicate Long-term Reduction in Liver Fibrosis in Patients With Sustained Virological Response to Treatment for HCV Infection. Clin Gastroenterol Hepatol 2016;14:1044-1055.

24. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77–87.

**FIGURE LEGEND**

**Figure 1. SVR Rates Overall and by Cirrhosis or Advanced Fibrosis Status.** Error bar represents 95% confidence interval. SVR, sustained virologic response.

**Table 1. Patient Demographics and Baseline Characteristics**

| | SOF–VEL (N=501) |
|---|---|
| Mean (SD) age, yr | 57 (8) |
| Male, n (%) | 366 (73) |
| Race, n (%) | |
| White | 419 (84) |
| Asian | 42 (8) |
| Black or African American | 29 (6) |
| American Indian or Alaska Native | 2 (0.4) |
| Other | 4 (0.8) |
| Mean (SD) BMI, $kg/m^2$ | 28 (5) |
| Genotype, n (%) | |
| 1 | 170 (34) |
| 1a | 117 (23) |
| 1b | 53 (11) |
| 2 | 85 (17) |
| 3 | 153 (31) |
| 4 | 60 (12) |
| 5 | 13 (3) |
| 6 | 20 (4) |
| Mean (SD) HCV RNA, $log_{10}$ IU/mL | 6.3 (0.63) |
| Prior HCV treatment, n (%) | |
| None | 311 (62) |
| DAA + PEG-IFN +RBV | 43 (9) |
| PEG-IFN + RBV | 127 (25) |
| Other | 20 (4) |
| *IL-28B*, n (%) | |
| CC | 171 (34) |
| CT | 262 (52) |
| TT | 65 (13) |
| Missing | 3 (1) |
| Median (IQR) Fibrotest, n=497 | 0.75 (0.64, 0.85) |
| Median (IQR) platelets $\times 10^3/\mu L$ | 174 (128, 220) |
| Platelets, n (%) | |
| <100,000/µL | 59 (12) |
| ≥100,000/µL | 442 (88) |
| Median (IQR) albumin, g/dL | 4.2 (3.9, 4.4) |
| Albumin | |
| <3.5 g/dL | 18 (4) |
| ≥3.5 g/dL | 483 (96) |
| Median (IQR) total bilirubin, mg/dL | 0.6 (0.5, 0.8) |
| Median (IQR) INR | 1.0 (1.0, 1.1) |
| Median (IQR) creatinine clearance,[a] mL/min | 105.1 (89.3, 125.6) |
| Median (IQR) APRI | 1.13 (0.68, 2.24) |

[a]Estimated by Cockroft Gault

APRI, AST to platelet ratio index; BMI, body mass index; DAA, directly acting antiviral; HCV, hepatitis C virus; INR, international normalized ratio of prothrombin time; IQR, interquartile range; PEG-IFN, peginterferon; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir.

**Table 2. Cirrhosis and Fibrosis Determination**

| | SOF–VEL (N=501) |
|---|---|
| Cirrhosis, n (%) | 220 (44) |
| Advanced fibrosis, n (%) | 281 (56) |
| Fibrotest, n (%) | |
| ≤ 0.59 | 71 (14) |
| > 0.59 and ≤ 0.75 | 187 (38) |
| > 0.75 | 239 (48) |

SOF, sofosbuvir; VEL, velpatasvir.

**Table 3. Treatment Response**

| | HCV Genotype | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 (n=170) | 2 (n=85) | 3 (n=153) | 4 (n=60) | 5 (n=13) | 6 (n=20) | Total (n=501) |
| HCV RNA <15 IU/mL, n/n (%) | | | | | | | |
| On treatment | | | | | | | |
| Week 2 | 85/170 (50) | 61/85 (72) | 86/153 (56) | 30/60 (50) | 10/13 (77) | 11/20 (55) | 283/501 (57) |
| Week 4 | 149/170 (88) | 81/85 (95) | 142/153 (93) | 51/60 (85) | 13/13 (100) | 18/20 (90) | 454/501 (91) |
| Week 6 | 168/170 (99) | 84/85 (99) | 149/153 (97) | 59/60 (98) | 13/13 (100) | 20/20 (100) | 493/501 (98) |
| After treatment | | | | | | | |
| Week 4 | 168/170 (99) | 85/85 (100) | 147/153 (96) | 60/60 (100) | 13/13 (100) | 20/20 (100) | 493/501 (98) |
| Week 12 (SVR) | 167/170 (98)[a] | 85/85 (100) | 145/153 (95) | 60/60 (100) | 13/13 (100) | 20/20 (100) | 490/501 (98) |
| 95% CI | 95% to 100% | 96% to 100% | 90% to 97% | 94% to 100% | 75% to 100% | 83% to 100% | 96% to 99% |
| SVR by Cirrhosis and Fibrosis Determination | | | | | | | |
| Cirrhosis | 72/73 (99) | 29/29 (100) | 73/80 (91) | 27/27 (100) | 5/5 (100) | 6/6 (100) | 212/220 (96) |
| Advanced fibrosis | 95/97 (98) | 56/56 (100) | 72/73 (99) | 33/33 (100) | 8/8 (100) | 14/14 (100) | 278/281 (99) |
| Virologic failure, n (%) | | | | | | | |
| On treatment | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Relapse | 2/170 (1) | 0 | 8/153 (5) | 0 | 0 | 0 | 10/501 (2) |

HCV: hepatitis C virus.
[a]1 patient was lost to follow-up after the posttreatment week 4 visit.

**Table 4. Treatment Response According to Baseline Characteristics**

| | HCV Genotype | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 (n=170) | 2 (n=85) | 3 (n=153) | 4 (n=60) | 5 (n=13) | 6 (n=20) | Total (n=501) |
| **Sustained virologic response, n/n (%)** | | | | | | | |
| Overall | 167/170 (98)[a] | 85/85 (100) | 145/153 (95) | 60/60 (100) | 13/13 (100) | 20/20 (100) | 490/501 (98) |
| *IL-28B* | | | | | | | |
| CC | 43/43 (100) | 31/31 (100) | 63/65 (97) | 14/14 (100) | 4/4 (100) | 14/14 (100) | 169/171 (99) |
| Non-CC | 121/124 (98) | 54/54 (100) | 82/88 (93) | 46/46 (100) | 9/9 (100) | 6/6 (100) | 318/327 (97) |
| CT | 89/91 (98) | 42/42 (100) | 71/75 (95) | 40/40 (100) | 8/8 (100) | 6/6 (100) | 256/262 (98) |
| TT | 32/33 (97) | 12/12 (100) | 11/13 (85) | 6/6 (100) | 1/1 (100) | 0/0 | 62/65 (95) |
| HCV treatment experience | | | | | | | |
| Naive | 92/94 (98) | 64/64 (100) | 100/103 (97) | 24/24 (100) | 7/7 (100) | 19/19 (100) | 306/311 (98) |
| Experienced | 75/76 (99) | 21/21 (100) | 45/50 (90) | 36/36 (100) | 6/6 (100) | 1/1 (100) | 184/190 (97) |
| NS5A resistance-associated substitutions | | | | | | | |
| Present | 23/25 (92) | 54/54 (100) | 11/14 (79) | 35/35 (100) | 1/1 (100) | 10/10 (100) | 134/139 (96) |
| Absent | 144/145 (99) | 30/30 (100) | 134/139 (96) | 25/25 (100) | 12/12 (100) | 10/10 (100) | 355/361 (98) |
| Not determined | 0 | 1/1 (100) | 0 | 0 | 0 | 0 | 1/1 (100) |

HCV: hepatitis C virus.
[a]1 patient was lost to follow-up after the posttreatment week 4 visit.

**Table 5. Characteristics of Patients Who Experienced Virologic Relapse After Treatment**

| Age | Sex | Race | BMI (kg/m$^2$)* | HCV GT | Prior HCV Treatment History | | Cirrhosis | *IL28B* GT | HCV RNA ($log_{10}$ IU/mL)* | Platelets (x103/μL)* | Albumin (g/dL)* | NS5A RASs* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Regimen | Response | | | | | | |
| 56 | M | White | 22.0 | 1a | None | | No | CT | 6.5 | 208 | 4.4 | No |
| 58 | M | White | 26.5 | 1b | PEG+RBV | Non responsive | Yes | TT | 5.8 | 91 | 3.8 | Yes |
| 53 | F | White | 23.7 | 3a | None | | No | CC | 6.9 | 158 | 3.8 | Yes |
| 58 | M | White | 24.5 | 3a | PEG+RBV | Non responsive | Yes | CC | 6.3 | 57 | 4.0 | No |
| 61 | M | White | 25.2 | 3a | None | | Yes | CT | 6.0 | 100 | 4.2 | Yes |
| 61 | M | White | 21.7 | 3a | PEG+RBV | Relapse/breakthrough | No | TT | 5.5 | 125 | 3.6 | No |
| 56 | M | White | 26.7 | 3a | PEG+RBV | Relapse/breakthrough | Yes | TT | 6.1 | 90 | 4.1 | No |
| 46 | M | White | 23.9 | 3a | PEG+RBV | Non responsive | Yes | CT | 6.1 | 159 | 4.1 | Yes |
| 57 | M | White | 26.8 | 3a | None | | Yes | CT | 6.3 | 109 | 3.8 | No |
| 56 | M | White | 28.1 | 3a | PEG+RBV | Non responsive | Yes | CT | 6.3 | 98 | 3.4 | No |

*Measurements at baseline. BMI, body-mass index; GT, genotype; HCV, hepatitis C virus; PEG, pegylated interferon; RBV, ribavirin; RAS, resistance-associated substitution.

**Table 6. Improvement in Hematology and Chemistry Parameters**

| | Median (IQR) Change Between Baseline and Posttreatment Week 4 |
|---|---|
| Platelets, $\times 10^3/\mu L$ | 7 (-7, 22) |
| Albumin, g/dL | 0.1 (-0.1, 0.2) |
| Total bilirubin, mg/dL | -0.1 (-0.2, 0.0) |
| INR | 0 (-0.1, 0.0) |
| Creatinine clearance, mL/min | -1.6 (-8.4, 5.6) |
| APRI | -0.68 (-1.59, -0.35) |

APRI, AST to Platelet Ratio Index; INR, international normalized ratio of prothrombin time

**Table 7. Adverse Events and Laboratory Abnormalities**

| | SOF–VEL (N=501) |
|---|---|
| **No. (%) of patients with any adverse event** | 398 (79) |
| **No. (%) of Grade 3 or 4 adverse events** | 12 (2) |
| **No. (%) of patients with a serious adverse event** | 8 (2) |
| **Adverse events leading to discontinuation, n (%)** | 0 |
| **Deaths, n** | 1 (0.2) |
| **Adverse events in ≥ 5% of patients, n (%)** | |
| Headache | 153 (31) |
| Fatigue | 104 (21) |
| Nausea | 66 (13) |
| Nasopharyngitis | 56 (11) |
| Insomnia | 45 (9) |
| Diarrhea | 41 (8) |
| Arthralgia | 32 (6) |
| Back pain | 29 (6) |
| Cough | 27 (5) |
| Irritability | 25 (5) |
| Asthenia | 24 (5) |
| Constipation | 24 (5) |
| Upper respiratory infection | 24 (5) |
| **Serious adverse events, n (%)** | |
| Acute myocardial infarction | 1 (0.2) |
| Appendicitis | 1 (0.2) |
| Food poisoning | 1 (0.2) |
| Gastroenteritis | 1 (0.2) |
| Hematochezia | 1 (0.2) |
| Intracranial aneurysm | 1 (0.2) |
| Ligament sprain | 1 (0.2) |
| Pneumonia | 1 (0.2) |
| Rotator cuff syndrome | 1 (0.2) |
| **Laboratory abnormalities** | |
| Grade 3 abnormalities | 43 (9) |
| Grade 4 abnormalities (lipase >5 x ULN) | 3 (1) |
| Hemoglobin | |
| <8.5 g/dL | 0 |
| <10 g/dL | 0 |
| Total bilirubin | |
| Grade 3 (>2.5 to 5 x ULN) | 0 |
| Grade 4 (>5 x ULN) | 0 |

SOF, sofosbuvir; VEL, velpatasvir.