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Article type : Short Communication

Deferred treatment with a fixed-dose combination of sofosbuvir-velpatasvir for chronic hepatitis C virus genotype 1, 2, 4, and 6 infection

Short title: **SOF-VEL for HCV 1, 2, 4 and 6 Infection**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jvh.13159

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List of abbreviations

AE, adverse event

DAA, direct-acting antiviral agent

HCV, hepatitis C virus

LLOQ, lower limit of quantification

NS, nonstructural protein

RAS, resistant associated substitutions

SVR, sustained virologic response

ULN, upper limit of normal

Financial support: This study was sponsored by Gilead Sciences, Inc.

Acknowledgements: An initial draft of this manuscript was prepared by Sameera Kongara of AlphaBioComm. Editorial assistance was provided by Sandra Chen of Gilead Sciences, Inc.

Conflicts of interest

Tarik Asselah: Consultant: AbbVie, Gilead Sciences, Janssen, Merck; Advisory Board: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Roche; Research Grant: AbbVie, Gilead Sciences, Janssen, Merck; Speaker: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Roche. **Stephen Shafran**: Consultant: Gilead; Advisory Board: AbbVie, Bristol-Myers Squibb, Gilead, Merck; Research Grant: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck; Speaker: Bristol-Myers Squibb, Gilead, Merck, Pfizer. **Stefan Bourgeois**: Advisory Board: AbbVie, Gilead, MSD, BMS, Janssen; Speaker: BMS, Gilead, AbbVie, Janssen. **Ching-Lung Lai**: Advisory Board: Gilead, AbbVie; Speaker: Gilead, AbbVie.

Philippe Mathurin: Consultant: MSD, Abbott, Bristol-Myers Squibb, Gilead, Janssen-Cilag, Boeringher, Novartis, Verlyx, Bayer; Advisory Board: Roche, MSD, Gilead, Boeringher, Bayer, Bristol-Myers Squibb; Research Grant: Roche, MSD, AbbVie, Gilead Bristol-Myers Squibb, Janssen-Cilag, Bayer. **Bernard Willems**: Consultant: Gilead, AbbVie, BMS, Intercept; Advisory Board: Gilead, AbbVie, BMS, Intercept; Research Grant: Gilead, AbbVie. **Mindie H. Nguyen**: Consultant: Gilead, Novartis, Laboratory of Advanced Medicine; Advisory Board: Bristol-Myers Squibb, Bayer AG, Gilead, Exact Sciences, Spring Bank, Anylam; Research Grant: Gilead, Janssen, Pfizer, Laboratory of Advanced Medicine. **Mitchell N. Davis**: Consultant: AbbVie, Gilead; Research Grant: Gilead, AbbVie, Janssen; Speaker: Gilead, AbbVie, Janssen.

Obaid S. Shaikh: Research Grant: Gilead, Merit, Shionogi. **KC Huang, Evguenia Svarovskaia, Anu Osinusi, John McNally, Diana M. Brainard, and Tram T. Tran**: Employment and stock ownership: Gilead.

Abstract

Sofosbuvir-velpatasvir is approved for the treatment of chronic hepatitis C virus (HCV) infection. In this single-arm, open-label, phase 3, deferred treatment study we investigated the efficacy and safety of sofosbuvir-velpatasvir among patients randomized to the placebo group in the ASTRAL-1 study. Patients received sofosbuvir-velpatasvir (400/100 mg) once daily for 12 weeks. The primary efficacy endpoint was the proportion of patients with sustained virologic response 12 weeks after the end of therapy (SVR12). The primary safety endpoint was any adverse events (AEs) leading to the permanent discontinuation of study drug. Overall, 108/111 (97%, 95% confidence interval [CI], 92-99%) achieved SVR12, and only one patient had virological failure. SVR12 was achieved by 61/63 (97%, 95%CI, 89−100%) genotype 1 patients, 20/20 (100%; 95%CI, 83−100%) with genotype 2, 19/19 (100%; 95%CI, 82−100%) with genotype 4, and 8/9 (89%; 95% CI, 52−100%) with genotype 6. All (19/19; 95%CI, 82-100) patients with cirrhosis, and all (31/31, 95%CI, 89-100) with prior treatment experience achieved SVR12.The safety profile during treatment was similar to that observed in patients receiving placebo treatment. The most common AEs were headache, fatigue, and nausea. One patient (1%) discontinued treatment due to an AE of gallbladder carcinoma, which was not considered related to treatment. Of five reported serious AEs, none were considered related to study drug. Sofosbuvir-velpatasvir for 12 weeks was effective and well-tolerated among untreated and previously treated patients with HCV genotype 1, 2, 4, or 6 infection, including those with compensated cirrhosis. (ClinicalTrials.gov NCT02346721)

Keywords: NS5A inhibitor, NS5B inhibitor, direct-acting antivirals, pangenotypic activity

Introduction

Sofosbuvir-velpatasvir is a ribavirin-free, all-oral regimen available for the treatment of hepatitis C virus (HCV) genotype 1–6 infected patients with or without compensated cirrhosis.[1,2] This therapy was approved based in part on the results of the phase 3, double-blind, placebo-controlled ASTRAL-1 trial, which evaluated the efficacy and safety of a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in patients with genotype 1, 2, 4, 5, or 6 infection.[3] Among 624 patients treated, 99% achieved a sustained virologic response (SVR). Afterward, patients who received blinded placebo in ASTRAL-1 were eligible to enroll in an open-label study in which they would receive sofosbuvir-velpatasvir for 12 weeks. Therefore, this original study evaluated the safety, tolerability, and antiviral efficacy of sofosbuvir-velpatasvir in patients with chronic HCV infection who previously received placebo in the ASTRAL-1 study.

Methods

This open-label, single-group, phase 3 study (ClinicalTrials.gov, NCT02346721) was conducted between February 2015 and June 2016 at 62 sites in the North America, Europe, and Asia. Patients with chronic HCV infection and HCV RNA >15 IU/mL who completed placebo treatment in the ASTRAL-1 study[3] (ClinicalTrials.gov, NCT02201940) were eligible for this study. Full ASTRAL-1 eligibility criteria were provided previously.[3] In brief, approximately 20% of patients enrolled in the ASTRAL-1 placebo group had cirrhosis. Prior HCV treatment with NS5A inhibitors or nucleotide analogue NS5B inhibitors, and discontinuation of prior HCV treatment due to an adverse event (AE), were exclusionary.

All patients in this study received a fixed-dose combination of sofosbuvir-velpatasvir (400 mg/100 mg) once daily for 12 weeks. The protocol was approved by institutional review boards at each site and all patients provided written informed consent.

Blood samples were collected at each study visit to quantify HCV RNA levels using the COBAS TaqMan HCV Test, v2.0 for use with AmpliPrep (lower limit of quantification [LLOQ] <15 IU/mL; Roche Molecular Diagnostics, Pleasanton, California). HCV genotype and subtype were determined using the Siemens VERSANT HCV Genotype INNO-LiPA 2.0 Assay (Siemens Healthcare GmbH, Erlangen, Germany).

To detect the emergence of treatment-emergence resistance-associated substitutions (RASs), HCV NS5A and NS5B coding regions were amplified by RT-PCR and deep sequenced from plasma samples obtained from all patients at baseline and from those patients with virologic failure at the time of failure. RASs were reported at a 15% assay cut off.

Safety was assessed by monitoring AEs, vital signs, clinical laboratory tests, and performing physical examinations.

Endpoints

The primary efficacy endpoint was the proportion of patients achieving sustained virologic response (HCV RNA <15 IU/mL) 12 weeks after the end of treatment (SVR12). The primary safety endpoint was any adverse events leading to the permanent discontinuation of study drug. Secondary endpoints included the proportion of patients with virologic failure, and the emergence of viral resistance to sofosbuvir and velpatasvir.

Statistical analysis

No formal power or sample size calculations were performed. The efficacy and safety analyses included all patients who received ≥1 dose of sofosbuvir-velpatasvir. For the SVR12 rate, point estimates and a 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method were calculated by genotype and overall. Safety assessments were summarized descriptively. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics and disposition

Of the 116 patients screened, 111 enrolled and received treatment. Of the five patients not enrolled, four did not meet eligibility criteria and one enrolled outside of the study window. Overall, 63 (57%) patients were infected with HCV genotype 1, 20 (18%) with genotype 2, 19 (17%) with genotype 4, and 9 (8%) with genotype 6. The majority were male (59%), white (77%), treatment-naïve (72%), and presented without cirrhosis (83%). Among patients who received prior therapy 71% had received pegylated-interferon plus ribavirin.

Efficacy

By week 4, HCV RNA levels were <LLOQ in 61 of 63 (97%) patients with HCV genotype 1, 17 of 20 (85%) patients with genotype 2, 18 of 19 (95%) patients with genotype 4, and 9 of 9 (100%) patients with genotype 6. By week 8 all patients had HCV RNA <LLOQ.

Overall, SVR12 was achieved by 108 of 111 (97%, 95% CI 92-99%) patients. All 19 patients with cirrhosis and all 31 treatment-experienced patients achieved SVR12. Of the three patients who did not achieve SVR12, two withdrew consent, and one experienced virologic relapse after completing treatment. This patient was a 67-year old, non-cirrhotic, treatment-naïve, male with genotype 1a infection, and relapse occurred by posttreatment week 4. One patient with genotype 1g infection withdrew consent after 10 weeks of therapy due to an AE of gallbladder adenocarcinoma. At the time of discontinuation, HCV RNA was not detectable. Another patient with genotype 6a/6b infection withdrew consent after posttreatment week 4 when HCV RNA was not detectable.

Resistance analysis

Of the 108 patients with successful NS5A deep sequencing, baseline NS5A RASs were detected in 39 (36%); all 39 achieved SVR12. Of the 69 patients without baseline NS5A RASs, 68 (98%) achieved SVR12. Pretreatment NS5B nucleoside (NI) RASs was detected in 12 (11%) of 107 patients with NS5B deep sequencing data; all 12 achieved SVR12. The patient with genotype 1a infection who relapsed had no baseline NS5A or NS5B NI RASs; NS5A RAS Y93H (>99%) was detected at relapse.

Safety

Sofosbuvir-velpatasvir treatment was discontinued in 1 patient (**Table**) due to an AE of gallbladder adenocarcinoma, which was not considered to be treatment-related; this patient withdrew from the study as mentioned earlier and died 261 days after study discontinuation. Sofosbuvir-velpatasvir was interrupted in 1 patient from day 67 to day 75 due to an AE of ventricular extrasystoles; this patient achieved SVR12.

Treatment-emergent AEs were reported in 79 (71%) patients, most of which were mild or moderate in severity. The most common AEs were headache (22%), fatigue (16%), and nausea (11%). Serious AEs were reported in 5 patients (5%), none of which were considered treatment-related. Observed serious AEs were cellulitis, lymphangitis, lower limb fracture, meniscus injury, gallbladder adenocarcinoma, and hepatocellular carcinoma.

Grade 3 laboratory abnormalities were detected in 7 patients (6%), and grade 4 abnormalities in 1 patient (1%). Grade 3 abnormalities of neutrophils and creatine kinase were observed in 1 patient each, glucose in 2 patients, and lipase in 3 patients. A grade 4 abnormality in bilirubin was detected in 1 patient, secondary to gallbladder adenocarcinoma.

Discussion

Treatment with 12 weeks of sofosbuvir-velpatasvir for patients in this deferred treatment study resulted in a high overall SVR12 rate of 97%. No patient experienced on-treatment virologic failure, and only 1 patient experienced virologic relapse. Treatment was effective regardless of cirrhosis status or prior treatment experience. The high SVR rate seen in this deferred treatment study is consistent with rates observed in the registrational phase 3 trials (ASTRAL -1, -2, and -3) where 95-99% of patients in each study achieved SVR12.[3,4]

Response rates were also not affected by baseline RASs. The genotype 1a patient who relapsed developed Y93H NS5A RAS (>99%) at failure. This substitution has been detected in genotype 1a- infected patients who failed sofosbuvir-velpatasvir treatment, and is associated with a >600-fold reduction in susceptibility to velpatasvir in-vitro relative to wild-type replicons.[5]

Sofosbuvir-velpatasvir was well-tolerated among patients, with 1 only patient discontinuing treatment due to an AE unrelated to treatment. Comparing the current study with data from the same patients while receiving placebo in the initial ASTRAL-1 study, 71% and 77%, respectively, experienced any adverse event (**Table**). The most common adverse events in both studies were headache (22% and 28%, respectively), fatigue (16% and 20%), and nausea (11% and 11%).[3] The consistency of these results further confirms the safety and tolerability of sofosbuvir-velpatasvir.

Several highly effective DAA-based regimens have become available for chronic HCV infection in recent years.[6,7] However, with many of these regimens, treatment strategies vary based on clinical characteristics, including HCV genotype, cirrhosis status, and prior treatment experience. Moreover, ribavirin, a component of some DAA-based therapies, is associated with hematological and fetal toxicity, a need for on-treatment blood tests and poorer health-related outcomes. The availability of pangenotypic, ribavirin-free DAA-regimen simplifies treatment decision-making.

There were a few limitations to this study. Due to the nature of the initial ASTRAL-1 study, no patients with genotype 3 or 5 were enrolled.[3] In ASTRAL-1, genotype 3 patients were excluded and patients with genotype 5 were automatically enrolled into active treatment because of the rarity of genotype 5 infection. Low numbers of patients enrolled with genotypes 4 and 6. Additionally, patients previously treated with sofosbuvir or a NS5A-containing regimen were excluded from this study. Finally, although observed results show no differences in safety and efficacy between this study and ASTRAL-1, no analyses between the studies were prespecified, precluding formal statistical comparison.

In conclusion, this study demonstrates that a once-daily sofosbuvir-velpatasvir for 12 weeks is effective and well tolerated among untreated and previously treated patients with HCV genotype 1, 2, 4, or 6 infection, with or without compensated cirrhosis, thereby confirming previous findings.[3]

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Table. Safety

Adverse Event, n (%)	**SOF-VEL for 12 weeks n = 111**	**ASTRAL-1 Placebo for 12 weeks[a] n = 116**
Any adverse event	79 (71)	89 (77)
Serious adverse event	5 (5)	0
Deaths	1 (1)[b]	0
Discontinuation of treatment due to adverse events	1 (1)	2 (2)
Common adverse events (≥5% of patients)		
Headache	24 (22)	33 (28)
Fatigue	18 (16)	23 (20)
Nausea	12 (11)	13 (11)
Cough	7 (6)	4 (3)
Diarrhea	7 (6)	8 (7)
Grade 3 or 4 laboratory abnormalities		
Neutrophils, Grade 3, 500 to <750/mm^3	1 (1)	0
Creatine kinase, Grade 3, 10.0–<20.0 × ULN	1 (1)	0
Glucose (hyperglycemia), Grade 3, 250 to 500 mg/dL	2 (2)	0
Lipase, Grade 3, >3.0–5.0 × ULN	3 (3)	0
Total Bilirubin (hyperbilirubinemia), Grade 4, >5.0 × ULN	1 (1)	0

SOF, sofosbuvir; ULN, upper limit of normal; VEL, velpatasvir.

[a]Placebo results from the primary ASTRAL-1 study (Feld et al 2015 N Engl J Med).

[b]One patient died 261 days after treatment discontinuation due to gallbladder adenocarcinoma.