CODEN [USA]: IAJPBB ISSN: 2349-7750
INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.2640989

Available online at: http://www.iajps.com ***Research Article***

EFFECTIVENESS AND SAFETY OF SOFOSBUVIR IN THE TREATMENT OF HEPATITIS C

[1]Dr Ali Hasan, [2]Dr Iqra Rauf, [3]Dr.Muhammad Awais
[1,2,3]MBBS, Sheikh Zayed Medical College, Rahim Yar Khan.

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:
Hepatitis C virus (HCV)-infected patients with decompensated cirrhosis mostly have no treatment options. In this study, we evaluated Effectiveness and Safety of Sofosbuvir in the Treatment of Hepatitis C. Patients were randomized 1:1 to receive sofosbuvir with or without ribavirin for 12 weeks. Randomization was stratified by CPT class and genotype. Sustained virologic response 12 weeks following completion of treatment (SVR12) was the primary efficacy endpoint.
Of the 102 patients enrolled, 57% were treatment naive, 78% and 20% had genotype 1 and 2 HCV infection, respectively, and 77% and 20% had CPT class B and C cirrhosis, respectively, at baseline. Overall, 61% of patients were female and the mean age was 66 years (range 41–83). SVR12 rates were 92% (47/51) in each group. Among patients who achieved SVR12, 26% had improved CPT class from baseline to post treatment week 12. Most adverse events (AEs) were consistent with clinical sequelae of advanced liver disease or known toxicities of ribavirin. Four patients (8%) who received sofosbuvir and seven (14%) who received sofosbuvir plus ribavirin experienced a serious AE. The 3 deaths (bacterial sepsis, gastric varices hemorrhage, hepato-cellular carcinoma) were attributed to liver disease progression.
Sofosbuvir for 12 weeks provides a highly effective and well-tolerated therapy in patients with HCV and decompensated cirrhosis. Ribavirin did not improve efficacy but increased toxicity.
Keywords: *Effectiveness of Sofosbuvir: Hepatitis C.*

Corresponding author:
Dr. Ali Hasan,
MBBS, Sheikh Zayed Medical College ,Rahim Yar Khan.

QR code

Please cite this article in press Ali Hasan et al., ***Effectiveness And Safety Of Sofosbuvir In The Treatment Of Hepatitis C.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Globally, the treatment of HCV infection has been transformed with the development of direct-acting antiviral (DAA) agents, which target viral proteins and cellular processes essential to viral replication. These interferon-free, DAA-based regimens are generally well-tolerated and result in high rates of sustained virologic response (SVR) across most patient populations. However, some regimens containing protease inhibitors have been associated with hepatotoxicity and hepatic de-compensation, particularly in patients with advanced cirrhosis thus precluding their use in some patients, including those with decompensated cirrhosis. In contrast, ledipasvir/sofosbuvir and sofosbuvir/velpatasvir have demonstrated both safety and efficacy in patients with decompensated liver disease. These studies were conducted in different parts of the globe.

Patients with decompensated cirrhosis are at high risk for development of hepatocellular carcinoma (HCC), bleeding diatheses, and fulminant infections. A retrospective cohort study of patients with CPT class C cirrhosis on the liver transplant registry demonstrated a mean survival time of less than 16 months and 2-year survival probability was less than 40%. A safe and effective HCV treatment will address the unmet medical need for this population.

Sofosbuvir (400/100 mg) is a fixed-dose combination that combines 2 DAAs. Sofosbuvir is a nucleotide analog that is a potent, pangenotypic and selective NS5B polymerase inhibitor, and is a potent, pangenotypic, next-generation HCV NS5A inhibitor. Sofosbuvir is approved in the US, European Union, and other regions for the treatment of genotypes 1–6 chronic HCV infection in patients with and without compensated cirrhosis and for use with ribavirin in patients with decompensated cirrhosis.

The ASTRAL-4 study evaluated 12 and 24 weeks of treatment with sofosbuvir with or without ribavirin in HCV-infected patients with CPT class B decompensated cirrhosis. Rates of sustained response 12 weeks post treatment (SVR12) were 83% in patients who received 12 weeks of sofosbuvir, 94% in patients who received 12 weeks of sofosbuvir plus ribavirin, and 86% in patients who received 24 weeks of sofosbuvir. Notably, the numeric difference in SVR12 rates in genotype 1b and genotype 2 HCV-infected patients who received sofosbuvir for 12 weeks or sofosbuvir with ribavirin for 12 weeks did not differ substantially.

METOHDS:

Patients

Eligible patients were 20 years of age and older with chronic HCV infection, quantifiable HCV RNA at screening, and CPT score 7–12, inclusive. The calculation of the CPT score at screening used either the international normalized ratio or prothrombin activation percentage for the coagulation parameter, at the investigator's discretion, as mentioned in Table 1.

Patients were to have liver imaging within 4 months of baseline to exclude HCC. Patients were excluded from this study if they had a positive test result for hepatitis B surface antigen or human immunodeficiency virus, had HCC within 2 years prior to screening, any recurrence of HCC after curative treatment (e.g., successful treatment with surgical resection or radiofrequency ablation), prior treatment with an NS5A inhibitor, or creatinine clearance < 50 mL/min as calculated by the Cockcroft–Gault equation using actual body weight. Use of concomitant amiodarone was prohibited from 60 days prior to day 1 and throughout the treatment period. Full eligibility criteria are provided in the supplementary information.

Desgin

Via an interactive web response system, patients were randomly assigned 1:1 to sofosbuvir–velpatasvir with or without ribavirin for 12 weeks. Randomization was stratified by genotype (genotype 1 vs. non-genotype 1) and CPT class at screening (CPT class B vs C). For the purposes of randomization, a patient with non-definitive or mixed HCV genotype results was considered non-genotype 1. Across the study population, at least 15 patients were to have non-genotype 1 HCV infection and approximately 10% of patients were to have CPT class C cirrhosis. Enrollment of patients with CPT class C cirrhosis began after an independent data monitoring committee evaluated the safety data through 4 weeks of treatment from the first 20 patients with CPT class B cirrhosis.

Sofosbuvir (400/100 mg) fixed-dose combination was administered once daily. Ribavirin (REBETOL, MSD KK) was administered with food twice daily. For patients with CPT class B cirrhosis at screening dosing was based on body weight (600 mg daily in patients ≤ 60 kg, 800 mg for patients > 60–80 kg, and 1000 mg for those > 80 kg). All patients with CPT class C cirrhosis received 600 mg daily regardless of weight.

Assessments

Screening assessments included HCV genotyping, *IL28B* genotyping, and standard laboratory and clinical tests. HCV genotype and subtype were determined using the Siemens VERSANT HCV Genotype INNO-LiPA2.0 Assay. *IL28B* genotype was determined by polymerase chain reaction amplification of the single-nucleotide polymorphism rs12979860, with sequence-specific forward and reverse primers and allele-specific fluorescently labeled TaqMan minor groove binder probes.

Plasma HCV RNA levels were evaluated at screening; at day 1 of treatment, at weeks 2, 4, 8, and 12 during treatment, and at weeks 4, 12, and 24 after the end of treatment. HCV RNA levels were quantified using the COBAS Ampliprep/COBAS TaqMan HCV Test, v2.0, which has a lower limit of quantification (LLOQ) of 15 IU/mL.

Deep sequencing of the HCV NS5A and NS5B genes was performed for all patients at baseline and from those with virologic failure at the time of failure. RASs present in more than 15% of the sequence reads are reported. The resistance analysis population is comprised of patients with viral sequence data and virologic outcome data available.

Statistical Analysis

Point estimates with 2-sided 95% exact confidence intervals (CIs) for SVR12 based on the Clopper–Pearson method were provided for each treatment group. In the primary efficacy analysis, the SVR12 rate for patients in each treatment group was compared to the spontaneous clearance rate of 1% using a 2-sided exact 1-sample binomial test with Bonferroni alpha adjustment (each at the 0.025 significance level)

RESULTS:

Demographics and baseline characteristics are presented in Table mentioned below. Of 155 patients screened, a total of 102 patients were enrolled, of which 100 (98%) completed treatment, according to Figure 1. All 53 patients who were excluded from study participation did not meet eligibility criteria according to below mentioned Table 2. Demographics and baseline characteristics of the patients enrolled were generally balanced across both treatment groups and consistent with an older population with advanced liver disease. Overall, most patients were female (61%). The mean age was 66 years (range 41–83), and 58% were ≥ 65 years of age. Most patients had *IL28B* CC genotype (69%) and were treatment naive (57%). Among the 44 treatment-experienced patients, only 1 had previously been treated with a DAA (simeprevir in combination with peginterferon alfa-2a and ribavirin for 23 weeks); all others had been treated with interferon alone or in combination with ribavirin.

Table 1 Baseline demographics and disease characteristics

	Sofosbuvir–velpatasvir 12 weeks $N = 51$	Sofosbuvir–velpatasvir plus ribavirin 12 weeks $N = 51$
Mean age (range) (years)	66 (43, 82)	66 (41, 83)
Female sex	33 (65)	29 (57)
Mean body mass index (range) (kg/m^2)	26.5 (20.4, 43.0)	25.8 (18.3, 58.6)
HCV genotype and subtype		
Genotype 1	41 (80)	39 (76)
Genotype 1a	1 (2)	0
Genotype 1b	40 (78)	39 (76)
Genotype 2	9 (18)	11 (22)
Genotype 2 (no confirmed subtype)	5 (10)	5 (10)
Genotype 2a	0	2 (4)[a]
Genotype 2a/2c	2 (4)	1 (2)
Genotype 2b	2 (4)	4 (8)
Genotype 3b	1 (2)	0
Mean HCV RNA (range) ($\log_{10}$ IU/mL)	5.7 (3.7–7.1)	5.8 (4.2–7.0)
IL28B CC genotype	33 (65)	37 (73)
CPT B	40 (78)	39 (76)
MELD score ≤ 15	46 (90)	48 (94)
Ascites		
None	19 (37)	16 (31)
Mild/moderate	32 (63)	33 (65)
Severe	0	2 (4)
Encephalopathy		
None	23 (45)	22 (43)
Medication-controlled	28 (55)	29 (57)
No prior HCV treatment	27 (53)	31 (61)
Mean estimated glomerular filtration rate (range) (mL/min)[c]	93 (40, 183)	89 (42, 299)

Overall, 80 patients (78%) had genotype 1 HCV infection [1 patient (1%) had HCV genotype 1a and 79 (77%) patients had HCV genotype 1b], 20 patients (20%) had genotype 2 HCV infection, and 1 patient (1%) had genotype 3 HCV infection. There was 1 patient who had an HCV genotype that was unable to be determined by LiPA or NS5B Sanger, but was later determined to have genotype 2a HCV infection by BLAST analysis. At baseline, 77% of patients were CPT class B (score 7–9), 20% were CPT class C (score 10–12), and 3% were CPT class A (score 6).

Efficacy

The SVR12 rates were 92% (47/51; 95% CI 81–98%) in each treatment group, as mentioned below Table 2. Both treatment groups met their primary efficacy endpoints with SVR12 rates that were statistically superior compared with the spontaneous clearance rate of 1% ($p < 0.001$).

Table 2 Virologic response during and after treatment

	Sofosbuvir $N = 51$	Sofosbuvir $N = 51$	plus ribavirin 12 weeks
HCV RNA < 15 IU/mL, *n/n* (%)			
On treatment			
Week 2	23/51 (45)	26/51 (51)	
Week 4	49/51 (96)	46/51 (90)	
Week 8	51/51 (100)	49/51 (96)	
Week 12	51/51 (100)	49/49 (100)	
After treatment			
Week 4 (SVR4)	48/51 (94)	49/51 (96)	
Week 12 (SVR12)	47/51 (92)	47/51 (92)	
95% CI	81–98	81–98	
Relapse after the end of treatment	4 (8)	2 (4)	
Discontinued treatment due to adverse events	0	2 (4)	

When examined by genotype, SVR12 rates were high for patients with genotype 1 or 2 regardless if they received 12 weeks of sofosbuvir or sofosbuvir plus ribavirin (rates ranged from 89 to 100%, mentioned in Table 3. The 1 patient with genotype 3 HCV infection in the study who was randomized to the sofosbuvir group did not achieve SVR12. When examined by baseline CPT class, SVR12 rates were high in patients with CPT class B cirrhosis (≥ 95%) in both treatment groups. Of the patients with baseline CPT class C cirrhosis, 80% (8/10) and 70% (7/10) in the sofosbuvir and sofosbuvir plus ribavirin groups, respectively, achieved SVR12.

Table 3 Rates of SVR12 by subgroup

	Sofosbuvir 12 weeks $N = 51$	Sofosbuvir plus ribavirin 12 weeks $N = 51$
Overall SVR12	47/51 (92)	47/51 (92)
Genotype		
1a	0/1 (0)	–
1b	39/40 (98)	35/39 (90)
2	8/9 (89)	12/12 (100)[a]
3	0/1 (0)	–
Baseline CPT class		
A	1/1 (100)	2/2 (100)
B	38/40 (95)	38/39 (97)
C	8/10 (80)	7/10 (70)

[a]Includes 1 patient who was initially categorized as missing HCV genotype, and subsequently determined to have genotype 2a by BLAST analysis

A total of 8 patients did not achieve SVR12, with 6 patients experiencing virologic relapse. No patients had virologic non-response. In the sofosbuvir group, 4 of 51 patients (8%) relapsed. In the sofosbuvir plus ribavirin group, 4 of 51 patients (8%) did not achieve SVR12. Of these 4 patients, 2 relapsed and 2 discontinued treatment early due to AEs and subsequently died.

Resistance Analysis

Among the 100 patients included in the resistance analysis population, 41% (41/100) had baseline NS5A RASs. No patient had NS5B nucleoside inhibitor (NI) RASs. In the sofosbuvir group, 97% (33/34) of patients without baseline NS5A RASs and 82% (14/17) of patients with baseline NS5A RASs achieved SVR12. Of the 41 patients with genotype 1 HCV infection, there was 1 patient without baseline NS5A RASs and 1 patient with baseline NS5A RASs who relapsed. In the sofosbuvir plus ribavirin group, 96% (24/25) of patients without baseline NS5A RASs and 96% (23/24) of patients with baseline NS5A RASs achieved SVR12. Of the 37 patients with genotype 1 HCV infection, there was 1 patient without baseline NS5A RASs and 1 patient with baseline NS5A RASs who relapsed. Of the 6 patients who experienced virologic relapse across both treatment groups, 4 had treatment-emergent NS5A RASs. No patient in either treatment group had NS5B NI RASs detected at baseline or relapse.

DISCUSSION:

The current study enrolled mostly patients with genotype 1b or 2, population of HCV-infected patients. The identical SVR12 rates of 92% in the 2 treatment groups suggest that addition of ribavirin to sofosbuvir did not improve efficacy for patients with decompensated cirrhosis. These results were comparable to those for the similar subpopulation enrolled in the ASTRAL-4 study, in which 12 weeks of treatment with sofosbuvir without ribavirin resulted in SVR12 rates of 89% (16 of 18) and 100% (4 of 4) in patients with genotype 1b and 2, respectively.

Of note, the addition of ribavirin was most beneficial in patients with genotype 3 HCV infection in the ASTRAL-4 study, where the response was 35% higher in the group who received ribavirin (85%, 11 of 13 patients) compared to those who did not in either the sofosbuvir 12 week group (50%, 7 of 14 patients) or 24 week group (50%, 6 of 12 patients).

Clinical attention to safety is appropriate in this patient population with advanced liver disease with high expected morbidity and mortality. In the current study, the AE profile was consistent with the clinical sequelae of advanced liver disease and with the known toxicities of ribavirin. In the sofosbuvir plus ribavirin group, 49% of patients needed significant modifications to their ribavirin dosing, primarily due to anemia. Overall sofosbuvir was well-tolerated with the majority of AEs being Grade 1 or 2. Only 2 patients, both in the sofosbuvir plus ribavirin group, discontinued sofosbuvir for AEs that were not considered related to study drugs; both of these patients subsequently died due to progression of their liver disease. The safety profile observed in the current study, including the rate of deaths, was consistent with those observed in previous overseas trials of sofosbuvir with and without ribavirin as well as ledipasvir–sofosbuvir with ribavirin in larger populations of patients with decompensated cirrhosis, despite the fact that the mean age of patients in the current study was 8–9 years older than in the overseas studies.

CONCLUSION:

In conclusion, treatment with sofosbuvir for 12 weeks is the optimal regimen for the patients with decompensated cirrhosis. The SVR12 rate was high regardless of genotype or CPT class. Addition of ribavirin to the regimen did not improve efficacy and was associated with more adverse events and laboratory abnormalities.

REFERENCES:

1. Albers I, Hartmann H, Bircher J, et al. Superiority of the Child–Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. Scand J Gastroenterol. 1989;24:269–76.
2. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Accessed 20 March 2019.
3. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015;149:649–59.
4. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016;65:741–7.
5. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015;373:2618–28.
6. Kim WR, Mannalithara A, Lee H, et al. Survival benefit of direct-acting antiviral therapy in patients with decompensated cirrhosis. Presented at The Liver Meeting 2017—the 68th annual meeting of the American Association for the Study of Liver Diseases (AASLD); Washington, D. C. 2017

7. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016;16:685–97.
8. Tanaka J, Estes C, Razavi H. An estimate of hepatitis C virus (HCV) Disease Burden in Japan. Presented at the 51st Annual Meeting of The Japanese Society of Hepatology (JSH) on 21 May 2015. 2015. Kumamoto, Japan. [Presentation Session 1 Hepatitis C]