

Real-World Single-Center Experience with Sofosbuvir-Based Regimens for the Treatment of Chronic Hepatitis C Genotype 1 Patients

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Background/Aims: The approval of sofosbuvir (SOF), a direct-acting antiviral, has revolutionized the treatment of chronic hepatitis C virus (HCV). **Methods:** We assessed the sustained virological response (SVR) of SOF-based regimens in a real-world single-center setting for the treatment of chronic HCV genotype 1 (G1) patients. This was a retrospective review of chronic HCV G1 adult patients treated with a SOF-based regimen at Virginia Mason Medical Center between December 2013 and August 2015. **Results:** The cohort comprised 343 patients. Patients received SOF+ledipasvir (LDV) (n=155), SOF+simeprevir (SIM) (n=154), or SOF+peginterferon (PEG)+ribavirin (RBV) (n=34). Of the patients, 50.1% (n=172) had cirrhosis. The SVR rate was 92.2% for SOF/LDV, 87.0% for SOF/SIM, and 82.4% for SOF/PEG/RBV. Compared with the cirrhotic patients, the patients without cirrhosis had a higher SVR (96.8% vs 85.5%, p=0.01, SOF/LDV; 98.2% vs 80.6%, p=0.002, SOF/SIM; 86.4% vs 75.0%, p=0.41, SOF/PEG/RBV). In this study, prior treatment experience adversely affected the response rate in subjects treated with SOF/PEG/RBV. **Conclusions:** In this single-center, real-world setting, the treatment of chronic HCV G1 resulted in a high rate of SVR, especially in patients without cirrhosis. (**Gut Liver 2017;11:711-720**)

Key Words: Hepacivirus; Sofosbuvir; Sustained virologic response; Real-world

INTRODUCTION

Chronic hepatitis C is a major health burden with approximately 180 million people infected worldwide and over 4 million in the United States alone.¹ The treatment of hepatitis C virus (HCV) infection has evolved dramatically. Key viral replication targets have been identified: the NS3 protease, NS5A, and the NS5B RNA polymerase. In 2011, first generation protease inhibitors, telaprevir and boceprevir, were approved for use along with peginterferon (PEG)/ribavirin (RBV).^{2,3} However, this regimen was associated with poor efficacy and high discontinuation rates due to adverse side effects. A major breakthrough in HCV treatment occurred in December 2013 with the approval of sofosbuvir (SOF), an NS5B polymerase inhibitor. Initial treatment regimens for genotype 1 (G1) combined SOF with PEG/RBV, and subsequently two all oral regimens for treatment of HCV G1 were approved: SOF with simeprevir (SIM), a second generation protease inhibitor with or without RBV (SOF/SIM/+/-RBV)⁴⁻⁶ and SOF in combination with ledipasvir (LDV), a potent NS5A inhibitor (SOF/LDV). These new regimens were highly effective, well tolerated, and allowing shorter treatment duration in clinical trials.

It is well known that results from clinical trials tend to have more favorable outcomes, and the question remains whether these results can be reproduced in real-world settings and with more difficult to treat patients. Given relatively recent approvals, real-world data regarding efficacy of SOF-based treatments are limited. For our patient population we sought to (1) characterize the population receiving HCV treatment and (2) assess effectiveness of SOF based regimens in G1 HCV patients (3) compare our data with data from clinical trials and other real-world data (4) and assess prognostic indicators that impact sustained virologic response rates.

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MATERIALS AND METHODS

Retrospective review of adult (>18 years) patients with HCV G1 who received SOF-based regimens treated at our institution from December 2013 and had completed treatment by August 2015; in whom the 12-week posttreatment HCV PCR was available by November 2015. Data was obtained by review of electronic records. This study was approved by the Institutional Review Board of Virginia Mason Medical Center.

Patients included in the study received among SOF/LDV, SOF/SIM or SOF/PEG/RBV. The decision to treat and the selection of treatment regimen was based on the current treatment guidelines and clinician preference.

A total of 360 patients met the inclusion criteria. Seventeen patients were excluded, one patient discontinued SOF/SIM after 4 weeks of treatment, two patients receiving SOF/LDV died during treatment from nonliver causes and 14 patients who received SOF/RBV regimen were excluded due to the small number. The final cohort included 343 patients. Patients were categorized as treatment-naïve or treatment experienced based on prior HCV treatment history. Patients were also characterized based on absence or presence of cirrhosis. The diagnosis of cirrhosis was made by liver biopsy, (transient) elastography with score of more than 12.5 kPa (on a scale of 1.5 to 75.0 kPa), HCVFibroSure result of more than 0.74, and/or imaging characteristics of cirrhosis and portal hypertension. Those patients with ascites, esophageal varices, and/or hepatic encephalopathy were defined as having decompensated cirrhosis.

1. Data collection

Data was extracted from the electronic medical record and entered into a study database. Data included demographic, clinical, and laboratory data at time of initiation of treatment. HCV RNA levels were obtained prior to initiation of treatment, at week four of treatment, at the end of treatment and 12 weeks after discontinuation of treatment. The primary outcome was sustained virological response (SVR), defined as a level of HCV RNA below <12 IU/mL for 12 or more weeks after discontinuation of treatment.

2. Statistical analysis

Categorical data are expressed as number (percentage), whereas continuous data are expressed as mean (range). An analysis of variance was used to compare means, and the chi-square test or Fisher exact test was used to compare proportions. $p < 0.05$ was considered statistically significant. Multivariate logistic regression was used to determine predictive factors of all treatment groups. Statistical analyses were performed using STATA/IC software version 13.1 for Windows (StataCorp LP, College Station, TX, USA).

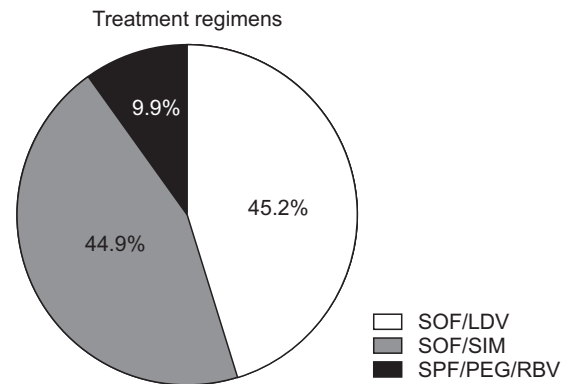


Fig. 1. Treatment groups by regimen.

SOF, sofosbuvir; LDV, ledipasvir; SIM, simeprevir; PEG, peginterferon; RBV, ribavirin.

RESULTS

1. Treatment regimens

Among the cohort of 343 patients with chronic HCV G1 infection, 155 patients (45.2%) received SOF/LDV, 154 patients (44.9%) received SOF/SIM and 34 patients received SOF/PEG/RBV (9.9%) (Fig. 1).

2. Baseline characteristics

Baseline characteristics are shown in Table 1. Mean age of the patients in the cohort was 59.2 years and majority of the patients were male (61.8%), and white (78.4%). Only 8.4% of the cohort patients were African American. A total of 172 patients (50.1%) had cirrhosis and the SOF/PEG/RBV group had fewer patients with cirrhosis. A total of 28 patients (16.3% of those with cirrhosis) had decompensated cirrhosis, and no patients with Child-Pugh C received HCV treatment during this time period.

The cohort included 148 patients (43.1%) who had previously failed treatment. Twenty-seven patients (7.9%) had a history of hepatocellular carcinoma, one patient had a co-infection with hepatitis B and four patients a co-infection with human immunodeficiency virus (HIV) infection. Two post-liver transplant and two post-renal transplant patients were included in the study. The three treatment groups were quite similar in their baseline characteristics; however, those treated with SOF/PEG/RBV were younger compared to the other two groups (52.6 yr vs 59.9 yr, $p < 0.001$), and the SOF/SIM group had a larger proportion of patients with cirrhosis compared to SOF/LDV and SOF/PEG/RBV group (63.6% vs 40% vs 35.3%, $p < 0.001$).

3. Virologic response to treatment and predictors

In the pooled analysis, 72.4% of subjects (234/323) had undetectable viral load at end of 4 weeks of treatment (rapid virologic response [RVR]), and all patients had undetectable viral

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristic	All patients (n=343)	SOF/LDV (n=155)	SOF/SIM (n=154)	SOF/PEG/RBV (n=34)	p-value
Age, yr	59.2 (25–78)	59.9 (32–78)	59.9 (26–77)	52.6 (25–78)	<0.001*
Male sex	212 (61.8)	100 (64.5)	88 (57.1)	24 (70.6)	0.22
BMI, kg/m ²	28.3 (15.2–54.0)	27.9 (18.2–49.7)	29 (15.2–54.0)	28.8 (20.6–53.8)	0.58
Race					0.26
White	269 (78.4)	117 (75.5)	124 (80.5)	28 (82.4)	
African American	29 (8.4)	17 (11.0)	12 (7.8)	0	
Other	45 (13.1)	21 (13.5)	18 (11.7)	6 (17.6)	
HCV genotype					0.04*
1a	263 (76.7)	115 (74.2)	116 (75.3)	32 (94.1)	
1b	80 (23.3)	40 (25.8)	38 (24.7)	2 (5.9)	
HCV RNA ≥800,000 IU/mL	233 (67.9)	103 (66.5)	110 (71.4)	20 (58.8)	0.31
Previous HCV treatment					0.81
Naïve	195 (56.9)	91 (58.7)	85 (55.2)	19 (55.9)	
Treatment experienced	148 (43.1)	64 (41.3)	69 (44.8)	15 (44.1)	
Diabetes patient	61 (17.8)	22 (14.2)	31 (20.1)	8 (23.5)	0.26
Cirrhosis	172 (50.1)	62 (40.0)	98 (63.6)	12 (35.3)	<0.001*
Child-Pugh score for cirrhosis (n=172)					0.02*
Class A	144 (83.7)	46 (74.2)	86 (87.8)	12 (100)	
Class B	28 (16.3)	16 (25.8)	12 (12.2)	0	
Prelaboratory test					
Hb, g/dL	14.3 (8.6–19.4)	14.5 (10.5–19.4)	14.1 (8.6–17.2)	14.7 (11.4–17.6)	0.03*
Platelet, 10 ⁹ /L	153.8 (29–357)	162.8 (29–357)	138.9 (34–315)	180.6 (83–328)	<0.001*
Albumin, g/dL	3.9 (2.4–4.7)	3.9 (2.4–4.6)	3.8 (2.8–4.7)	4.1 (3.5–4.2)	<0.001*
ALT, U/L	90.3 (6–542)	84.2 (6–324)	89.0 (17–257)	123.6 (23–542)	0.01*
AST, U/L	80.0 (13–311)	76.1 (13–311)	81.9 (19–202)	88.6 (23–283)	0.46
Bilirubin, mg/dL	0.9 (0.2–4.5)	0.9 (0.2–4.5)	1.0 (0.3–2.2)	0.8 (0.3–1.8)	0.44

Data are presented as mean (range) or number (%).

BMI, body mass index; SOF, sofosbuvir; LDV, ledipasvir; SIM, simeprevir; PEG, peginterferon; RBV, ribavirin; HCV, hepatitis C virus; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase.

*p<0.05 is considered statistically significant.

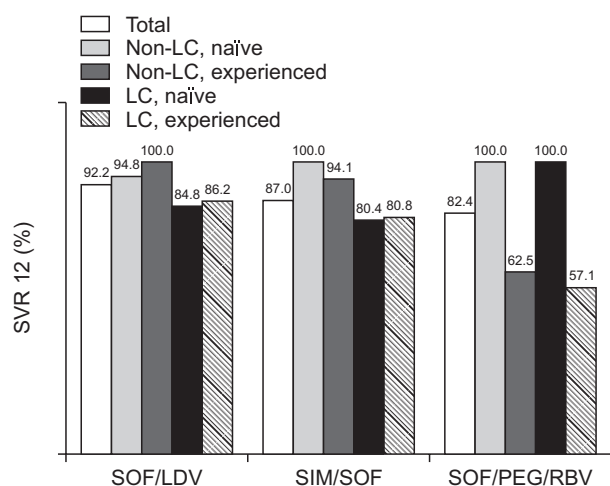


Fig. 2. Sustained virological response (SVR) week 12 in each treatment regimen according to treatment experience and presence or absence of cirrhosis.

SOF, sofosbuvir; LDV, ledipasvir; SIM, simeprevir; PEG, peginterferon; RBV, ribavirin; Non-LC, non-liver cirrhosis; LC, liver cirrhosis.

load end of treatment. 88.9% (305/343) achieved SVR12, and 11.1% (38/343) relapsed at 12 weeks after completing treatment. Overall SVR rates were high and similar in all three treatment groups. Except for the subjects receiving SOF/PEG/RBV, previous treatment history did not impact SVR. Fig. 2 shows SVR rates in each treatment divided into naïve and experienced, and the presence or absence of cirrhosis.

In our study 38 patients failed to achieve a SVR. Baseline characteristics of patients based on treatment results are shown in Table 2. Male sex, diabetes and cirrhosis were identified as predictors of failure of achieve SVR by univariate analysis. However, only male sex and cirrhosis were as negative predictors of SVR in multivariate analysis.

4. Virologic response in SOF/LDV group

In this group, 92.2% achieved SVR (Table 3). Patients who achieved a RVR had significantly higher SVR rates compared to those who did not achieve RVR (94.9% vs 84.4%, p=0.03). Simi-

Table 2. Baseline Characteristics of Patients According to Treatment Results

Characteristic	All patients (n=343)	SVR (n=305)	No SVR (n=38)	p-value
Age, yr	59.2±8.0	59.2±7.9	59.3±9.4	0.89
≥65	76 (22.2)	64 (21.0)	12/38 (31.6)	0.14
Male sex	212 (61.8)	178 (58.4)	34 (89.5)	<0.001*
BMI, kg/m ²	28.3±6.0	28.2±6.0	29.2±5.4	0.34
≥30	103 (30.0)	93 (30.2)	11 (28.9)	0.88
Race				0.31
White	269 (78.4)	242 (79.3)	27 (71.1)	
African American	29 (8.4)	26 (8.5)	3 (7.9)	
Other	37 (12.1)	8 (21.1)	18 (11.7)	
HCV genotype				0.20
1a	263 (76.7)	237 (77.7)	26 (68.4)	
1b	80 (23.3)	68 (22.3)	12 (31.6)	
HCV RNA ≥800,000 IU/mL	233 (67.9)	204 (69.6)	29 (78.4)	0.27
Previous HCV treatment				0.11
Naïve	195 (56.9)	178 (58.4)	17 (44.7)	
Treatment experienced	148 (43.1)	127 (41.6)	21 (55.3)	
Diabetes patient	61 (17.8)	49 (16.1)	12 (31.6)	0.018*
Cirrhosis	172 (50.1)	141 (46.2)	98 (63.6)	<0.001*
Child-Pugh score for cirrhosis				0.11
Class A	144 (83.7)	121(85.8)	23 (74.2)	
Class B	28 (16.3)	20 (14.2)	8 (25.8)	
Prelaboratory test				
Hb, g/dL	14.3±1.5	14.3±1.5	14.4±1.5	0.71
Platelet, 10 ⁹ /L	153.8±67.7	158.6±67.4	115.5±56.6	<0.001*
Albumin, g/dL	3.9±0.5	3.9±0.4	3.6±0.6	0.001*
ALT, U/L	90.3±71.5	88.2±72.4	106.8±62.2	0.13
AST, U/L	80.0±59.2	76.1±56.7	110.7±70.0	0.001*
Bilirubin, mg/dL	0.9±0.6	0.8±0.5	1.2±0.8	0.002*

Data are presented as mean±SD or number (%).

BMI, body mass index; SVR, sustained virological response; HCV, hepatitis C virus; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*p<0.05 is considered statistically significant.

larly, patients without cirrhosis had higher SVR rates compared to those with cirrhosis (96.8% vs 85.5%, p=0.01). Furthermore, SVR rates in patients with Child-Pugh class A were higher compared to those with Child-Pugh class B (91.3% vs 68.8%, p=0.04). SVR rates were lower in patients with diabetes compared to those without diabetes in this group of patients (94.7% vs 77.3%, p=0.005). Older patients had slightly lower SVR rates and this difference approached significance. Race, previous treatment history and alcohol use did not impact SVR rates significantly.

5. Virologic response in SOF/SIM group

In patients treated with SOF/SIM, 87.0% achieved SVR (Table

4). Similar to SOF/LDV group, patients who achieved RVR had higher SVR compared to those without RVR (90.9% vs 75.7%, p=0.02) and subjects without cirrhosis had higher SVR compared to those with cirrhosis (98.2% vs 80.6%, p=0.002). The Child-Pugh class did not significantly impact response rate. Women had higher SVR (98.5% female vs 78.4% male, p<0.001) and patients with normal alanine aminotransferase (ALT) had higher SVR compared to those with elevated ALT (97.2% vs 83.9%, p=0.04). However, unlike the SOF/LDV group, the presence of diabetes did not impact SVR rate.

Similar to SOF/LDV, subject race, genotype (1a vs 1b), previous treatment history, and pretreatment HCV viral load did not significantly impact SVR rates.

Table 3. SVR12 Rates in Patients Receiving SOF/LDV by Population Subgroup

Response	SVR12 rates	p-value
Overall	143/155 (92.2)	
RVR		0.03*
Patients without RVR	38/45 (84.4)	
Patients with RVR	94/99 (94.9)	
Cirrhosis		0.01*
Patients without cirrhosis	90/93 (96.8)	
Patients with cirrhosis	53/62 (85.5)	
CTP classification		0.04*
Class A	42/46 (91.3)	
Class B	11/16 (68.8)	
Treatment duration, wk		0.88
8	19/20 (95.0)	
12	89/97 (91.8)	
24	35/38 (92.1)	
DM		0.005*
Patients without DM	126/133 (94.7)	
Patients with DM	17/22 (77.3)	
Sex		0.16
Male	90/100 (90.0)	
Female	53/55 (96.4)	
Age, yr		0.07
<65	115/122 (94.3)	
≥65	28/33 (84.8)	
BMI, kg/m ²		0.83
<30	103/112 (92.0)	
≥30	40/43 (93.0)	
Alcohol		0.30
No significant alcohol use history	123/132 (93.2)	
Significant alcohol use history	20/23 (87.0)	
Pretreatment HCV RNA, IU/mL		0.12
<800,000	43/44 (97.7)	
≥800,000	93/103 (90.3)	
ALT, U/L		0.45
<40	38/40 (95.0)	
≥40	105/115 (91.3)	
Treatment experience		0.56
Treatment naïve	83/91 (91.2)	
Treatment experienced	60/64 (93.8)	
Genotype		0.95
1a	106/115 (92.2)	
1b	37/40 (92.5)	
Race		0.92
Caucasian	108/117 (92.3)	
African American	16/17 (94.1)	
Other	19/21 (90.5)	

Data are presented as number/total number (%).
SOF, sofosbuvir; LDV, ledipasvir; SVR, sustained virological response; RVR, rapid virologic response; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase.

*p<0.05 is considered statistically significant.

Table 4. SVR12 Rates in Patients Receiving SOF/SIM by Population Subgroup

Response	SVR12 rates	p-value
Overall	134/154 (87.0)	
RVR		0.02*
Patients without RVR	28/37 (75.7)	
Patients with RVR	100/110 (90.9)	
Cirrhosis		0.002*
Patients without cirrhosis	55/56 (98.2)	
Patients with cirrhosis	79/98 (80.6)	
CTP classification		0.60
Class A	70/86 (81.4)	
Class B	9/12 (75.0)	
Treatment duration, wk		1
12	130/150 (86.7)	
24	4/4 (100)	
DM		0.99
Patients without DM	107/123 (87.0)	
Patients with DM	27/31 (87.1)	
Sex		<0.001*
Male	69/88 (78.4)	
Female	65/66 (98.5)	
Age, yr		0.33
<65	101/114 (88.5)	
≥65	33/40 (82.5)	
BMI, kg/m ²		0.80
<30	91/104 (87.5)	
≥30	43/50 (86.0)	
Alcohol		<0.001*
No significant alcohol use history	113/120 (94.2)	
Significant alcohol use history	21/34 (61.8)	
Pretreatment HCV RNA, IU/mL		0.81
<800,000	36/41 (87.8)	
≥800,000	95/110 (86.4)	
ALT, U/L		0.04*
<40	35/36 (97.2)	
≥40	99/118 (83.9)	
Treatment experience		0.33
Treatment naïve	76/85 (89.4)	
Treatment experienced	58/69 (84.1)	
Genotype		0.09
1a	104/116 (89.7)	
1b	30/38 (79.0)	
Race		0.12
Caucasian	111/124 (89.5)	
African American	10/12 (83.3)	
Other	13/18 (72.2)	

Data are presented as number/total number (%).

SOF, sofosbuvir; SIM, simeprevir; SVR, sustained virological response; RVR, rapid virologic response; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase.

*p<0.05 is considered statistically significant.

Table 5. SVR12 Rates in Patients Receiving SOF/PEG/RBV by Population Subgroup

Response	SVR12 rates	p-value
Overall	28/34 (82.4)	
RVR		0.20
Patients without RVR	7/7 (100)	
Patients with RVR	20/25 (80.0)	
Cirrhosis		0.41
Patients without cirrhosis	19/22 (86.4)	
Patients with cirrhosis	9/12 (75.0)	
CTP classification		
Class A	9/12 (75.0)	
DM		0.09
Patients without DM	23/26 (88.5)	
Patients with DM	5/8 (62.5)	
Sex		0.45
Male	19/24 (79.2)	
Female	9/10 (90.0)	
Age, yr		0.40
<65	25/31 (80.6)	
≥65	3/3 (100)	
BMI, kg/m ²		0.45
<30	19/24 (79.2)	
≥30	9/10 (90.0)	
Alcohol		0.22
No significant alcohol use history	22/28 (78.6)	
Significant alcohol use history	6/6 (100)	
Pretreatment HCV RNA, IU/mL		0.82
<800,000	10/12 (83.3)	
≥800,000	16/20 (80.0)	
ALT, U/L		0.32
<40	4/4 (100)	
≥40	24/30 (80.0)	
Treatment experience		0.003*
Treatment naïve	19/19 (100)	
Treatment experienced	9/15 (60.0)	
Genotype		0.22
1a	27/32 (84.4)	
1b	1/2 (50.0)	
Race		0.94
Caucasian	23/28 (82.1)	
African American	0	
Other	5/6 (83.3)	

Data are presented as number/total number (%).

SOF, sofosbuvir; PEG, peginterferon; RBV, ribavirin; SVR, sustained virological response; RVR, rapid virologic response; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase.

*p<0.05 is considered statistically significant.

Table 6. Treatment Adverse Events and Hematologic Abnormalities

Adverse event	SOF/LDV (n=155)	SOF/SIM (n=154)	SOF/PEG/RBV (n=34)
Common adverse events	58 (34.8)	64 (41.6)	23 (67.6)
Headache	34 (21.9)	15 (9.7)	4 (17.4)
Fatigue	22 (14.2)	22 (14.3)	5 (21.7)
Insomnia	11 (7.1)	10 (6.5)	2 (8.7)
Anorexia/nausea	10 (6.5)	12 (7.8)	4 (17.4)
Abdominal discomfort	2 (1.3)	4 (2.6)	3 (13.0)
Rash	0	13 (8.4)	4 (17.4)
Itching	0	3 (1.9)	0
Upper respiratory infection	3 (1.9)	0	0
Joint pain	2 (1.3)	3 (1.9)	0
Dizziness	0	0	3 (13.0)
Syncope	0	0	2 (8.7)
Alopecia	0	1 (<1)	2 (8.7)
Depression	1 (<1)	0	2 (8.7)
Muscle pain	1 (<1)	1 (<1)	0
Diarrhea	1 (<1)	1 (<1)	0
Urinary tract infection	1 (<1)	1 (<1)	0
Cough	0	1 (<1)	1 (4.3)
Anxiety	0	2 (1.3)	0
Constipation	0	1 (<1)	0
Cellulitis	0	1 (<1)	0
Vomiting	0	1 (<1)	0
Confusion	0	1 (<1)	0
Dyspnea	0	0	1 (4.3)
Vision change	0	0	1 (4.3)
Chill	0	0	1 (4.3)
Hematologic adverse events			
Decreased hemoglobin level, g/dL			
<10.0	0	1 (<1)	3 (13.0)
<8.5	0	0	4 (17.4)
Decreased lymphocyte level, mm ³			
<500	1 (<1)	1 (<1)	1 (4.3)
Decreased neutrophil count, mm ³			
<500	0	0	1 (4.3)

Data are presented as number (%).

SOF, sofosbuvir; LDV, ledipasvir; SIM, simeprevir; PEG, peginterferon; RBV, ribavirin.

6. Virologic response in SOF/PEG/RBV group

In this treatment group, 82.4% achieved SVR (Table 5). The only significant finding was that previous HCV treatment history reduced the odds of achieving a treatment response. One hundred percent of the treatment naïve patients achieved SVR (19/19), whereas only 60% (9/15) in treatment experienced patients achieved an SVR.

7. Multivariate analysis of SVR across treatment groups

Multivariate logistic regression of all treatment groups, included variables that were significant on univariate analysis (data not shown) and found only absence of cirrhosis (odds ratio [OR], 3.23; 95% confidence interval [CI], 1.30 to 8.05; p=0.012) and female sex (OR, 4.92; 95% CI, 1.66 to 14.61; p=0.004) to be positive predictors of SVR.

Patients who achieved RVR, those without diabetes, and those

with pretreatment ALT <40 U/L, while significant for higher SVR in univariate analysis, did not remain significant in multivariate analysis.

8. Safety

Of the 343 patients in this study, no patient discontinued treatment because of an adverse event. A full list of any adverse events is provided in Table 6. Headache, fatigue, insomnia, anorexia/nausea were the most common events noted; however, no serious adverse events occurred among those on all-oral regimens. Subjects who received SOF/PEG/RBV, in turn, had a higher incidence of adverse events.

DISCUSSION

In this single center retrospective study of HCV G1 subjects treated with a SOF based regimens, we observed high SVR rates in all treatment arms. This represents real-world data regarding the effectiveness of HCV treatment in a diverse group of both treatment naïve and experienced subjects, and those with and without cirrhosis.

Among subjects who received SOF/LDV, the overall SVR rate was high at 92.2%, similar to other real-world data. The HCV-TARGET study, which is a multicenter, prospective observational cohort study which included 969 patients treated with SOF/LDV+/-RBV for 8 to 24 weeks also reported a very high SVR of 95% to 97%, and is comparable to ION trial results.⁷ In our study, patients receiving SOF/LDV had SVR rates higher with the absence of cirrhosis, and previous HCV treatment history did not significantly impact treatment response. Such results are comparable to what has been seen in the clinical trials. In the ION-1 clinical trial, which included G1 treatment naïve subjects, the overall SVR12 rate was 97% to 99%, with no difference in SVR between subjects with cirrhosis and without cirrhosis (97% vs 98%).⁸ In the ION-2 clinical trial, which included subjects who failed previous HCV treatment, the SVR was 94% to 99% following 12 to 24 weeks of treatment.⁹ In the ION-2 trial, previously treated patients with cirrhosis had a higher SVR with 24 weeks and therefore 24 weeks has been recommended in this subgroup. We too treated treatment experienced patients with cirrhosis for 24 weeks. The ION-1 and ION-2 trials included 15% to 20% of patients with cirrhosis. In our study, the subgroup of SOF/LDV patients with cirrhosis had a significantly lower SVR of 85.5%, compared to those with cirrhosis of 96.8% ($p=0.01$). This difference in SVR may be due to our higher proportion of patients with cirrhosis (40%), including 16% with clinically decompensated cirrhosis, though none were Child-Pugh C.

In the SOF/SIM group the overall SVR was 87%; however, in subjects without cirrhosis it was an impressive 98.2%, and again previous treatment history did not significantly impact response rate. However, in subjects with cirrhosis the SVR was 80.6%.

Our results were again similar to those seen in clinical trials. In the OPTIMIST-1 study which included both treatment naïve and treatment experienced patients without cirrhosis, SVR was 97% and in OPTIMIST-2 trial which included patients with cirrhosis, the SVR was 83%.^{10,11} Other multicenter real-world data has reported similar SVR rates. The HCV-TARGET study which included over 800 patients reported an overall SVR of 84%; however, Backus *et al.*¹² in their analysis of over 1,550 U.S Veterans treated with SOF/SIM observed lower response rates of 77.8%.¹³

In contrast, for the cohort treated with SOF/PEG/RBV, a smaller group of patients, the overall SVR rate was 82.4%, and response rate did not defer between subjects with and without cirrhosis. Response rate was, however, significantly affected by previous treatment history, with SVR of 100% in the treatment naïve group and only 60.0% in the experienced group. In the NEUTRINO trial which analyzed this regimen, SVR was reported as 89% in naïve patients, while treatment experienced patients were not studied.¹⁴ Based on our results, retreatment with SOF/PEG/RBV should not be recommended, and hence, our real-world data is quite informative.

In the PEG/RBV era, male sex, black race, cirrhosis, coinfection (HIV and hepatitis B), insulin resistance, obesity, and high viral load ($\geq 600,000$ IU/mL) were considered negative predictors of SVR.^{15,16} However, this does not hold true with newer direct acting antivirals. A subgroup analysis of ION-1 and ION-3 demonstrated that SVR rates were independent of all prior negative predictors in G1 patients.^{8,17}

In our study, patients with undetectable 4-week on treatment HCV RNA (RVR) were more likely to experience SVR, while those with cirrhosis were less likely to have SVR in both SOF/LDV and SOF/SIM group. Although only a small number of patients with diabetes (17.7%) were included in the study, those with diabetes had lower rates of SVR and was statistically significant in the SOF/LDV group (77.3% vs 94.7%, $p=0.005$). Diabetes and hepatitis C are intimately related and a number of studies in the past using interferon based regimens showed a lower SVR in patients with diabetes. However, data regarding influence of diabetes on SVR in the direct-acting antiviral (DAA) era is lacking. Similar to our study, preliminary data from other studies show lower SVR in patients with diabetes.¹⁸ Further studies are needed to better understand the effect of diabetes on treatment response with DAA treatment regimens. Alcohol is an independent marker of severe fibrosis; however, recent studies have not shown any difference in SVR rates in patients with history of alcohol excess.¹⁹ In our study we noticed that in the SIM/SOF group, patients with no significant alcohol use had a higher SVR compared to those with significant alcohol. This was an interesting observation and further prospective studies should be done to adequately study association of SVR and alcohol in the DAA era.

In our study, female sex was a significant predictor of SVR

in multivariate analysis including all treatment groups. This is an interesting finding not documented in previous studies and should be further studied in future studies. Our assumption is that, though not statistically significant, female patients had better response predictors compared to male patients with less cirrhosis (female vs male, 43.5% vs 54.2%) and diabetes (female vs male, 15.2% vs 19.3%), it is an interesting finding that should be investigated further.

This study has unique strengths. First, we cite real-world treatment response and safety data with various SOF-based regimens, including those with interferon, from a large single center treatment population. Patients with clinically significant comorbidities have been included. A large proportion of patients had advanced liver disease, and hepatocellular carcinoma was not exclusionary. Limitations of this study include retrospective analysis of the data, and that patient characteristics differed across the three treatment groups. Lastly, diagnosis of cirrhosis was made by different methods including liver biopsy, FibroScan, and liver imaging in conjunction with liver synthetic function, although this is what occurs in the real-world clinical setting.

In conclusion, sofosbuvir based regimens achieved high SVR rates, especially when combined with other new direct acting antivirals. Both SOF/LDV and SOF/SIM groups showed high favorable treatment outcomes for genotype 1 hepatitis C patients without cirrhosis. Characteristics associated with response were dependent upon the regimen used but included presence of diabetes, alcohol use, and sex. Additional prospective studies should be performed to clarify their relation to SVR.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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