Sofosbuvir and Simeprevir Combination Therapy for HCV Genotype 1 Infection: Results of a Single-Center VA Experience

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Abstract: Treatment of chronic hepatitis C virus (HCV) infection remains a priority in the veterans affairs (VA) health care system nationwide, as there is a high burden of liver disease due to HCV infection among US veterans. The combination of sofosbuvir and simeprevir was the first all-oral antiviral regimen used in clinical practice to treat veterans with HCV infection. In this study, we report a single-center experience showing both the feasibility and effectiveness of this all-oral combination to treat HCV genotype 1 infection. One hundred patients with HCV genotype 1 infection were treated between December 2013 and June 2014. Eighty-six patients were treated with sofosbuvir and simeprevir, with or without ribavirin, for 12 weeks; 12 patients were treated with sofosbuvir, pegylated interferon, and ribavirin for 12 weeks; and 2 patients were treated with sofosbuvir and ribavirin for 24 weeks. Overall, treatment was well tolerated and feasible, with compliance rates over 95% in patients treated with all-oral therapy. The sustained virologic response (SVR) rate for sofosbuvir and simeprevir (88.4%) was superior to the rate for sofosbuvir, pegylated interferon, and ribavirin (50.0%). Subgroup analysis showed diminished SVR rates in cirrhotic patients vs noncirrhotic patients. There were no significant differences in SVR when comparing treatment with or without ribavirin or among genotype subtypes. In conclusion, this study demonstrated excellent completion rates for all-oral treatment of veterans with chronic HCV infection. Additionally, treatment was highly effective, nearing a 90% cure rate. Thus, we recommend that the VA health care system continue to incorporate new HCV medications into its formulary so as to expand HCV treatment for US veterans.

There are an estimated 3.2 million Americans infected with chronic hepatitis C virus (HCV). Nationally, the veterans affairs (VA) health care system is the single largest HCV care provider, with over 170,000 US veterans afflicted with chronic HCV infection.[1,2] This represents a prevalence rate of 5.4%, which is

approximately 3 times the prevalence rate in the general US population. The number of veterans with HCV infection and cirrhosis has tripled over the past decade, and there has been a corresponding 10-fold increase in hepatocellular carcinoma (HCC), underscoring the need to treat the veteran population.[1,2] Furthermore, successful treatment of HCV infection and achievement of sustained virologic response (SVR) have been shown to decrease overall and liver-related mortality in both the veteran and general populations.[3,4]

After the US Food and Drug Administration (FDA)'s approval of the first generation of direct-acting antiviral (DAA) agents (boceprevir [Victrelis, Merck] and telaprevir [Incivek, Vertex]) in the middle of 2011, boceprevir became the protease inhibitor of choice in the VA system.[5,6] Treatment was resource-intensive, while outcomes were modest—only SVR rates of approximately 50% were achieved in those who were treated.[5,6] Cross-sectional studies at tertiary care centers reported that only 19% of HCV genotype 1–infected patients were initiating treatment, and therapy was deferred due to contraindications, patient choice, and the presence of less advanced liver disease.[7]

Over the past 3 years, HCV treatment has evolved at a very rapid pace with the introduction of many new DAA agents. The VA health care system faces unique challenges in evaluating and incorporating new DAA agents into its formulary as these drugs enter the market, resulting in major implications regarding cost and treatment outcomes. As a closed health care system, the VA system is an important stakeholder in HCV care, as the system faces the care and costs related to treatment as well as complications from cirrhosis, including hepatic decompensation, HCC, and liver transplantation.

Simeprevir (Olysio, Janssen) is a once-daily nonstructural (NS) 3/4A protease inhibitor that was first approved by the FDA in November 2013 to treat HCV genotype 1 infection in combination with pegylated interferon and ribavirin.[8-10] Sofosbuvir (Sovaldi, Gilead) is a once-daily NS5B polymerase inhibitor that was originally approved by the FDA in December 2013 for treatment of HCV genotypes 1 through 4 in various combinations with pegylated interferon and/or ribavirin with treatment durations ranging from 12 to 24 weeks.[11,12] Although the FDA did not approve the combination of these 2 DAA agents until November 2014, treatment guidelines endorsed by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America recommended treatment with 12 weeks of combination therapy for HCV genotype 1 infection based upon preliminary results of the COSMOS trial. This phase 2 trial randomized patients to regimens with sofosbuvir and simeprevir, with or without ribavirin, and studied the safety and efficacy of these regimens.[13] This represented the first all-oral DAA combination used to treat HCV genotype 1 infection in general practice. In November 2014, the FDA approved this combination therapy but required a treatment duration of 24 weeks for cirrhotic patients.

Treatment recommendations published by the Department of Veteran Affairs National Hepatitis C Resource Center Program and the Office of Public Health initially recommended in a 2014 report that it was "reasonable to defer therapy for future treatment" if there was no evidence of advanced fibrosis or cirrhosis or if there was no significant extrahepatic disease.[14] An updated 2016 version states that the "Veterans Health Administration expects to treat all veterans with chronic HCV infection who wish to be treated and are suitable for treatment."[14]

This article reports the results of an initial treatment experience over a 10-month period of time using the combination of sofosbuvir and simeprevir for treatment of HCV genotype 1 infection at a single VA health care system. Treatment effectiveness of sofosbuvir and simeprevir is also compared to a smaller group of patients with HCV genotype 1 infection who were treated with pegylated interferon, sofosbuvir, and ribavirin or just sofosbuvir and ribavirin during the same period of time.

Methods

Site and Patient Population

The Miami VA Healthcare System provides inpatient and outpatient services to approximately 175,000 veterans in South Florida. The main facility is located in the Miami Health District and is affiliated with the University of Miami. There is a high burden of HCV infection consistent with the national prevalence of HCV in VA health systems across the country. There is a dedicated hepatology section with a longstanding academic affiliation with the University of Miami. The section is comprised of 3 staff hepatologists, a nurse practitioner, and research staff. This study was approved by the Miami VA Institutional Review Board (IRB). A database was prospectively maintained by the clinical pharmacy service as part of standard clinical care to monitor medication distribution, compliance, adverse events, and costs of treatment associated with all patients started on sofosbuvir-based HCV regimens. The database was then modified to be compliant with the local IRB standards and augmented with retrospective collection of additional relevant clinical information related to HCV treatment.

Providers began prescribing sofosbuvir with pegylated interferon and ribavirin (and in 2 cases of interferon-intolerant patients, sofosbuvir with ribavirin alone) in December 2013. Initially, only a small number of patients

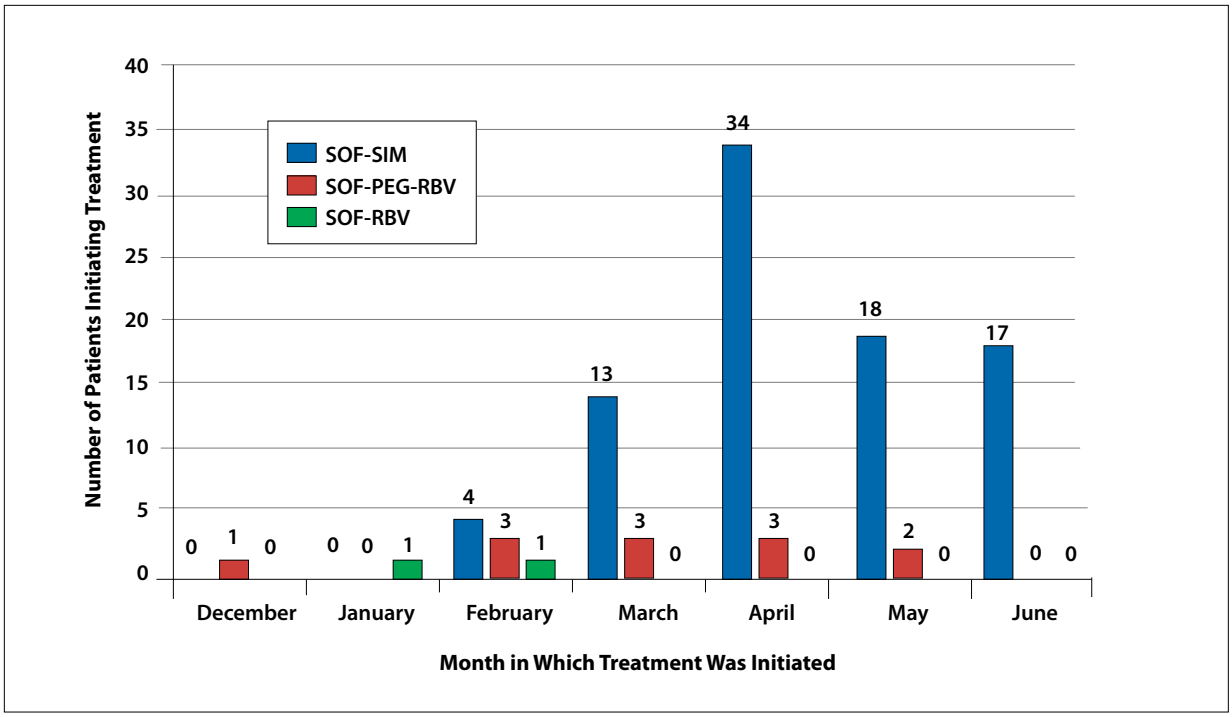

Figure 1. Prescribing patterns during the study period.

SOF-PEG-RBV, sofosbuvir, pegylated interferon, and ribavirin; SOF-RBV, sofosbuvir and ribavirin; SOF-SIM, sofosbuvir and simeprevir.

started treatment with these medications—which was an internal decision made by the administrative, pharmacy, and hepatology services. As the local treatment process was established during the initial weeks and budgeting for HCV treatment increased, the treatment program expanded. Combination therapy with simeprevir was initiated in the middle of February 2014 (Figure 1).

For consideration in this study, any patient with HCV genotype 1 infection who initiated treatment from December 2013 through June 2014 was included. Patients were eligible for therapy with pegylated interferon, sofosbuvir, and ribavirin for 12 weeks or sofosbuvir and simeprevir, with or without ribavirin, for 12 weeks. There were 2 additional HCV genotype 1–infected patients who were treated with sofosbuvir and ribavirin for 24 weeks (as they were interferon-intolerant and treatment was started prior to the internal approval of combination therapy of sofosbuvir and simeprevir). Sofosbuvir was dosed at 400 mg daily, and simeprevir was dosed at 150 mg daily. Weight-based ribavirin therapy (1000 mg daily for patients <75 kg and 1200 mg daily for patients ≥75 kg) was used at the discretion of the treating hepatologist, as the benefit of using ribavirin was still unclear and results of the phase 2 COSMOS study were not released until July 28, 2014 (after our study period ended).[13]

Patients with HCV genotype 2 or 3 infection were treated with sofosbuvir and ribavirin for 12 or 24 weeks, respectively. Patients with HCV genotype 4 infection were treated with sofosbuvir, pegylated interferon, and ribavirin. This paper only reports the treatment outcomes of patients with HCV genotype 1 infection.

In general, patients were adults with established chronic HCV infection with preserved kidney function (glomerular filtration rate >30). Treatment priority was given to patients with advanced fibrosis or cirrhosis, HCC, history of liver transplant with recurrent infection, and coinfection with HIV.

Patients came for an initial evaluation for HCV treatment with a HCV provider (hepatologist or nurse practitioner). If the veteran was deemed a good candidate for therapy and agreed to treatment, he or she was also seen by a clinical pharmacist at the initial visit. Baseline laboratory work included blood counts, a complete metabolic panel, and coagulation profiles. The patient's HCV viral load was obtained if it had not already been done in the previous 3 months. HCV genotype was established if unknown. The degree of liver fibrosis was assessed clinically; liver biopsies, imaging, platelet count, and signs of portal hypertension were all reviewed. Elastography technologies were not available at this VA system during the study period and therefore were not

used. Following the initial evaluation, some patients underwent a staging liver biopsy prior to initiating therapy. The Q80K polymorphism was not checked prior to starting therapy, nor was viral sequencing performed to look for potential resistance.

An initial 2-week prescription was distributed to the patient with a follow-up appointment 2 weeks later (treatment week 2) with a clinical pharmacist to monitor compliance and provide another 2-week refill of medication. At treatment week 4, patients met with a hepatologist or nurse practitioner for a 2-week refill and likewise at treatment week 6 with a clinical pharmacist. At treatment week 8, patients received a final 4-week refill. This follow-up system was put in place to maximize patient adherence. If patients did not follow through with laboratory work or appointments, their medications were not refilled. Laboratory work was obtained at treatment week 12 (end of treatment) and at 12 to 24 weeks posttreatment. (Laboratory work and visits at 4 weeks posttreatment were done at the discretion of the treating hepatologist.) SVR12 (ie, successful treatment outcome) was defined as undetectable HCV RNA testing 12 weeks posttreatment (COBAS Taqman lower limit of quantitation <15 IU/mL). Major adverse events, such as anemia (particularly in those treated with ribavirin), hepatic decompensation, and need for hospitalization, were followed closely by the treatment team.

The following baseline demographic and clinical information was collected: age, sex, race, body mass index, HCV genotype, presence or absence of cirrhosis, fibrosis stage (when a biopsy was performed), viral load, treatment experience, history of liver transplantation, coinfection with HIV, and, for cirrhotic patients, Child-Pugh score and Model for End-Stage Liver Disease score.

The primary objective of this study was to assess the overall effectiveness (SVR12) of combination therapy with sofosbuvir and simeprevir in this patient population of veterans. Secondary measures were completion of intended therapy (representing compliance and feasibility), overall safety, and comparative effectiveness with the other sofosbuvir regimens for HCV genotype 1–infected patients. We further analyzed the effectiveness of therapy with and without ribavirin, in cirrhotics vs noncirrhotics, and in patients with HCV genotype 1a vs 1b infection.

Statistical Analysis

As the preference was to treat with all-oral therapy whenever possible, this was not designed as a randomized prospective trial, and an initial sample size calculation was not performed. Rather, patients were treated as part of routine clinical care, and the analysis was performed on retrospectively collected data. Fisher's exact tests and chi-square tests were used to analyze categorical variables, and a P value of less than .05 was considered significant. All data were analyzed using SAS data management software.

Results

Overall, 112 veterans initiated therapy during the study period. One hundred patients had HCV genotype 1 infection, 6 had HCV genotype 2 infection, 5 had HCV genotype 3 infection, and 1 had HCV genotype 4 infection. A total of 86 (of the 100 HCV genotype 1–infected patients) initiated 12 weeks of combination DAA therapy (60 patients with sofosbuvir and simeprevir and 26 patients with sofosbuvir, simeprevir, and ribavirin). Also during this time period, 12 HCV genotype 1–infected patients initiated 12 weeks of treatment with sofosbuvir, pegylated interferon, and ribavirin, and 2 HCV genotype 1–infected patients initiated 24 weeks of treatment with sofosbuvir and ribavirin (Figure 2).

The first patient started treatment (sofosbuvir, pegylated interferon, and ribavirin) on December 24, 2013. The first patient on combination DAA therapy started treatment on February 14, 2014. As mentioned above, patients were initially selected to be treated with sofosbuvir, pegylated interferon, and ribavirin or just sofosbuvir and ribavirin. Sofosbuvir-and-simeprevir combination therapy was not an option at the beginning of the study until the combination received approval internally by the pharmacy. Treatment initiation patterns by month are shown in Figure 1.

Treatment With Sofosbuvir and Simeprevir With or Without Ribavirin

Patient demographics are shown in Table 1. Nearly all of the patients were men (94%), 40.7% were black, and nearly two-thirds had HCV genotype 1a infection. Importantly, 69% of patients had confirmed cirrhosis. Only 8% of patients, who were clinically noncirrhotic, did not undergo fibrosis assessment. Additionally, 5% of patients had concomitant HCC, 8% had HIV coinfection, and 8% had undergone liver transplantation. Comparisons between those who were treated with ribavirin and those who were not are shown in Table 2.

Other Sofosbuvir Cohorts

Patient demographics and clinical characteristics of patients treated with sofosbuvir, pegylated interferon, and ribavirin and those treated with sofosbuvir and ribavirin are shown in Table 3. Overall, patients had similar baseline characteristics.

Outcomes

Overall, the SVR rate with sofosbuvir and simeprevir, with or without ribavirin, was 88.4% (76/86; 95% CI,

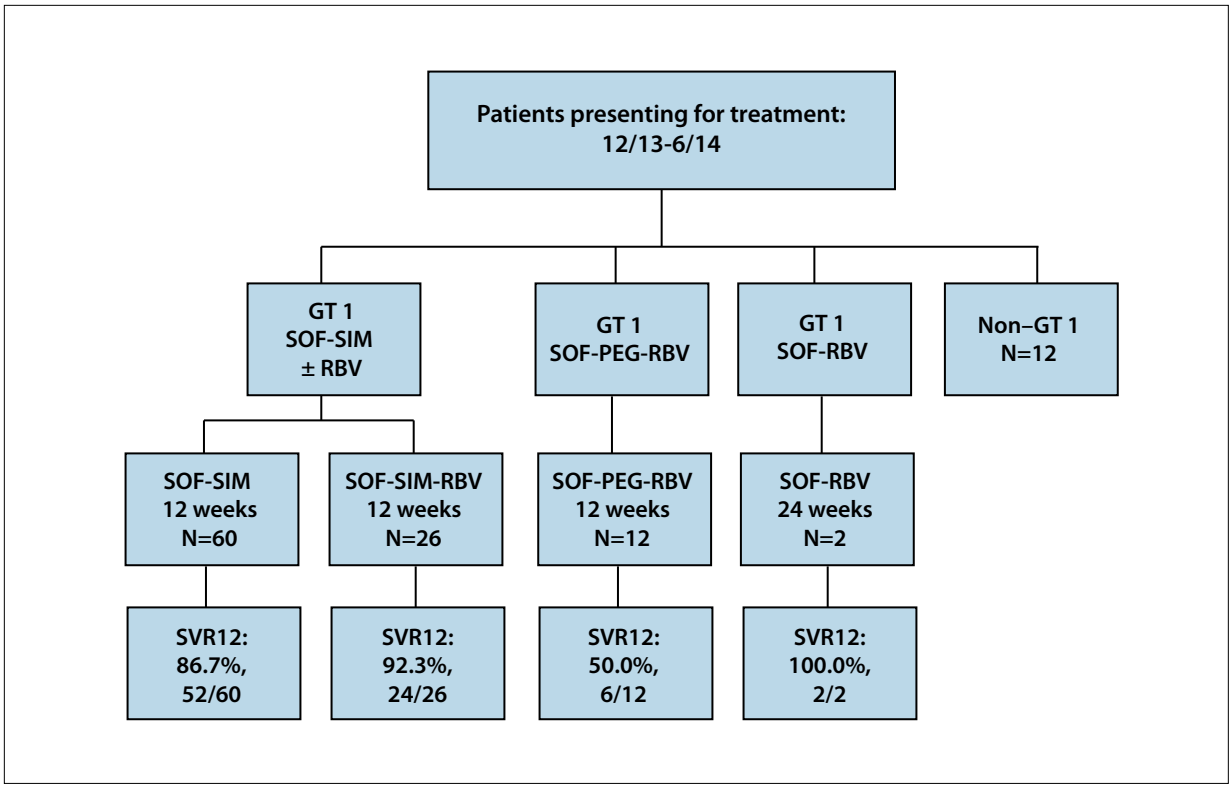

Figure 2. Patient groups and treatment outcomes.

GT, genotype; RBV, ribavirin; SOF-PEG-RBV, sofosbuvir, pegylated interferon, and ribavirin; SOF-RBV, sofosbuvir and ribavirin; SOF-SIM, sofosbuvir and simeprevir; SOF-SIM-RBV, sofosbuvir, simeprevir, and ribavirin; SVR12, sustained virologic response at 12 weeks.

79.9-93.6). The SVR rate was higher in those treated with ribavirin (92.3%; 24/26; 95% CI, 73.4-98.7) than in those not treated with ribavirin (86.7%; 52/60; 95% CI, 74.9-93.4; *P*=0.45). In comparison, the SVR rate for sofosbuvir, pegylated interferon, and ribavirin for HCV genotype 1–infected patients was 50.0% (6/12; 95% CI, 22.3-77.7; *P*<.001). Both patients with HCV genotype 1 infection who were treated with sofosbuvir and ribavirin for 24 weeks achieved SVR12.

Subgroup Analysis

Overall, there were 10 treatment failures among patients treated with the all-oral DAA combination of sofosbuvir and simeprevir, with or without ribavirin. There were 7 relapsers and 3 patients in whom therapy was stopped for other reasons (1 each because of progressive liver failure and death, decompensated heart disease, and active alcohol consumption). Thus, the completion rate was 96.5% (83/86). All 10 treatment failures were cirrhotic; therefore, the SVR rate was 100% (26/26; 95% CI, 84.0-100.0) for noncirrhotics and 83.3% (50/60; 95% CI, 71.0-91.3) for cirrhotics (*P*=.03). This lower efficacy in cirrhotics is the reason that the treatment recommendations for cirrhotic patients were eventually modified to 24 weeks.

Furthermore, when analyzing treatment outcomes by genotype subtype and then by the presence or absence of cirrhosis, the results were as follows: HCV genotype 1a: SVR12 of 89.3% (50/56; 95% CI, 77.5-95.6) and HCV genotype 1b: SVR12 of 86.2% (25/29; 95% CI, 67.4-95.5), with a *P* value of .73; and HCV genotype 1a cirrhosis: SVR12 of 85.0% (34/40; 95% CI, 69.5-93.8) and HCV genotype 1b cirrhosis: SVR12 of 79.0% (15/19; 95% CI, 53.9-93.0), with a *P* value of .71. HCV genotype 1a patients treated with ribavirin had a SVR rate of 92.0% (23/25; 95% CI, 72.5-98.6) and those without ribavirin had a SVR rate of 87.1% (27/31; 95% CI, 69.2-95.8), with a *P* value of .68.

In the treatment cohort of sofosbuvir, pegylated interferon, and ribavirin, SVR12 rates were also lower in cirrhotics: 37.5% (3/8; 95% CI, 10.2-74.1). One patient stopped therapy early (after 2 weeks) due to side effects.

Treatment Failures and Adverse Events

Seven patients relapsed after completing 12 weeks of combination DAA therapy. Three patients discontinued

Table 1. Characteristics of Patients on All-Oral Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection

Variable	All-Oral Therapy (N=86)
Age, yrs	61.6 ± 5.8
Sex	
Male	81 (94.2%)
Female	5 (5.8%)
Race	
White	47 (54.7%)
Black	35 (40.7%)
Body Mass Index	
<25	17 (19.8%)
25-29.9	40 (46.5%)
≥30	29 (33.7%)
Genotype	
1a	56 (65.1%)
1b	29 (33.7%)
1a/1b	1 (1.2%)
Viral Load	
<800,000	3 (3.5%)
≥800,000	83 (96.5%)
Prior Treatment History	
Treatment-naive	42 (48.8%)
Treatment-experienced (PI)	3 (3.5%)
Treatment-experienced (PEG)	41 (47.7%)
Fibrosis Stage	
F1	1 (1.2%)
F2	7 (8.1%)
F3	12 (14.0%)
F4	59 (68.6%)
Not assessed	7 (8.1%)
Cirrhosis	
No	27 (31.4%)
Yes	59 (68.6%)
Special Populations	
Hepatocellular carcinoma	4 (4.7%)
Hepatitis B virus	1 (1.2%)
HIV	7 (8.1%)
Liver transplant	7 (8.1%)
Treatment Regimen	
SOF-SIM-RBV	26 (30.2%)
SOF-SIM	60 (69.8%)

PEG, pegylated interferon; PI, protease inhibitor; SOF-SIM, sofosbuvir and simeprevir; SOF-SIM-RBV, sofosbuvir, simeprevir, and ribavirin.

Table 2. Characteristics of Patients Treated With Sofosbuvir and Simeprevir With and Without Ribavirin

Variable	SOF-SIM (N=60)	SOF-SIM-RBV (N=26)
Age, yrs	61.5 ± 5.8	61.6 ± 5.8
Sex		
Male	58 (97%)	23 (88%)
Female	2 (3%)	3 (12%)
Race		
White	35 (58%)	12 (46%)
Black	21 (35%)	14 (54%)
Body Mass Index		
<25	12 (20%)	2 (10%)
25-29.9	26 (43%)	13 (65%)
≥30	22 (37%)	5 (25%)
Genotype		
1a	31 (52%)	25 (96%)
1b	28 (47%)	1 (4%)
1a/1b	1 (2%)	0 (0%)
Viral Load		
<800,000	1 (2%)	2 (8%)
≥800,000	59 (98%)	24 (92%)
Cirrhosis	40 (67%)	19 (73%)
Fibrosis Stage		
F1	1 (2%)	0 (0%)
F2	5 (8%)	2 (8%)
F3	8 (13%)	4 (15%)
F4	40 (67%)	19 (73%)
Not assessed	6 (10%)	1 (4%)

SOF-SIM, sofosbuvir and simeprevir; SOF-SIM-RBV, sofosbuvir, simeprevir, and ribavirin.

therapy, one because of hepatic decompensation and death, as mentioned previously. Other adverse events included 3 ribavirin-treated patients with anemia (hemoglobin drop >2 g/dL), 3 patients with fatigue, 2 patients with rash (which, in retrospect, may have been a photosensitivity reaction related to simeprevir), 2 patients with nausea, 2 patients with headache, and 1 patient with pruritus.

Discussion

The treatment results showed overall excellent compliance and follow-through of all treatment regimens, with over 95% of patients able to complete therapy. The SVR12 rate for patients receiving sofosbuvir and simeprevir was 88.4% and slightly higher for those treated with ribavirin

Table 3. Characteristics of Patients Treated With Sofosbuvir and Ribavirin With and Without Pegylated Interferon

Variable	SOF-PEG-RBV (N=12)	SOF-RBV (N=2)
Age, yrs	60.7	70.5
Sex		
Male	11	2
Female	1	0
Race (%)		
Black	25%	50%
Body Mass Index (%)		
>30	25%	50%
Genotype		
1a	9	2
1b	3	0
Cirrhosis (%)	67%	50%
Fibrosis Stage		
F1	0	0
F2	1	1
F3	2	0
F4	8	1
Not assessed	1	0
Special Populations (%)		
Coinfection	8%	0%
OLT	8%	50%
HCC	0%	0%

HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; SOF-PEG-RBV, sofosbuvir, pegylated interferon, and ribavirin; SOF-RBV, sofosbuvir and ribavirin.

(92.3%) than those treated without ribavirin (86.7%). All relapses and failures occurred in cirrhotic patients. The difference between the SVR12 rate in noncirrhotics (100%) and the SVR12 rate in cirrhotics (83.3%) was significant. There were small differences among outcomes in genotype subtypes, but it was difficult to make conclusions due to insufficient sample size and the use of ribavirin. When compared to a smaller cohort of similar HCV genotype 1–infected patients treated with a combination of sofosbuvir, pegylated interferon, and ribavirin, treatment outcomes with sofosbuvir and simeprevir were superior (P<.001).

Our overall SVR12 results of 89% were similar to those reported in the COSMOS trial (92% for cohort 1 and 90% for cohort 2).[13] However, there were some differences when breaking down results by F0 to F2 and F3 to F4. Compensated cirrhotics in the COSMOS study had a SVR12 rate of 93% vs a SVR12 rate of 83% in our study.[13] Lower SVR rates for cirrhotics in a real-world setting were also reported by the national VA experience (70.0%)[15] and HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network; 80.5%; 95% CI, 76.7-84.0).[16] However, the national VA report was only able to identify patients as cirrhotics based upon the FIB-4 and aspartate aminotransferase to platelet ratio index tests.[15] In contrast, one strength of our study was the presence of more complete and definitive clinical data to identify cirrhotic patients. Our treatment outcomes were more in line with those reported by HCV-TARGET.[16]

One patient developed jaundice, progressive liver failure, and decompensation and ultimately died of sepsis precipitating gastrointestinal bleeding. Detailed review of the patient's medical records revealed that he was a Child-Pugh class B cirrhotic with a baseline low serum albumin level in whom esophageal varices were seen on endoscopy. Another patient had cardiac decompensation in the beginning of therapy (2 weeks), which was probably unrelated, but was still concerning considering the reported cardiac toxicity associated with amiodarone. A third patient had alcohol abuse, and treatment was stopped halfway through, as part of our local treatment agreement with veterans. Other reported side effects included anemia, fatigue, rash, and nausea, although at lower rates than in the COSMOS trial.

Strengths of our study include real-world outcomes data from a well-defined and -characterized VA cohort of patients. The national VA data report,[15] which relied on data extraction from a national database, reported inferior treatment outcomes and may not be entirely reflective of the VA treatment experience. In comparison, our data, which came from a single VA center, utilized highly accurate data from reviewing patient charts. Additionally, nearly 70% of patients were cirrhotic in this study, representing a difficult-to-treat group. Our structured treatment program was interdisciplinary and succeeded in promoting compliance; only 1 patient was terminated from the treatment program due to noncompliance and substance abuse.

There were differences and selection bias in those patients treated with and without ribavirin; therefore, it is difficult to fully determine whether there was a benefit from the addition of ribavirin. However, our major focus was to determine the feasibility of all-oral DAA treatment in a VA setting, including completion of the intended therapy and a lessening of clinically significant side effects (hospitalization, anemia, and hepatic decompensation).

Twelve weeks of therapy with sofosbuvir and simeprevir in patients with compensated cirrhosis was likely inadequate, largely explaining why all 10 treatment failures

had cirrhosis. Nineteen of the 59 cirrhotic patients were treated with weight-based ribavirin (with only 2 relapses) compared to 8 relapses in the 40 cirrhotic patients who were not treated with ribavirin, which suggests that the addition of ribavirin may have improved outcomes in cirrhotic patients (P=.47). Currently, 24 weeks of therapy is recommended by the Infectious Disease Society of America and the American Association for the Study of Liver Diseases for better SVR outcomes in cirrhotic patients.[17] However, this recommendation was not made until after our study was completed, and the relevant data on extending treatment in cirrhotic patients was not known when these patients initiated therapy.

Summary

This study provides important data for treating US veterans with HCV infection. Our results appear comparable to findings from the COSMOS trial and HCV-TARGET. The data presented in this paper show better outcomes than those presented in a recent report of the national VA treatment experience. The combination of sofosbuvir and simeprevir was effective and superior to regimens of sofosbuvir, pegylated interferon, and ribavirin.

Dr Peyton has had advising and speaking roles for AbbVie, Gilead, Bristol-Myers Squibb, and Merck. The other authors have no relevant conflicts of interest to disclose.

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