LIVER

Treatment of Chronic HCV With Sofosbuvir and Simeprevir in Patients With Cirrhosis and Contraindications to Interferon and/or Ribavirin

Mitchell L. Shiffman, MD[1], Amy M. James, ANP[1], April G. Long, FNP[1] and Philip C. Alexander, FNP[1]

OBJECTIVES: **Patients with chronic hepatitis C virus (HCV) and cirrhosis are in critical need of treatment that is both effective and tolerable. The combination of simeprevir (SMV), a protease inhibitor, and sofosbuvir (SOF), a polymerase inhibitor, without peginterferon and/or ribavirin (PEGINF/RBV) has been shown to achieve sustained virologic response (SVR) exceeding 90% in patients with HCV genotype 1 with prior nonresponse and/or cirrhosis. The present report describes the efficacy of SMV and SOF in patients with cirrhosis, prior or current hepatic decompensation, and other contraindications to PEGINF/RBV.**

METHODS: **A total of 120 consecutive patients with cirrhosis and contraindications to PEGINF/RBV were treated with SMV and SOF for 12 weeks. The primary end point was SVR at 12 weeks after the completion of treatment.**

RESULTS: **The mean age of the cohort was 60 years; 63% were male, 48% were Caucasian, 44% were African American, 69% were of genotype 1A, 49% were treatment naïve, 96% were interleukin-28B non-CC, 33% were of Child class B or C, and 25% had prior hepatic decompensation. The SVR by intention-to-treat was 81% with a relapse rate of 14%. The SVR by per-protocol analysis was 87% with a relapse rate of 13%. The only baseline factor associated with SVR by multifactor analysis was Child class. SVR in patients with Child class A, B, and C was 87, 77, and 67%, respectively. Eleven percent of the patients developed severe adverse events, which included sepsis (two), variceal bleeding (two), hepatocellular carcinoma (two), and hyperbilirubinemia (eight). One of the patients with sepsis died. Two patients developed relapse more than 12 weeks after stopping SMV and SOF.**

CONCLUSIONS: **The combination of SMV and SOF achieves high rates of SVR in patients with advanced cirrhosis but is lower with worsening Child class.**

Am J Gastroenterol 2015; 110:1179–1185; doi:10.1038/ajg.2015.218; published online 28 July 2015

INTRODUCTION

Patients with chronic hepatitis C virus (HCV) and cirrhosis are in critical need of treatment that is both effective and tolerable. Without therapy, these patients are at the greatest risk of developing hepatic decompensation, hepatocellular carcinoma (HCC), and death (1–3). Once patients develop decompensated cirrhosis or HCC, the only effective long-term solution is liver transplantation (4). Many patients with cirrhosis cannot tolerate treatment that contains either peginterferon and/or ribavirin (PEGINF/RBV) (5–7). These patients experience much more frequent and severe adverse events with interferon (INF)-based therapy and have a significant risk of bacterial infection and hepatic decompensation, especially when thrombocytopenia is present and/or serum albumin is reduced (7,8).

Simeprevir (SMV), a protease inhibitor, and sofosbuvir (SOF), a polymerase inhibitor, are each highly effective against HCV genotype 1. Each agent was initially developed and utilized with PEGINF and RBV (9,10). Sustained virologic response (SVR) rates in the 80–90% range were reported. Combining SMV and SOF with or without RBV was shown to be highly effective in treating HCV in patients with prior nonresponse and/or cirrhosis. SVR rates exceeding 95% were observed without PEGINF and RBV (11). Shortly after these agents were made available in late 2013, SMV and SOF were prescribed together and this became

[1]Liver Institute of Virginia, Bon Secours Health System, Richmond, Virginia, USA. **Correspondence:** Mitchell L. Shiffman, MD, Liver Institute of Virginia, Bon Secours Health System, 5855 Bremo Road, Suite 509, Richmond, Virginia 23226, USA. E-mail: Mitchell_shiffman@bshsi.org
Received 10 March 2015; accepted 4 June 2015

the first INF-free, direct-acting all oral antiviral combination to be widely utilized for treatment of chronic HCV genotype 1. This combination was formally approved by the United States Food and Drug Administration (FDA) in the fall of 2014. Several other oral antiviral combinations are now also available to treat HCV genotype 1 (12–18).

The availability of INF-free oral antiviral therapies allows for the first time many patients with cirrhosis, including those with hepatic decompensation and other contraindications to PEGINF, to receive highly effective HCV treatment. Whether treatment of these patients is both safe and achieves similar SVR rates as reported in carefully controlled clinical trials conducted in patients with stable cirrhosis remains to be determined (13,14,16). The present report describes the clinical and virologic response to SMV–SOF in patients with cirrhosis and either previous or current hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy), treated HCC, and other contraindications to PEGINF and/or RBV.

METHODS

The study is a retrospective analysis of 120 consecutive patients with chronic HCV genotype 1 and cirrhosis in whom treatment with SMV and SOF was initiated at the Liver Institute of Virginia between 10 December 2013 and 15 April 2014. The various options for HCV treatment available at the time were discussed with every patient prior to prescribing SMV and SOF. Patients were informed of the data available on SMV and SOF (11) and that this combination was not formally approved by the FDA at the time these medications were prescribed. Approval to tabulate and analyze these data was obtained from the Institutional Review Board at the Bon Secours St Mary's Hospital, Richmond, VA. The study was not supported by any pharmaceutical company or other funding agency.

After the FDA approval of SMV and SOF a treatment algorithm for patients with cirrhosis was developed by the authors. SMV and SOF were prescribed to all patients with HCV genotype 1, cirrhosis, and contraindications to PEGINF-based therapy, who were able to receive these medications from their insurance carriers or through alternative programs. Cirrhosis was documented by liver biopsy in 102 patients or on the basis of clinical criteria for cirrhosis, which included at least two of the following: a Child-Pugh score >8, a history of ascites or hepatic encephalopathy, endoscopic evidence of variceal or portal hypertension with or without previous hemorrhage, and thrombocytopenia. Contraindications to treatment with PEGINF included at least one of the following: age greater than 65 years, hepatic decompensation (Child class B or C), a platelet count <70,000/cc, a hemoglobin level <10 gm/dl, HCC treated with either ablation (transarterial chemoembolization and/or microwave ablation) or surgical resection and without recurrence for at least 6 months, symptomatic cryoglobulinemia, serum creatinine >1.5 mg/ml, and an inability to tolerate a previous course of PEGINF and RBV-based therapy. All patients were treated with SMV (150 mg every day) and SOF (400 mg every day) for only 12 weeks. RBV was not utilized. Patients were scheduled for monitoring at weeks 2, 4, 8, and 12 after treatment had been initiated and at weeks 4 and 12 after treatment had been completed. The primary end point for analysis was SVR12. Because they have cirrhosis, patients continue to be monitored at regular intervals. HCV RNA was also measured 6, 12, and 24 months after treatment in accordance with our routine standard of care for monitoring patients who have achieved SVR. An ultrasound is performed to screen for HCC at 6-month intervals prior to, during, and following HCV treatment. α-fetoprotein is evaluated at 3-month intervals in accordance with the standard of care we provide for all patients with cirrhosis. HCV genotyping, subtyping, and interleukin-28B (IL28B) genotyping were performed in standard medical laboratories. IL28B genotyping was not ordered or available for all patients because this test was not approved for payment by some insurance carriers. The vast majority of patients with IL28B genotype results had the test performed historically. The Q80K mutation was not tested for in any patient because this test was not required for preauthorization of SMV or approved for payment by the patients' insurance carriers.

Data were reported as mean and range. Single followed by multiple logistic regression analysis was performed on all baseline and on-treatment variables to define predictors of SVR. A P value <0.05 was considered significant.

RESULTS

Patient population

A summary of the baseline clinical characteristics of the cohort is provided in **Table 1**. The oldest patient was 79 years old and 7% were over 70 years of age. The racial distribution between Caucasian and African American was similar. About 70% of the patients were of genotype 1A. Four patients could not be subtyped. IL28B genotype was available in only 102 (85%) patients. Approximately half of the patients were treatment naïve. The distribution was weighted against IL28B genotype CC primarily because of the racial composition of the cohort and because half had previously failed previous PEGINF-based therapy.

Laboratory evidence of hepatic decompensation or portal hypertension was present in 30% of patients at the initiation of HCV treatment. Hemoglobin <12 gm/dl was present in 24% of the patients and 10% had a hemoglobin level <10 gm/dl. Platelet count less than 90,000/cc was present in 32%, and 20% had a platelet count less than 70,000/cc. Total bilirubin greater than 2 mg/dl was present in 9% of patients at baseline, and 5% had a total bilirubin greater than 3 mg/dl. Serum albumin less than 3.5 gm/dl was present in 35%, and 8% of the patients had a serum albumin <2.8 gm/dl.

A prior episode of hepatic decompensation, variceal bleeding, ascites, or hepatic encephalopathy was present in over 25% of patients. Several of the patients had more than one of these events. Four patients (3%) had previously been treated for HCC without recurrence for at least 6 months. None of these patients were candidates for liver transplantation at the time HCV treatment was initiated. At the time of enrollment 67% of patients were of Child class A. However, 33% had decompensated cirrhosis and 12% were Child class C at the time HCV treatment was initiated. None of the patients were on a liver transplant waiting list at the time treatment was initiated.

Table 1. Patient characteristics at baseline

N	120
Age (years)	60 (29–79)
>70 years	7%
Male	63%
Race	
Caucasian	48%
African American	44%
Hispanic	3%
HCV genotype	
1 (not specified)	3%
1A	69%
1B	28%
Treatment	
Naive	49%
Prior PEGINF/RBV	36%
Prior DAA/PEGINF/RBV	15%
Interleukin-28B genotype (N=102)	
CC	4%
CT	59%
TT	37%
Child class	
A	67%
B	21%
C	12%
Selected baseline laboratory features	
White blood cell count (/cc)	5.4 (1.7–16.0)
Hemoglobin (gm/dl)	13.1 (6.4–17.6)
Platelet count (/cc)	136.7 (22–353)
Total bilirubin (mg/dl)	1.0 (0.2–8.5)
Albumin (gm/dl)	3.6 (1.8–5.0)
Alpha-fetoprotein (ng/ml)	51.4 (1.3–606)
Contraindications to PEGINF/RBV	
Hematologic values	
Platelet count <70,000/cc	20%
Hemoglobin <10 gm/dl	10%
Previous complications of cirrhosis	
Variceal bleeding	15%
Ascites	10%
Hepatic encephalopathy	22%
Hepatocellular carcinoma	3%
Age >65 years	20%
Symptomatic cryoglobulinemia	5%
Serum creatinine >1.5 mg/dl	5%
Prior intolerance to PEGINF/RBV	15%

HCV, hepatitis C virus; PEGINF, peginterferon; RBV, ribavirin.Values are given as mean with ranges in parentheses.

Virologic response

The virologic response to SMV and SOF is illustrated in **Figure 1**. By treatment week 2, 32% of patients were HCV RNA undetectable; 87% were HCV RNA undetectable by week 4, and all patients became HCV RNA undetectable by the end of the 12-week treatment period. The SVR 12 weeks after stopping SMV and SOF by an intention-to-treat analysis was 81%. The overall relapse rate was 14%. Five patients (4%) failed to return for follow-up after they had become HCV RNA undetectable while on treatment. Another 6 stopped therapy prematurely because of adverse events or other issues. By per-protocol analysis the SVR12 rate was 87% and the relapse rate was 13%.

The HCV RNA level in patients who remained positive at various times points during therapy is illustrated in **Figure 1b**. At treatment week 2, HCV RNA ranged from 15 to 3,340 IU/ml in the 81 patients who remained HCV RNA positive. At treatment week 4 HCV RNA ranged from 15 to 760 IU/ml in 16 patients. **Figure 1c** compares SVR rates in patients who were HCV RNA undetectable with those who remained HCV RNA positive at various time points during treatment. No significant relationship existed between the time that patients became HCV RNA undetectable and their ability to achieve SVR. Patients who were HCV RNA undetectable at week 2 had an SVR of 86% compared with 80% in patients who were still HCV RNA positive at week 2. The single patient who became HCV RNA undetectable after week 8 went on to achieve SVR.

Table 2 summarizes SVR according to various baseline features. There was no significant difference in SVR based upon age, race, prior treatment, HCV subtype, HCV RNA level, or platelet count. There was a significant downward trend in SVR related to IL28B genotype: from genotype CC to CT to TT ($P<0.05$). There was a 10% decline in SVR with each worsening Child class from A to C. This trend was also significant ($P<0.05$). When all baseline and on-treatment virologic factors were assessed for their impact on SVR the only factor that was significant by multifactorial logistic regression analysis was Child class ($P<0.05$).

Table 3 summarizes the changes in various hematologic and biochemical parameters observed in those patients who achieved SVR. A mean improvement of 8 points in the platelet count, 61–65 points in liver transaminases, 0.2 points in total bilirubin, 0.3 points in serum albumin, and a mean improvement of 58 points in alfa-fetoprotein were observed. Overall, over 50% of patients with SVR had an improvement in 1 or more hematologic parameters, essentially all patients had improvements in serum liver transaminases, over 60% had an improvement in parameters of hepatic synthetic and/or metabolic function, and 91% of patients had a decline in α-fetoprotein.

Adverse events

Fourteen patients (11%) developed complications of cirrhosis or a worsening in liver function during the 12 weeks of HCV treatment. This included two patients with variceal bleeding, two with sepsis, and two patients who developed HCC. One of the patients with sepsis died at treatment week 8 after becoming HCV RNA undetectable at treatment week 2. These complications were felt to be due to cirrhosis and were not attributed to either SMV

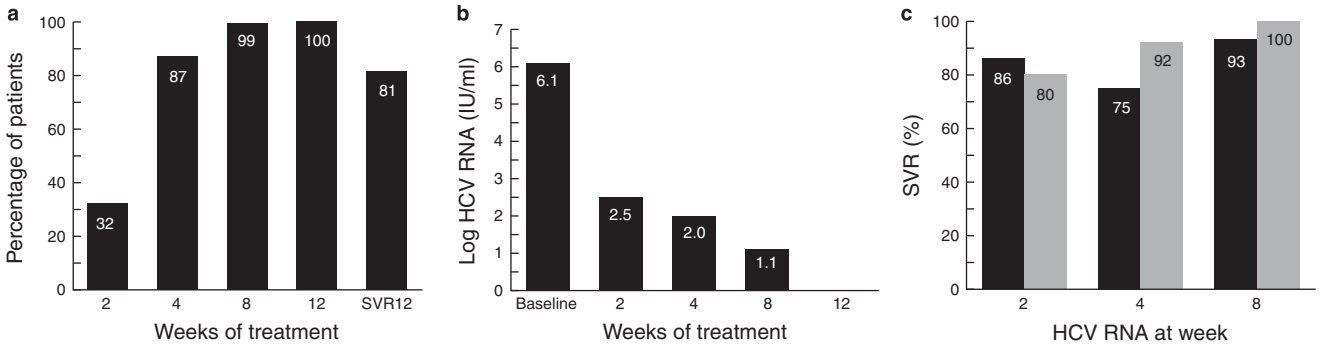

Figure 1. Virologic response to treatment. (**a**) Percentage of patients who were HCV RNA undetectable at various time points during and after treatment. (**b**) Mean HCV RNA in patients who were not HCV RNA undetectable at various time points during treatment. (**c**) SVR rates in patients who were HCV RNA undetectable or positive at various time points during treatment. HCV RNA negative=black. HCV RNA positive=gray. HCV, hepatitis C virus; SVR, sustained virologic response.

or SOF. Another eight patients developed more than a twofold increase in total bilirubin from the pretreatment baseline level. All eight of these events were felt to be related to SMV. The total bilirubin declined to the pretreatment baseline level or lower after treatment with SMV and SOF had been completed in all but two patients who continued to have persistent elevations in total bilirubin above 10 mg/dl. One of these two patients has since undergone a liver transplantation.

HCV treatment was prematurely stopped in only 4 of the 14 patients with serious adverse events: in the 2 patients with sepsis, in 1 patient with variceal bleeding, and in 1 patient in whom total bilirubin increased to 24 mg/dl. Two additional patients stopped treatment before week 12: one lost insurance coverage and was unable to continue treatment and the other refused to continue treatment after developing chest pain and nausea. Chest pain and nausea in this patient were felt to be unrelated to SMV or SOF. Of the six patients who stopped treatment prematurely, 3 achieved SVR.

Long-term follow-up

As all of the patients in this cohort have cirrhosis they continue to be seen at regular intervals for HCC screening and to ensure they remain HCV RNA undetectable in the long term. To date, two additional patients have developed a new HCC. One of these patients relapsed following HCV RNA treatment. The other achieved SVR12 and remains HCV RNA undetectable. So far, none of the four patients with treated HCC prior to initiating HCV treatment has developed a recurrence. These patients remain under regular surveillance for HCC recurrence.

Two patients who achieved SVR12 relapsed and became HCV RNA positive 24 weeks after treatment had been completed. Both patients had Child class B cirrhosis at the time treatment was initiated.

DISCUSSION

This report represents one of the first large experiences with the all oral antiviral regimen SMV and SOF in patients with HCV and cirrhosis. Not only did all of the patients in this cohort have cirrhosis, they also had one or more contraindications to receiving PEGINF and RBV. Decompensated Child class B or C cirrhosis was present in 33% of the patients. Very few data are currently available on the response of patients with decompensated cirrhosis to HCV treatment with all oral antiviral regimens. The results of this analysis indicate that SVR declines with the severity of cirrhosis, from 87% to 77% to 67% in patients with Child class A, B, and C cirrhosis, respectively. Child class was the single most important predictor of SVR.

The current study was initiated in December 2013 soon after the FDA approved SMV and SOF. Each of these oral antiviral agents was approved to be utilized with PEGINF and RBV for treatment of patients with HCV genotype 1. At the time of their approval, SMV and SOF had already been evaluated as a treatment modality for patients with HCV genotype 1 in the COSMOS study and had been shown to achieve SVR rates in excess of 95% (11). The regimen we chose, 12 weeks of SMV and SOF without RBV, was supported by the COSMOS study, which failed to demonstrate any significant differences in SVR with 12 or 24 weeks of treatment with or without RBV. The HCV treatment guidelines issued jointly by the American Association for the Study of Liver Diseases and the Infectious Disease Society of America also supported the 12-week regimen (19). In November 2013, the FDA formally approved SMV and SOF for treatment of HCV genotype 1. However, the duration of treatment they recommended for patients with cirrhosis was 24 as opposed to 12 weeks (20). This recommendation was based on an SVR rate of 6/7 (86%) and a relapse rate of 1/7 (14%) in patients with cirrhosis treated for 12 weeks compared with an SVR rate of 10/10 (100%) in patients with cirrhosis treated for 24 weeks. Prolonging the duration of therapy from 12 to 24 weeks in patients with cirrhosis has been shown to increase SVR when genotype 1 patients and those with prior nonresponse are treated with ledipasvir (LDV) and SOF (21,22), or when patients with genotype 1A are treated with pirataprevir (with ritonavir), ombitasvir, dasabuvir, and RBV (23). Treatment for 12 weeks with LDV–SOF and RBV appears to be as equally efficacious as 24 weeks of LDV–SOF in patients with cirrhosis and prior failure with PEGINF-based therapy (24). It is certainly possible that this patient cohort with cirrhosis, half of whom had failed previous PEGINF-based therapy, may have benefited from an

Table 2. Sustained virologic response according to various baseline and on-treatment features

	N	SVR (%)
Age		
≤65 years	96	77
>65 years	24	94
Sex		
Female	44	83
Male	76	80
Race		
African American	53	77
Asian	2	100
Caucasian	61	84
Hispanic	4	75
Prior treatment		
None	58	87
Standard INF TIW/RBV	1	100
PEGINF/RBV	42	75
BOC or TPV with PEGINF/RBV	19	81
IL28B genotype		
CC	4	100
CT	60	84
TT	38	74
HCV genotype		
1 (Not specified)	4	75
1A	82	81
1B	34	83
HCV RNA level		
<1 Million (IU/ml)	39	75
1–10 Million (IU/ml)	75	87
>10 Million (IU/ml)	6	67
Platelet count		
<70,000	25	88
70,000–150,000	52	70
>150,000	43	90
Child class		
A	81	87
B	25	77
C	14	67
Time to first negative HCV RNA		
2 Weeks	39	86
4 Weeks	65	75
>4 Weeks	16	93

HCV, hepatitis C virus; INF TIW, interferon three times weekly; PEGINF, peginterferon; RBV, ribavirin; SVR, sustained virologic response.

Table 3. Changes in various laboratory values in patients with SVR

	Mean absolute change	Patients with improvement (%)
WBC	–0.1	62
Absolute neutrophil count	–0.2	51
Hemoglobin (gm/dl)	0.1	36
Platelet count	8.6	51
AST	–64.5	100
ALT	–61.2	98
Total bilirubin (mg/dl)	–0.2	60
Albumin (gm/dl)	0.3	82
AFP (ng/ml)	–58.3	91

AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SVR, sustained virologic response; WBC, white blood cell.

additional 12 weeks of treatment, especially in the absence of RBV, or by adding RBV to the 12-week regimen.

It is also possible that the lower SVR rate observed in the present study, 81% by ITT analysis and 87% by per-protocol analysis, was also due to the severity of cirrhosis present in this cohort. SVR declined stepwise with increasing Child class in this series. A similar stepwise decline in SVR with worsening Child class was observed when either patients with worsening cirrhosis or liver transplant recipients with recurrent HCV and worsening cirrhosis were treated with LDV–SOF–RBV (25,26).

Another explanation for the lower SVR rate is that the current data simply reflect a nonclinical trial "real-world" environment. Two multi-site "real-world" studies have reported similar SVR rates for 12 weeks of SMV and SOF in patients with cirrhosis as was observed in the present study. In HCV, target SVR rates of 87% were reported for patients with stable cirrhosis and 75% for patients with decompensated cirrhosis (27). In the Trio study an SVR rate of 76% was reported for patients with cirrhosis (28).

Achieving SVR in patients with cirrhosis has been shown to reduce all-cause mortality, liver-related mortality, and HCC (29–32). Unfortunately, using INF-based therapy (with or without ribavirin and with or without a protease inhibitor) to treat patients with cirrhosis and prior decompensation is associated with much higher rates of adverse events and mortality compared with patients with stable cirrhosis (5–8). The availability of all oral antiviral regimens has, for the first time, enabled patients with prior hepatic decompensation to be treated for HCV. The present data clearly indicate that patients with HCV and decompensated cirrhosis can be treated successfully with an all oral antiviral regimen. However, these patients appear to have higher rates of hepatic decompensation during treatment compared with patients with stable cirrhosis (13,14,16). Hepatic decompensation developed in 11% of patients with advanced cirrhosis in this cohort compared with <2% in patients with stable cirrhosis without prior decompensation in three other studies (13,14,16). The complications reported in the current report included sepsis, variceal hemorrhage, HCC,

and hyperbilirubinemia. The latter is a unique complication of SMV, which is known to interfere with bilirubin transport and is unlikely to be seen with other antiviral agents that lack this property (33). Hyperbilirubinemia was well tolerated in most patients, did not require premature discontinuation of HCV treatment, and resolved within a few weeks after treatment was completed in all but two patients with Child class C cirrhosis who had elevated total bilirubin at baseline and a rise in total bilirubin to greater than 10 mg/dl during treatment. As complications of cirrhosis could derail therapy it is important to assess each patient with cirrhosis prior to initiating treatment. This includes evaluating for esophageal varices and screening for HCC just prior to initiating HCV treatment.

Patients with cirrhosis remain at increased risk for HCC even after they have been cured of HCV (29–32,34). Patients with more advanced cirrhosis and thrombocytopenia are at increased risk for HCC (34). Two patients in this series developed HCC after they became HCV RNA undetectable while still on HCV treatment, and two patients developed HCC after they completed HCV treatment. One of these patients had achieved SVR. This finding demonstrates the importance of continuing HCC surveillance in patients with cirrhosis during and following HCV treatment, even in patients who have achieved SVR.

The current standard for defining SVR has recently been reduced from 24 weeks following the completion of HCV treatment to 12 weeks (35). This is based upon several studies from the PEGINF era, which have demonstrated that late relapse occurs in <1% of patients with SVR, and several recent studies utilizing various INF-free regimens (10,15–17,35–38). In the present study, two patients developed relapse between 12 and 24 weeks following the completion of HCV treatment. Whether patients with advanced cirrhosis are at a higher risk for relapse more than 12 weeks after the completion of treatment remains to be determined. However, this observation stresses the importance of monitoring all patients with cirrhosis for HCV RNA 6 months and possibly again 12 months after HCV treatment has been completed.

In summary, the present study has demonstrated that treating patients with advanced cirrhosis using SMV and SOF for 12 weeks is associated with an SVR of about 81–87%. In contrast, the SVR rate reported for patients with stable Child class A cirrhosis using various INF-free all oral antiviral regimens generally exceeds 90–95% (13,14,16). The most important factor leading to the lower SVR rate in the current report was liver disease severity as assessed by Child class. We believe that other oral antiviral regimens given for the same duration would likely yield similar results. We speculate that higher SVR rates would likely only be achieved by extending the duration of therapy in patients with advanced cirrhosis.

CONFLICT OF INTEREST

Guarantor of the article: Mitchell L. Shiffman, MD.

Specific author contributions: MLS is an advisor for Abbvie, Achillion, Bristol-Myers-Squibb, Boehringer-Ingelheim, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Roche/Genentech; speaks on behalf of Abbvie, Bayer, Bristol-Myer-Squibb, Gilead, and Janssen; and receives grant support from Abbvie, Achillion, Beckman-Coulter, Bristol-Myers-Squibb, Boehringer-Ingelheim, Conatus, Gilead, Hologic, Intercept, Lumena, Merck, and Novartis. AMJ is an advisor for Gilead and Janssen and speaks on behalf of Janssen. AGL is an advisor for Abbvie and Gilead and speaks on behalf of Abbvie, Bristol-Myers-Squibb, and Gilead. PCA is an advisor for Gilead.

Financial support: None.

Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The combination of sofosbuvir (SOF) and simeprevir (SMV) is highly effective for the treatment of chronic HCV in patients with genotype 1 and cirrhosis.
- ✓ SMV may interfere with bilirubin transport and cause an elevation in serum bilirubin.
- ✓ SVR rate is now defined as being HCV RNA undetectable 12 weeks after HCV treatment has been completed.

WHAT IS NEW

- ✓ Patients with decompensated cirrhosis can be effectively treated with SOF and SMV.
- ✓ The SVR rate achieved in patients with HCV genotype 1 and cirrhosis is reduced in patients with worsening Child class.
- ✓ SMV can cause a marked elevation in serum bilirubin in patients with cirrhosis.
- ✓ A small percentage of patients with advanced cirrhosis can relapse more than 12 weeks after HCV treatment has been completed.

REFERENCES

1. Di Bisceglie AM, Shiffman ML, Everson GT *et al.* Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008;359:2429–41.
2. Ly KN, Xing J, Klevens RM *et al.* The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med 2012;156:271–8.
3. Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. Clin Liver Dis 2008;12:733–46.
4. Fox RK. When to consider liver transplant during the management of chronic liver disease. Med Clin North Am 2014;98:153–68.
5. Everson GT, Trotter J, Forman L *et al.* Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology 2005;42:255–62.
6. Bruno S, Shiffman ML, Roberts SK *et al.* Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis in patients with advanced fibrosis and cirrhosis. Hepatology 2010;51:388–97.
7. Hézode C, Fontaine H, Dorival C *et al.* Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 2014;147:132–42.
8. Carrion JA, Martinez-Bauer E, Crespo G *et al.* Antiviral therapy increases the risk of bacterial infections in HCV infected cirrhotic patients awaiting liver transplantation: a retrospective study. J Hepatol 2009;50:719–28.
9. Manns M, Marcellin P, Poordad F *et al.* Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014;384:414–26.
10. Lawitz E, Mangia A, Wyles D *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878–87.

11. Lawitz E, Sulkowski MS, Ghalib R *et al.* Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756–65.
12. Kowdley KV, Gordon SC, Reddy KR *et al.* Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879–88.
13. Afdhal N, Zeuzem S, Kwo P *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–98.
14. Afdhal N, Reddy KR, Nelson DR *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483–93.
15. Ferenci P, Bernstein D, Lalezari J *et al.* ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983–92.
16. Poordad F, Hezode C, Trinh R *et al.* ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973–82.
17. Feld JJ, Kowdley KV, Coakley E *et al.* Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594–603.
18. Zeuzem S, Jacobson IM, Baykal T *et al.* Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604–14.
19. Recommendations for testing, managing and treating hepatitis C. American Association for the Study of Liver Diseases and Infectious Disease Society of American http://www.hcvguidelines.org/full-report-viewAASLD guidelines, Accessed on 1 March 2014.
20. Simeprevir package insert. Revised November 2014.
21. Afdhal N, Zeuzem S, Kwo P *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–98.
22. Afdhal N, Reddy KR, Nelson DR *et al.* Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483–93.
23. Poordad F, Hezode C, Trinh R *et al.* ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973–82.
24. Bourliere M, Sulkowski MS, Omata M *et al.* An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with lepisasvir/sofosbuvir with or without ribavirin. Hepatology 2014;60:239A.
25. Reddy KR, Everson GT, Flamm SL *et al.* Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with post-transplant recurrence: Preliminary results of a prospective, multicenter study. Hepatology 2014;60:209A.
26. Manns M, Forns X, Samuel D *et al.* Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post-liver transplant patients with HCV infection: preliminary results of the prospective SOLAR 2 trial. J Hepatol 2015;62:S187–8.
27. Jensen DM, O'Leary JG, Pockros PJ *et al.* safety and Efficay of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. Hepatology 2014;60(suppl):219A.
28. Dieterich D, Bacon BR, Flamm SL *et al.* Evaluation of sofosbuvir and simeprevir based regimens in the TRIO network: academic and community treatment of a real-world, heterogeneous population. Hepatology 2014;60:220A.
29. Veldt BJ, Heathcote EJ, Wedemeyer H *et al.* Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677–84.
30. Morgan TR, Ghany MG, Kim HY *et al.* HALT-C Trial Group. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833–44.
31. Backus LI, Boothroyd DB, Phillips BR *et al.* A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509–16.
32. van der Meer AJ, 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;308:2584–93.
33. Stine JG, Intagliata N, Shah NL *et al.* Hepatic Decompensation likely attributable to simeprevir in patients with advanced cirrhosis. Dig Dis Sci 2014;60:1031–5.
34. Lok AS, Seeff LB, Morgan TR *et al.* Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009;136:138–48.
35. Yoshida EM, Sulkowski MS, Gane EJ *et al.* Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology 2015;61:41–5.
36. Swain MG, Lai MY, Shiffman ML *et al.* A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterol 2010;139:1593–601.
37. Manns MP, Pockros PJ, Norkrans G *et al.* Long-term clearance of hepatitis C virus following interferon α-2b or peginterferon α-2b, alone or in combination with ribavirin. J Viral Hepat 2013;20:524–9.
38. Jacobson IM, Gordon SC, Kowdley KV *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867–77.