pISSN 2287-2728
eISSN 2287-285X

CMH

http://dx.doi.org/10.3350/cmh.2015.21.4.358
Clinical and Molecular Hepatology 2015;21:358-364

Original Article

Sofosbuvir-based therapy for patients with chronic hepatitis C: Early experience of its efficacy and safety in Korea

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Background/Aims: The previous standard treatment for chronic hepatitis C (CHC) patients, comprising a combination of pegylated interferon (IFN) and ribavirin, was associated with suboptimal efficacy and severe adverse reactions. A new era of direct-acting antivirals is now dawning in Korea. Early experience of applying sofosbuvir-based therapy to CHC patients in Korea is reported herein.

Methods: Data on efficacy and safety were collected for CHC patients treated with a combination of sofosbuvir plus ribavirin or sofosbuvir/ledipasvir with or without ribavirin.

Results: This retrospective study included 25 consecutive patients who received sofosbuvir-based therapy (19 with genotype 1b and 6 with genotype 2) at Seoul National University Hospital from May 2014 to April 2015. A virologic response was achieved at week 4 by 85.7% and 80% of the patients with genotypes 1b and 2, respectively. The HCV-RNA level decreased more slowly in IFN-experienced than in treatment-naïve patients with genotype 1b. However, the sustained virologic response at week 12 (SVR12) rate did not differ among these patients, and was as high as 100%. The presence of cirrhosis significantly increased the risk of a virologic response failure at week 4 (OR, 11.0; P=0.011) among patients with HCV genotype 1b. Only five patients (20%) experienced minor adverse events, including grade 1 fatigue and headache. The hemoglobin level decreased slightly after sofosbuvir-based therapy, but there was no case of premature discontinuation of this therapy.

Conclusions: In a real clinical practice, sofosbuvir-based therapy for CHC patients in Korea achieved optimal antiviral efficacy with insignificant adverse events. Long-term follow-up data are warranted to ensure the sustained antiviral efficacy and long-term safety of sofosbuvir-based IFN-free therapy. **(Clin Mol Hepatol 2015;21:358-364)**

Keywords: Chronic hepatitis C; Direct-acting antiviral; Korea

INTRODUCTION

Previous standard treatment option for chronic hepatitis C (CHC) patients was a combination of pegylated interferon (IFN) and ribavirin.[1-3] However, this combination treatment shows suboptimal efficacy in viral response with severe adverse reactions.[4,5] Currently, new era of CHC treatment has been coming. Now, direct-acting antivirals (DAAs) are available in Korea with well-established efficacy for CHC patients. First-wave protease inhibitors including telaprevir or boceprevir were introduced in 2014. How-

Abbreviations:

ALT, alanine aminotransferase; CHC, chronic hepatitis C; CI, confidence interval; DAA, direct-acting antiviral; HCV, hepatitis C virus; IFN, interferon; NS, nonstructural protein; OR, odds ratio; PT, prothrombin time; RNA, ribonucleic acid; SD, standard deviation; SVR, sustained virologic response; TE, transient elastography; WBC, white blood cell

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Received : Aug. 25, 2015 / **Revised :** Nov. 21, 2015 / **Accepted :** Nov. 23, 2015

ever, many other second-generation DAAs targeting nonstructural protein (NS) 3 protease, NS5A and NS5B polymerase are being developed.

Many studies from Western countries reported that several DAAs exhibit potent antiviral activity with high sustained virologic response (SVR) rate, even in difficult-to-treat patients including old patients, patients with a liver cirrhosis, and those who failed to previous pegylated IFN plus ribavirin treatment. Use of pegylated IFN-free regimen with DAAs has shown very high SVR rates, up to nearly 100%, with insignificant side effects. In Western countries, interferon-free regimen is the new standard treatment for CHC patients. Now, second-generation DAAs including sofosbuvir or sofosbuvir/ledipasvir are available in Korea through the Korea Orphan Drug Center.

Sofosbuvir is an oral nucleotide analogue inhibitor targeting hepatitis C virus (HCV)-specific NS5B polymerase.[6] Sofosbuvir-based IFN-free therapies for patients with HCV genotype 1 infection include sofosbuvir/ledipasvir with/without ribavirin for 8–12 weeks.[7,8] Ledipasvir is a new HCV-NS5A inhibitor with antiviral activity against HCV genotype 1.[9] A combination of sofosbuvir plus ribavirin without ledipasvir had been used as one of the alternative treatment options against HCV genotype 1,[10,11] although which is no more recommended in current guidelines.[7,8] For the treatment against HCV genotype 2, sofosbuvir plus ribavirin for 12 weeks (or 16 weeks for cirrhosis) is recommended in both American Association for the Study of Liver Diseases (AASLD)[7] and European Association for the Study of the Liver (EASL) guidelines.[12]

For the patients in Western countries, sofosbuvir-based therapy has showed high rate of SVR in CHC patients with both HCV genotype 1 and 2.[13,14] However, the real-life clinical outcomes of these new DAAs in Korea, where ethnic difference exists, are not yet available. Therefore, in this study, we report the real-life experience of sofosbuvir-based IFN-free therapies in Korea including its efficacy and safety.

MATERIALS AND METHODS

Study subjects

All patients who received sofosbuvir-based therapy (sofosbuvir 400 mg or sofosbuvir 400 mg/ledipasvir 90 mg plus ribavirin per day) in Seoul National University Hospital were included in this study. All of the patients were older than 18 years old. Sofosbuvir was administered at a dose of 400 mg per day. A combination tablet of sofosbuvir/ledipasvir was administered at a fixed dose of 400 mg and 90 mg per day, respectively. Ribavirin was administered twice per day with doses according to patient's body weight (1,000 mg daily for the patients with <75 kg; 1,200 mg daily for the patient with ≥75 kg).

HCV RNA levels and genotype were determined with the Abbott Real-Time PCR HCV assay (Abbott Molecular Inc., IL, USA), with a lower limit of quantification of 12 IU/mL. Virologic response was defined as undectetable HCV RNA. We defined virologic breakthrough as the presence, during treatment, of serum HCV RNA concentrations ≥12 IU/mL after previous documentation of on-treatment HCV RNA <12 IU/mL.[7] Virologic relapse was defined as the presence of serum HCV RNA ≥12 IU/mL at any time during the post-treatment follow-up period after documentation of serum HCV RNA <12 IU/mL at the end of treatment.[7]

Safety was assessed by reviewing adverse events and clinical laboratory tests including hematological assessments, and physical examinations.

Follow-up

Physical examinations, assessment of vital signs, laboratory tests, and serum HCV RNA levels were assessed during the treatment. The virologic responses were obtained at baseline, 4 weeks, 12 weeks, right after the completion of treatment, and 4 and 12 weeks after the completion of sofosbuvir-based therapy, retrospectively. Serum alanine aminotransferase (ALT), albumin, total bilirubin concentration, and prothrombin time (PT) were measured using standard laboratory procedures. Virologic response at 12 weeks after the end of treatment was defined as SVR 12.[7] The presence of LC was evaluated by noninvasive liver fibrosis test including transient elastography (TE) or by the clinical manifestations including thrombocytopenia, splenomegaly, esophageal/gastric varices, or ascites. Patient with TE score of more than 12.5 kPa (on a scale of 1.5 to 75.0 kPa) was regarded as cirrhotic patient.[15] The upper limit of normal ALT was defined as 40 IU/L. Adherence to drug therapy was assessed by counting the number of remaining pills during each visit. Non-compliant patients were excluded from the study.

The study was approved by the Institutional Review Board of Seoul National University Hospital.

Statistical analysis

The efficacy parameter included serum HCV-RNA on a logarith-

 http://dx.doi.org/10.3350/cmh.2015.21.4.358

mic scale. To evaluate the prognostic factors for virologic response at week 4, so called rapid virologic response which is a significant surrogate marker for SVR in the patients treated with DAAs, we performed logistic regression analyses.[7,10] Statistical analysis was performed with SPSS version 22.0 (SPSS Institute Inc.; Chicago, IL, USA). Statistical hypotheses with $P<0.05$ were considered statistically significant.

RESULTS

Baseline characteristics

This retrospective study included 25 consecutive CHC patients who were treated with sofosbuvir-based therapy (13: sofosbuvir plus RBV; 12: sofosbuvir/ledipasvir plus RBV) in Seoul National University Hospital from May 2014 to April 2015. Nineteen patients were with genotype 1b and six were with genotype 2 (Table 1). The median HCV RNA was 6.1 $\log_{10}$ IU/mL (range, 4.2–7.1 $\log_{10}$ IU/mL). Eight (32%) patients were with liver cirrhosis. Among eight patients, three patients were diagnosed as liver cirrhosis with TE. Patients with HCV genotype 1b (n=19) were treated with sofosbuvir/ledipasvir + ribavirin for at least 12 weeks (n=12) or sofosbuvir + ribavirin for 24 weeks (n=7). Patients with HCV genotype 2 were treated with sofosbuvir + ribavirin for at least 12 weeks (n=6). One IFN-experienced cirrhotic patient with HCV genotype 2 who had been treated with sofosbuvir + ribavirin for 26.1 weeks was included in this study. There was no patient who did not complete the treatment course nor who were not compliant to therapy. Treatment regimen was decided according to the availability of drug at the time of starting therapy and the costs.

Virologic responses in genotype 1b

The median duration of sofosbuvir-based therapy was 14.9 weeks (range, 12.6–25.7 weeks). During treatment, 85.7% (12/14) of patients achieved virologic response at week 4 and 92.9% (13/14) of patients achieved virologic response at week 12. After treatment, 100% of patients achieved SVR 12.

Among 19 patients with HCV genotype 1b, 12 patients completed a combination therapy of sofosbuvir/ledipasvir + ribavirin for at least 12 weeks. Among those 12 patients, only one patient was with detectable HCV RNA at week 4, as high as 40 IU/mL. After week 12, all patients achieved virologic response with unde-

Table 1. Baseline characteristics

Variable	Genotype 1b (n=19)	Genotype 2 (n=6)	Total (n=25)
Age, year (range)	65 (23–80)	52 (48–66)	57 (23–80)
Male sex (%)	12 (63.2%)	3 (50%)	15 (60%)
BMI (kg/m^2)	21.1 (18.6–31.6)	23.4 (19–26.6)	21.8 (18.6–31.6)
HCV RNA ($\log_{10}$ IU/mL)	6.1 (4.2–7.1)	6.2 (4.9–6.5)	6.1 (4.2–7.1)
Serum ALT (IU/L)	35 (14–235)	48 (15–112)	37 (14–235)
Normal ALT (<40 IU/L)	8 (42.1%)	2 (33.3%)	10 (40%)
WBC (×10^3/μL)	4.8 (1.4–8.0)	4.9 (3.6–8.4)	4.8 (1.4–8.4)
Hemoglobin (g/dL)	14.1 (6.9–17.1)	14.9 (11.3–16.5)	13.7 (6.9–17.1)
Serum total bilirubin (mg/dL)	0.7 (0.2–1.4)	3.8 (0.4–4.7)	0.8 (0.2–4.7)
Serum albumin (g/dL)	4.3 (3.3–4.7)	3.9 (2.7–4.2)	4 (2.7–4.7)
Prothrombin time-INR	1 (0.9–1.1)	1.2 (1–1.5)	1 (0.9–1.5)
Liver cirrhosis (%)	5 (26.3%)	3 (50%)	8 (32%)
Treatment regimen			
Sofosbuvir + ribavirin	7	6	13 (52%)
Sofosbuvir/ledipasvir + ribavirin	12	0	12 (48%)
Duration of treatment, weeks	14.9 (12.6–25.7)	15.4 (12.9–26.1)	15.4 (12.6–26.1)
History of previous IFN-based treatments	5 (26.3%)	1 (16.7%)	6 (24%)

NOTE. Data are expressed as n (%) or median with range.
BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase; WBC, white blood cell; INR, international normalized ratio; IFN, interferon.

http://dx.doi.org/10.3350/cmh.2015.21.4.358

Table 2. Virologic responses to sofosbuvir-based therapy

Response	Treatment-naïve	Prior IFN-treatment	Total
HCV RNA <12 IU/mL, no./total no. (%)			
Genotype 1b	n=14	n=5	n=19
During treatment			
Week 4	12/14 (85.7%)	3/5 (60%)	15/19 (78.9%)
Week 12	13/14 (92.9%)	4/5 (80%)	17/19 (89.5%)
Week 24	4/4 (100%)	3/3 (100%)	7/7 (100%)
After treatment			
Week 4	14/14 (100%)	5/5 (100%)	19/19 (100%)
Week 12	7/7 (100%)	3/3 (100%)	10/10 (100%)
Genotype 2	n=5	n=1	n=6
During treatment			
Week 4	5/5 (100%)	0/1 (0%)	5/6 (83.3%)
Week 12	5/5 (100%)	1/1 (100%)	6/6 (100%)
After treatment			
Week 4	5/5 (100%)	1/1 (100%)	6/6 (100%)
Week 12	3/3 (100%)	1/1 (100%)	4/4 (100%)

IFN, interferon; HCV, hepatitis C virus; no., number.

Table 3. Treatment regimen and duration of sofosbuvir-based therapy and sustained virologic response at week 12 (SVR12)

	Treatment regimen	Duration	SVR12
Genotype 1b (n=19)			
Treatment-naïve patients with LC (n=2)	Sofosbuvir/ledipasvir + ribavirin (n=2)	17.0-16.9 weeks	100% (1/1)
IFN-experienced patients with LC (n=5)	Sofosbuvir/ledipasvir + ribavirin (n=5)	16.9-25.7 weeks	100% (3/3)
Treatment-naïve patients without LC (n=12)	Sofosbuvir/ledipasvir + ribavirin (n=5)	12.6-14.9weeks	100% (4/4)
	Sofosbuvir+ ribavirin (n=7)	16.9-23.6 weeks	100% (2/2)
Genotype 2 (n=6)			
Treatment-naïve patients with LC (n=2)	Sofosbuvir+ ribavirin	15.7-17.1 weeks	100% (1/1)
IFN-experienced patients with LC (n=1)	Sofosbuvir+ ribavirin	26.1 weeks	100% (1/1)
Treatment-naïve patients without LC (n=3)	Sofosbuvir+ ribavirin	12.9-15.4 weeks	100% (2/2)

LC, liver cirrhosis; IFN, interferon; SVR, sustained virologic response.

tectable HCV RNA.

Seven patients with HCV-genotype 1b completed a combination therapy of sofosbuvir + ribavirin for at least 24 weeks. Among those seven patients, one patient (14.3%) was with detectable HCV RNA at week 4, as high as and 119 IU/mL, respectively. During the median 20.9 weeks (range, 14.7–77.7 weeks) of follow-up period, all patients achieved virologic response without any relapse or virologic breakthrough during treatment.

Among five patients with previous history of IFN-based therapy, three patients (60%) achieved virologic response, at week 4 (Table 2). At week 12, four patients (80%) achieved virologic response. All five patients achieved SVR at 4 weeks after the end of sofosbuvir-based therapy (Table 2). SVR 12 rate was 100%, even among IFN-experienced cirrhotic patients (Table 3).

Previous history of IFN-based therapy was not associated with virologic response at week 4 (odds ratio [OR], 0.2; 95% confidence interval [CI], 0.1–2.9; P=0.505). However, the presence of liver cirrhosis significantly increased the risk of failure for virologic response at week 4 (OR, 11.0; 95% CI, 1.7–71.3; P=0.011). Five patients with liver cirrhosis at baseline were with Child-Pugh class A and achieved virologic response during the treatment period.

 http://dx.doi.org/10.3350/cmh.2015.21.4.358

Virologic responses in genotype 2

The median duration of sofosbuvir-based therapy for five patients with HCV-genotype 2 was 15.4 weeks (range, 12.9–26.1 weeks). All patients were treated with sofosbuvir + ribavirin for at least 12 weeks. Only one patient (16.7%) was with detectable HCV RNA at week 4, as high as 44 IU/mL, who had previous history of IFN-based therapy. At week 12, all patients achieved virologic response. SVR 12 rate was 100% (Table 2 and Table 3).

Previous history of IFN-based therapy (P=0.8) or the presence of liver cirrhosis (P=0.6) was not associated with virologic response at week 4.

Safety

There was no case of premature discontinuation of sofosbuvir or sofosbuvir/ledipasvir + ribavirin due to adverse events. Only five patients (20%) with HCV-genotype 1b experienced minor adverse events (all grade 1) including fatigue (n=2), mild depressive mood (n=1), and headache (n=2), which were under control with medication or supportive management.

Initial mean white blood cell (WBC) count was 5.15×10^3/μL (standard deviation [SD] 0.38×10^3/μL). After sofosbuvir-based therapy, the mean WBC changed to 4.18×10^3/μL (SD 0.42×10^3/μL). However, WBC did not decrease significantly after sofosbuvir-based therapy. While, hemoglobin decreased significantly from 13.8 g/dL (SD 2.4 g/dL) to 12.2 g/dL (SD 2.0 g/dL) (P=0.044). However, no patient needed transfusion due to sofosbuvir-based therapy.

DISCUSSION

In this retrospective study analyzing the efficacy of sofosbuvir-based therapy for the CHC patients in Korea, a remarkable SVR 12 rate was noted, as high as 100% in both HCV genotype 1b and 2, and in both treatment-naïve and previously-treated patients. For the HCV genotype 1b patients with previous history of IFN-based therapy, HCV RNA was slowly suppressed by sofosbuvir-based therapy. However, SVR rate was not different among treatment-naïve patients and patients with previous history of IFN-based therapy. Sofosbuvir-based IFN-free therapy showed high response rates among patients with both HCV genotype 1b and 2 with negligible adverse effects. Hemoglobin slightly decreased after sofosbuvir or sofosbuvir/ledipasvir + ribavirin. However, no patient needed transfusion, and there was no premature discontinuation of sofosbuvir-based therapy. The presence of liver cirrhosis significantly increased the risk of failure for virologic response at week 4. However, SVR 12 rate was as high as 100%.

No clinically significant treatment-emergent adverse events were noted in patients receiving sofosbuvir or sofosbuvir/ledipasvir + ribavirin combination. Hematological abnormality except for mild anemia was noted in patients receiving ribavirin. The low incidence of adverse events related with the relatively short duration of treatment as compared to IFN-based therapy might improve treatment adherence and completion.

Among patients with HCV infection and liver cirrhosis in whom pegylated IFN + ribavirin treatment has failed, SVR rates to retreatment with IFN-containing regimens are as low as 14%.[16-21] In addition, treatment for HCV infection, especially with IFN-based regimens, in patients with liver cirrhosis is associated with increased toxic effects.[22,23] In this study, we found that sofosbuvir-based therapy shows potent antiviral effect even in CHC patients with liver cirrhosis. However, slightly slow response rate was noted among the patients with cirrhosis which is known as a factor associated with a poor response. Cirrhotic patients with HCV infection have experienced low response rate with interferon-based therapy or protease-inhibitor containing regimen in many studies.[16,18,19,24,25] The exact mechanism of cirrhosis on response to treatment has not been identified yet. Serum HCV RNA declines in two phases: the rapid first phase and followed by a more gradual second phase of decline. Cirrhotic patients experience slower second phase decline as compared to non-cirrhotic patients.[26] Therefore, close follow-up and monitoring HCV RNA is needed for cirrhotic CHC patients and sufficient duration of DAAs-combination is warranted to achieve SVR 12, as high as 100%.[18,19,24,27] In EASL guideline, 8 weeks of duration for sofosbuvir/ledipasvir is also recommended for CHC genotype 1 patients without cirrhosis.[8] However, all patients included in this study received sofosbuvir/ledipasvir plus ribavirin for more than 12 weeks, due to lack of Korean experiences. Based on our results, 8 weeks of sofosbuvir/ledipasvir plus ribavirin might be sufficient to achieve SVR 12 in CHC genotype 1 patients without cirrhosis in Korea. Moreover, efficacy of sofosbuvir/ledipasvir without ribavirin in Korea should be further investigated.

Combinations of DAAs for 12–24 weeks have established the potential of IFN-free regimens for both treatment-naive patients and IFN-experienced patients with HCV genotype 1b or 2 infections.[28-32] IFN-free regimens are becoming the new standard of treatment for CHC patients in Western countries. Official approval

http://dx.doi.org/10.3350/cmh.2015.21.4.358

for DAAs in Asia countries lags behind that in the Western countries. However, several DAAs are becoming available for clinical use in Korea. This study demonstrates real-life management data of initial experiences for sofosbuvir-based therapy which has highly potent antiviral activity against HCV, and has been approved and will be commercially available in a few months in Korea. Our initial experience might provide helpful guidance for clinical use of DAAs, as to the best strategies for CHC management in Korea.

In conclusion, sofosbuvir-based IFN-free therapy could provide a short, all-oral treatment which is effective in both treatment-naive and previously treated CHC patients. Further large scale real world studies are warranted when sofosbuvir-based therapy is commercially available in Korea. Importantly, sofosbuvir-based IFN-free therapy might be highly effective and safe in CHC patients including those who have not responded to standard of-care IFN-based regimens.

Author contributions

YJ Kim was the principal investigator and was responsible for the design of the study. Y Cho undertook data assembly, analysis, writing the manuscript, and interpretation. EJ Cho, JH Lee, SJ Yu, and JH Yoon provided technical and material support. All authors critically reviewed the manuscript and approved the final version for journal submission.

Conflicts of Interest

The authors have no conflicts to disclose.

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http://dx.doi.org/10.3350/cmh.2015.21.4.358