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Efficacy and safety of daclatasvir and asunaprevir for hepatitis C virus genotype 1b infection

Hee Chul Nam[1], Hae Lim Lee[1], Hyun Yang[1] and Myeong Jun Song[1,2]

[1]Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, Korea

Background/Aims: The treatment strategy for hepatitis C virus (HCV) has been changing rapidly since the introduction of direct-acting antivirals such as daclatasvir (DCV) and asunaprevir (ASV). We evaluated the efficacy and safety of DCV and ASV for HCV in real-life practice.

Methods: Patients were treated with 60 mg of DCV once daily plus 200 mg of ASV twice daily for 24 weeks, and followed for 12 weeks. The primary endpoint was a sustained virological response at 12 weeks after treatment (SVR_{12}) and safety.

Results: This retrospective study included eight patients with chronic HCV genotype 1b infection. All of the enrolled patients were diagnosed with liver cirrhosis, and their mean age was 65.75 years. One patient was a nonresponder and two patients relapsed with previous pegylated interferon (PegIFN) and ribavirin (RBV) treatment. None of the patient showed NS5A mutation. An SVR_{12} was achieved in 88% of cases by the DCV and ASV combination therapy. The serum transaminase level and the aspartate-aminotransferase-to-platelet ratio were improved after the treatment. DCV and ASV were well tolerated in most of the patients, with treatment discontinuation due to adverse events (elevated liver enzyme and decompensation) occurring in two patients.

Conclusions: In this study, combination of DCV and ASV treatment achieved a high sustained virological response with few adverse events even in those with cirrhosis, advanced age, and nonresponse/relapse to previous interferon-based therapy. Close monitoring of safety issues may be necessary when treating chronic HCV patients receiving DCV and ASV, especially in older patient and those with cirrhosis. **(Clin Mol Hepatol 2016;22:259-266)**

Keywords: Hepatitis C virus; Liver cirrhosis; Direct-acting antivirals; Daclatasvir; Asunaprevir

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is affecting approximately 130 to 150 million individuals worldwide, and it is one of the leading causes of chronic liver disease, liver cirrhosis and hepatocellular carcinoma (HCC).[1] HCV is the most common indication of liver transplantation in the United States.[2] Six major HCV genotypes (GTs) have been identified. GT 1 is the most difficult to treat and the most common worldwide.[3] Especially, GT 1b is the most predominant subtype in eastern Asia; proportions of GT 1b infection in Korea, Taiwan, China, and Japan are reported to be 46%, 45%, 57%, and 65%, respectively.[4]

Abbreviations:

HCV, hepatitis c virus; GTs, genotypes; DCV, daclatasvir; ASV, asunaprevir; PegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response; NS5A, nonstructural protein 5A; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; RAV, resistance-associated variants

Corresponding author : Myeong Jun Song
Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daeheung-ro 64, Jung-gu, Daejeon 34943, Korea
Tel: +82-42-220-9291, Fax: +82-42-252-6807
Email: mjsong95@gmail.com

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Until 2011, the combination of pegylated interferon (PegIFN) and ribavirin (RBV) was the only approved treatment for chronic hepatitis C. With this regimen, patients infected with HCV GT 1 had sustained virological response (SVR) rates of approximately 40% to 50%.[5] Because of the low efficacy and treatment-limiting adverse events associated with PegIFN/RBV regimen, many patients cannot tolerate or are ineligible for this treatment.[6] Twenty to fifty percent of patients treated with PegIFN and RBV did not achieve an SVR and those patients had been the major challenge to treatment of HCV.[3] And an estimated 20% of patients with chronic HCV infection will develop cirrhosis. Patients with cirrhosis have increased risk of severe complications, such as hepatic decompensation, HCC, and death.[7]

Recently, therapeutic regimens for patients with chronic HCV infection have been changed with the use of oral direct acting antivirals (DAAs).[8,9] Daclatasvir (DCV) is a first-in-class, a nonstructural protein 5A (NS5A) replication complex inhibitor with potent pan-genotypic antiviral activity in vitro (HCV GT 1-6).[10] Asunaprevir (ASV) is a potent, selective nonstructural protein 3 (NS3) protease inhibitor with antiviral activity against HCV GT 1, 4, 5, and 6 in vitro.[11] Dual combination therapy with DCV and ASV, without PegIFN/RBV provided high SVR rates in treatment-naïve patients and in those who are ineligible, intolerant or nonresponsive to PegIFN/RBV treatment.[12-15] Moreover, DCV and ASV provided favorable SVR rates and low adverse events even in patients with compensated cirrhosis.[15,16]

Although the efficacy of DCV and ASV has been assessed in various studies,[12-17] real-life data on the chronic HCV infected patients are limited. The aim of our study was to assess of virological, biochemical responses and safety of DCV and ASV in compensated liver cirrhosis.

MATERIALS AND METHODS

Patients

We included chronic hepatitis C patients who were treated with DCV and ASV in Daejeon St. Mary`s hospital, Daejeon, Korea form March 2015 to November 2015. The doses of medications were as follows: DCV 60 mg once daily plus ASV 200 mg twice daily. Patients were treated for 24 weeks and followed for 12 weeks.

The inclusion criteria for this study were age older than 20 years old, chronic HCV GT 1b infection for at least 6 months with detectable HCV RNA titer, and patients with liver cirrhosis. Liver cirrhosis was defined by documented imaging studies such as ultrasonography or computed tomography (CT) scan. Patients nonresponsive or relapsing to previous treatment with PegIFN/RBV were also included. Nonresponse was defined as failure to clear HCV RNA from serum after 24 weeks of therapy and relapse was defined as reappearance of HCV RNA in serum after cessation of the therapy.[3] Exclusion criteria were evidence of HCC or decompensated cirrhosis, coinfection with human immunodeficiency virus or hepatitis B virus.

Outcome measurement

The primary outcome measurement was SVR_{12}, defined as undetectable HCV RNA (less than 15 IU/mL) at 12 weeks post-treatment. The baseline characteristics assessed included age, sex, BMI, HCV GT, HCV RNA titer, comorbidities (diabetes, hypertension), prior treatment history of HCV, and presence of cirrhosis or NS5A mutation. Clinical assessment of patients included complete blood cell counts, serum transaminase levels, serum creatinine levels, and HCV RNA titer. Clinical assessment was done at consecutive weeks of 4, 12, 24 and 36.

Table 1. Demographics and baseline characteristics of the patients (n = 8).

Age, mean years (SD)	65.75 (10.22)
Sex (male/female)	3/5
Liver status (chronic hepatitis/cirrhosis)	0/8
HCV genotype 1b, n (%)	8 (100)
Prior treatment history of HCV (naïve/relapse/nonresponse)	5/2/1
NS5A mutation, n (%)	0 (0)
HCV RNA, mean log IU/mL (SD)	6.03 (0.45)
ALT, mean U/L (SD)	36.00 (12.66)
Platelets x 10^9 cells/mL, median (min, max)	84.50 (6, 133)
Total bilirubin, mean mg/dL (SD)	0.78 (0.21)
Albumin, mean g/dL (SD)	3.83 (0.53)
INR, median (min, max)	1.03 (0.97, 1.13)
BMI, mean (SD)	26.40 (3.58)
Diabetes, n (%)	3 (37.50)
Hytertension, n (%)	3 (37.50)

HCV, hepatitis c virus; NS5A, nonstructural protein 5A; ALT, alanine aminotransferase; INR, international normalized ratio; BMI, body mass index.

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RESULTS

Baseline characteristics

Eight patients were treated with DCV and ASV. Table 1 shows demographics and baseline characteristics of the above eight patients. The mean age was relatively old (65.75 years). All patients were diagnosed as liver cirrhosis. One patient was nonresponder and two patients relapsed with previous PegIFN/RBV treatment. Five patients were treatment-naïve. None of the patient showed NS5A mutation. Mean BMI of patients was 26.40, which was defined as obese according to WHO Regional Office for the Western Pacific Region classification.[18] Nearly one third of the patients had comorbidities such as diabetes or hypertension.

Virological response

Seven patients (88%) completed 24 weeks of treatment. Serum HCV RNA levels decreased dramatically in all patients after the treatment initiation. After 4 weeks of treatment, all patients achieved undetectable HCV RNA levels below the lower limit of quantitation (15 IU/mL). Seven patients sustained undetectable HCV RNA levels until the end of the treatment and this was maintained throughout 12 weeks of post-treatment. SVR_{12} was achieved in 7 out of 8 patients (88%). Figure 1 shows rapid decline of HCV RNA titers in patients with different baseline characteristics. SVR_{12} was achieved in all patients with the following conditions: treatment naïve (Fig. 1A), advanced age (Fig. 1B), and relapsing/nonresponsive to the previous PegIFN/RBV treatment

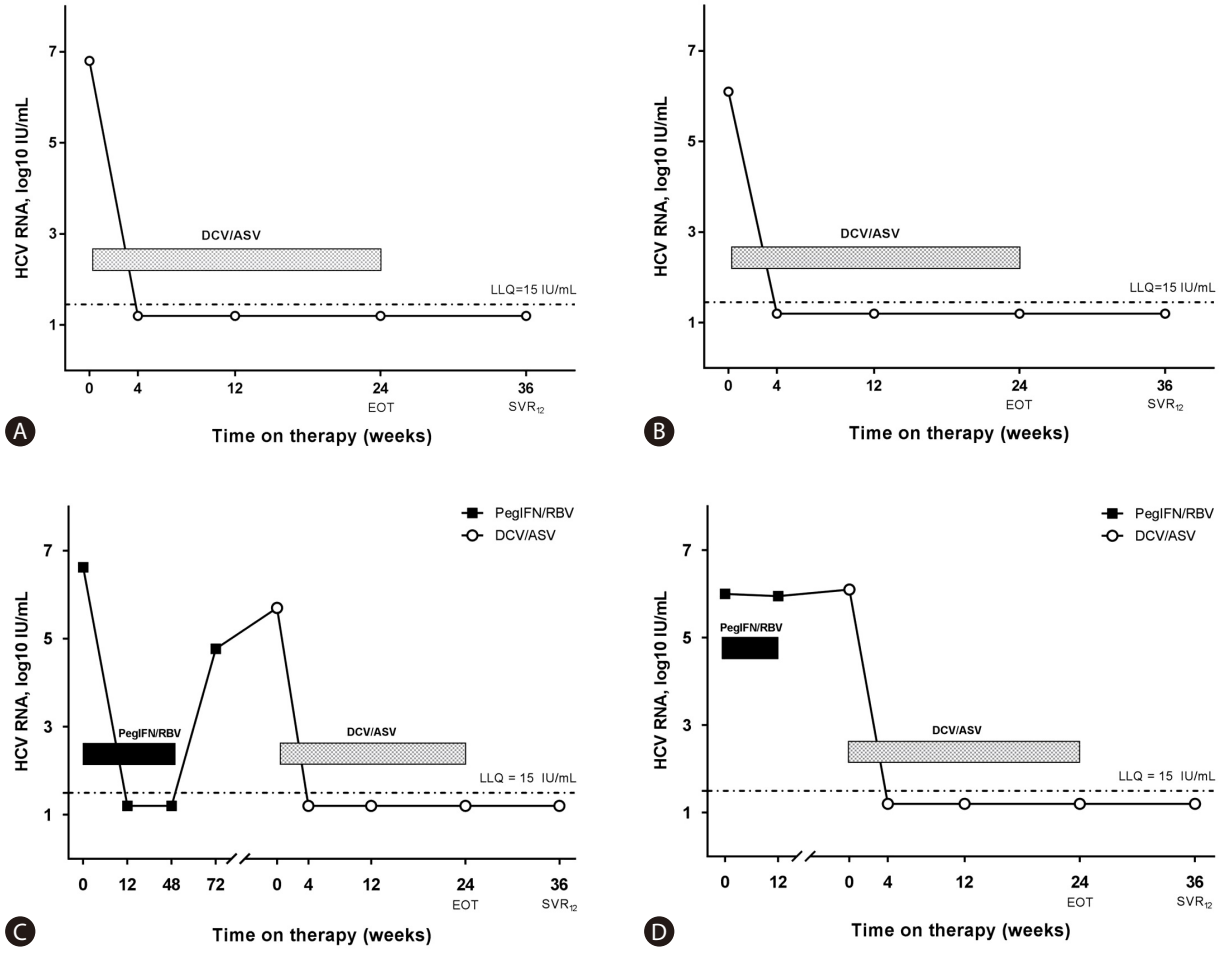

Figure 1. Serum HCV RNA levels of patients during 24 weeks of treatment and at 12 weeks posttreatment. (A) Treatment naïve patient. (B) Treatment naïve patient with advanced age. (C) Patient who relapsed after previous PegIFN/RBV therapy. (D) Patient who had nonresponsiveness to previous PegIFN/RBV therapy. HCV, hepatitis c virus; DCV, daclatasvir; ASV, asunaprevir; LLQ, lower limit of quantitation; PegIFN, pegylated interferon; RBV, ribavirin; EOT, end of treatment; SVR_{12}, sustained virological response at 12 weeks after cessation of treatment.

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Table 2. Clinical laboratory data during treatment*

	Baseline	Week 4†	Week 12†	Week 24†	Week 36†
Leukocyte count (/μL)	3,975.00 (949.81)	362.50 (261.14)	197.14 (196.17)	571.43 (350.32)	1,583.33 (875.75)
Neutrophil count (/μL)	1,870.00 (621.43)	81.25 (191.55)	37.14 (156.02)	277.14 (224.54)	1,390.00 (855.05)
Hemoglobin (g/dL)	13.33 (3.05)	-0.48 (0.41)	-0.31 (0.41)	-0.30 (0.46)	0.50 (0.58)
Platelet count (/μL)	76.38 (39.98)	18.25 (15.48)	15.71 (18.16)	14.57 (11.01)	10.17 (2.63)
INR	1.04 (0.06)	0.01 (0.01)	0.01 (0.01)	0.06 (0.09)	-0.04 (0.02)
Total bilirubin (mg/dL)	0.78 (0.21)	0.21 (0.11)	-0.03 (0.08)	0.94 (0.98)	-0.03 (0.08)
AST (IU/L)	74.50 (42.52)	-31.50 (19.53)	-41.43 (16.44)	-34.29 (22.46)	-49.17 (17.63)
ALT(IU/L)	36.00 (12.66)	-20.63 (5.96)	-14.14 (7.62)	5.71 (23.79)	-20.33 (6.82)
Creatinine (mg/dL)	0.74 (0.14)	0.02 (0.03)	0.02 (0.03)	0.07 (0.04)	0.13 (0.04)
APRI	4.32 (4.79)	-3.30 (1.72)	-3.74 (1.82)	-3.53 (1.59)	-2.27 (1.16)

INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST to platelet ratio index.
*Data are baseline mean value (standard deviation) or mean change from baseline (standard error).
†Data are mean change from baseline to treatment weeks.

(Fig. 1C, D). The patients in Figure 1A and 1B were treatment naïve. Patient in Figure 1A was a 54 year old male and his baseline HCV RNA level was 5,910,000 IU/mL. Figure 1B shows a female patient with advanced age (73 years old) and her baseline HCV RNA level was 1,080,000 IU/mL. We found that DCV/ASV regimen can achieve prompt reduction in HCV RNA titers and sustain virological response in patients with advanced age. Patient in Figure 1C had been treated with PegIFN/RBV regimen, and HCV RNA level was sustained undetectable during 48 weeks of the treatment period. But, HCV reappeared at the time of 72 weeks after the PegIFN/RBV therapy initiation. Patient in Figure 1D shows nonresponsiveness to previous 24 weeks of PegIFN/RBV therapy. Figure 1C and 1D provide favorable virological response of the DCV/ASV therapy in patients with relapsed/nonresponded to previous PegIFN/RBV treatment. Consequently, DCV/ASV achieved rapid decrease of HCV RNA level below the lower limit of quantitation within 4 weeks of treatment, even though enrolled patient had poor prognostic factor such as advanced age, unsuccessful outcome to previous PegIFN/RBV.

Biochemical response

Table 2 shows clinical laboratory data during the treatment. Patients achieved favorable biochemical response with the treatment. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels reduced after the treatment initiation and sustained throughout the treatment; mean reduction of ALT level at week 4 was 20.63 U/L. AST to platelet ratio index (APRI), which is widely used as a noninvasive predictive factor for fibrosis and cirrhosis in chronic hepatitis C patients,[19] decreased with the treatment.

Safety

The most frequently reported adverse events were mild grade of nausea and dizziness, which were controlled by supportive management or medication. Two patients experienced treatment related serious adverse events (see below). None of the grade 3 or 4 laboratory abnormalities occurred in the rest of 6 patients. Most importantly, hemoglobin level was maintained consistently (Table 2). No single patient required transfusion due to DCV/ASV therapy. Also, white blood cell count (WBC) and neutrophil count did not decrease after the DCV/ASV therapy.

Two serious adverse events were reported along the treatment duration, including hepatic decompensation and AST flare up. A 68 year old female patient experienced hepatic decompensation. Her HCV RNA was undetectable at week 4 till week 12 and she did not complain of significant symptoms except for mild abdominal discomfort throughout the treatment. At week 15, she was hospitalized due to the development of jaundice and ascites. Laboratory findings revealed total bilirubin 7.8 mg/dL, AST 102 IU/L, ALT 179 U/L and Albumin 3.2 g/dL. Her liver dynamic CT scan showed moderate amount of ascites (Fig. 2). Both total bilirubin and transaminase elevations were improved after discontinuation of DCV/ASV therapy. HCV RNA was undetectable and sustained for follow up period.

The other adverse event was associated with serum AST flare up (Fig. 3). In 82 year old female, HCV RNA was undetectable

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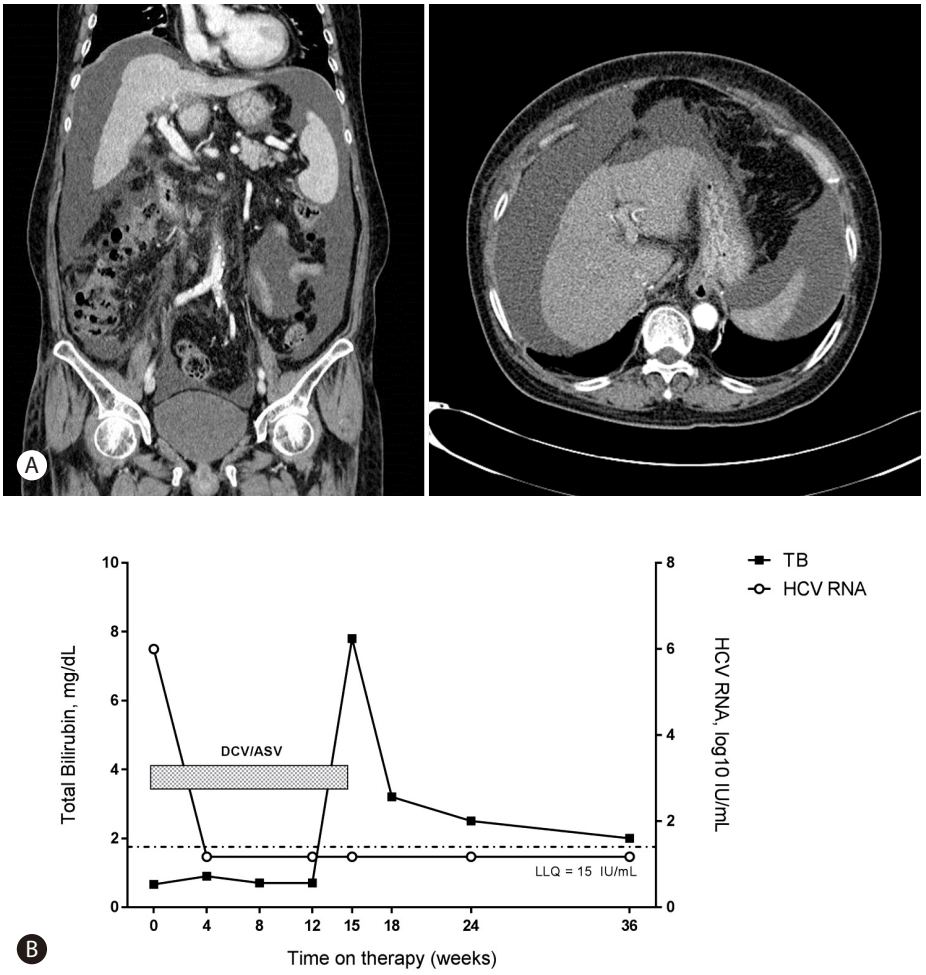

Figure 2. Liver dynamic CT scan (A) and clinical course (B) of a patient who experienced hepatic decompensation during DCV and ASV treatment. HCV, hepatitis c virus; RNA, ribonucleic acid; DCV, daclatasvir; ASV, asunaprevir; LLQ, lower limit of quantitation; TB, total bilirubin.

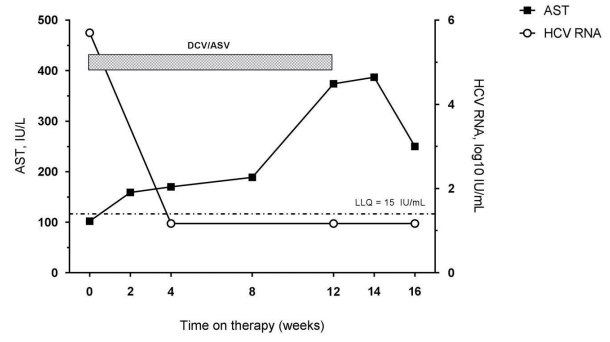

Figure 3. Clinical course of a patient who showed AST flare up during DCV and ASV treatment. AST, aspartate aminotransferase; HCV, hepatitis c virus; RNA, ribonucleic acid; DCV, daclatasvir; ASV, asunaprevir; LLQ, lower limit of quantitation.

(<15 IU/ml) at week 4 till 12 and she complained of generalized weakness during the DCV/ASV therapy. The baseline AST and ALT levels were 102 IU/L and 42 IU/L, respectively. Following the treatment initiation, AST level increased from 170 IU/L to 374 IU/L at week 4 and 12, respectively. Because of AST flare up, antiviral therapy was discontinued at week 12 and AST level became decreased during follow-up. HCV RNA was still undetectable even at 4 weeks after the cessation of DCV/ASV.

DISCUSSION

This is the first report evaluating the efficacy of interferon and ribavirin free regimen composed only of oral agents including DCV and ASV in chronic HCV GT 1b patients in real-life practice in Korea. Patients with HCV GT 1b carried a higher risk for advanced liver disease such as cirrhosis or HCC than those with non-1b GTs (GTs 2, 3, 4, and 6).[20] HCV 1b is an independent risk factor of HCC and patients with HCV GT 1b had a greater life-time cumulative risk for HCC development than those with non-1b GTs.[21] HCV

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GT 1b is the most prevalent subtype in Korea that proportion of the GT 1b is up to 45.4%.[4,20] Korea shares the similar trend with Japan toward GT1b being the predominant HCV genotype and DCV with ASV combination therapy is widely used in real-life practice in Japan. DCV and ASV recently been approved for the treatment of HCV infected patients in Korea. In our study, Korean patients with HCV GT 1b infection showed promising outcomes.

Patients who had no response or a partial response to previous therapy and those with liver cirrhosis are particularly difficult to cure.[22-24] Furthermore, patients with cirrhosis are frequently contraindicated for PegIFN due to anemia, renal insufficiency, or thrombocytopenia.[16] Therefore, the need for interferon-free regimen consisting of DAAs such as DCV and ASV is increasing among the patients with cirrhosis. The combination of DCV and ASV achieved 87% SVR_{12} rate in chronic hepatitis C patients with GT 1b and cirrhosis in previous study.[13] In this study, DCV and ASV treatment provided 88% SVR_{12} rates, despite the fact that all enrolled patients had underlying liver cirrhosis. Even in patients with poor responsive factors such as advanced age, obesity, and failed response to previous PegIFN/RBV treatment, SVR_{12} were achieved. In addition, there was neither a virological breakthrough nor a relapse during and after the treatment in this study. Meanwhile, some previous studies report 3% to 13% of virological breakthrough in patients with DCV and ASV therapy.[12-15]

In this study, serum AST, ALT levels and APRI decreased and the values were sustained during the treatment. These findings represent recovery of liver injury. Also, platelet count tends to increase with the treatment, which might be associated with improvement of portal hypertension. Successful treatment of HCV can provide prevention of the disease progression, cirrhosis regression and improvement of survival rates.[25]

Few years ago, HCV protease inhibitors such as telaprevir, boceprevir were introduced for HCV treatment. HCV protease inhibitors in combination with PegIFN and RBV, achieved higher SVR rates than conventional PegIFN/RBV that 68% to 89% SVR rates in treatment-naïve patients with HCV GT 1.[22,26-28] However, prevalence and severity of adverse events increased to the greater extent in patients with PegIFN/RBV and HCV protease inhibitor combination therapy than that in patients with PegIFN/RBV alone.[22,26-28] We found that the combination of two highly potent DAAs such as DCV and ASV showed significantly higher SVR rates and low adverse events than HCV protease inhibitors with PegIFN/RBV therapy.

Patients with cirrhosis had more side effects related to interferon based therapy than in those without cirrhosis.[27,29,30] The most troublesome side effect of interferon based regimen was hematologic abnormalities that led to dose reduction or discontinuation of therapy, and resulting suboptimal virological response.[3,30,31] Furthermore, hematologic adverse events, including anemia, neutropenia and thrombocytopenia were more common in patients with cirrhosis than in those without cirrhosis in PegIFN/RBV based therapy.[3,30,31] However, DCV and ASV were well tolerated in patients with and without compensated cirrhosis.[15,16] In the previous clinical trial, the incidence of grade 3 or 4 laboratory abnormalities in patients who treated with DCV/ASV were as follows: Neutropenia (1%), ALT elevation (2%), and AST elevation (2%), respectively.[15] By the most recently introduced guidelines, a 10-fold increase in ALT activity should prompt discontinuation of DAAs therapy.[8] And DCV/ASV therapy provided only 1% of patients with more than 10-fold increase of ALT levels that leading to discontinuation.[15] In this study, there was no significant decreases in hemoglobin level, WBC, neutrophil, and platelet counts during the treatment. Two patients experienced treatment related adverse events with hepatic decompensation and AST flare up. Despite adverse events occurred in these particular cirrhosis patients, safety profile of the DCV/ASV therapy seems to be more favorable than that of PefIFN/RBV. We need to pay close attention to safety issues concerning DCV/ASV treatment especially in those with old age and cirrhosis.

Limitations of this study include a relatively small number of patients enrolled and lack of NS5A mutation. In previous study, DCV/ASV therapy achieved 90% to 100% rates of SVR_{12} with the absence of NS5A resistance-associated variants (RAV).[32] However, patients who did not achieved SVR with DCV/ASV had a higher frequency of baseline NS5A RAV as compared to those who achieved SVR.[15] In Japanese study, 11.2% of HCV GT 1b infected patients have the RAV associated with strong resistance to the DCV and 0.4% of patients have variant that confer resistance to both of NS3 protease inhibitor and NS5A inhibitor.[33] Therefore, Baseline NS5A mutation test is important before the treatment initiation of DCV and ASV.

In conclusion, this all-oral, interferon and ribavirin free treatment of DCV and ASV is very effective and safe in real-life practice. DCV and ASV achieved SVR with low adverse events in patients with cirrhosis, previous nonresponsive to or relapsed after PegIFN/RBV. These results suggest that DCV and ASV combination therapy could be the effective treatment option in HCV genotype 1b patients, especially those ineligible or intolerant to interferon-based therapy.

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Conflicts of Interest

The authors have no conflicts to disclose.

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