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Assessing the Effectiveness and Safety of Direct-acting Antiviral Treatment in Korean Patients with Hepatitis C Virus Genotype 1b or 2 at a Tertiary Care Hospital

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ABSTRACT

Background: Direct-acting antivirals are recommended for the treatment of chronic hepatitis C virus in Korea. However, evaluation of direct-acting antiviral regimens in a real-world setting is limited. The aims of this study were to investigate the effectiveness and safety of direct-acting antiviral treatment in Korean patients infected with chronic hepatitis C virus genotype 1b or 2 at a tertiary care hospital. **Methods:** This was a retrospective study conducted with patient data obtained between August 2015 and August 2019 at Jeonbuk National University Hospital. The primary effectiveness endpoint was sustained virological response 12 weeks post-treatment (SVR12) via intention-to-treat (ITT) and modified intention-to-treat (mITT) analyses. **Results:** Of the 270 patients, 47.0% were infected with genotype 1b and 53.0% with genotype 2. ITT analysis revealed that SVR12 was achieved in 78.9% of all patients, 77.2% in genotype 1b patients, and 80.4% in genotype 2 patients. Of the 21.1% of all patients who did not achieve SVR12, the majority of treatment failures were non-virologic failures (19.7%). mITT analysis revealed that SVR12 was achieved in 98.2% of all patients, 98.0% in genotype 1b patients, and 98.3% in genotype 2 patients. Almost half of all patients experienced one or more adverse events (43.3%), leading to 2.6% discontinuing scheduled treatment. The most common adverse event was anemia. **Conclusions:** Direct-acting antiviral-based treatment regimens showed high effectiveness and safety. Non-virological factors, such as premature treatment discontinuation due to adverse events or loss of follow-up, were the major disruptors in achieving SVR12.

KEYWORDS: Direct-acting antiviral treatment, effectiveness, hepatitis C virus, safety, sustained virological response (SVR)

Hepatitis C caused by the hepatitis C virus (HCV) is an infectious disease leading to acute or chronic liver damage.[1,2)] Acute HCV infection is generally asymptomatic and can spontaneously resolve within 6 months without any antiviral treatments in approximately 15-45% of cases.[2)] However, the remaining cases may develop chronic HCV infection, if appropriate treatments are not given, and may result in advanced liver damage (such as liver cirrhosis and hepatocellular carcinoma [HCC]) and even death.[2)]

According to the World Health Organization (WHO), the prevalence rate of HCV infections in 2015 was approximately 1%, indicating that 71 million individuals had been living with HCV infections worldwide.[3)] In addition, new HCV infections occurred in 1.75 million people globally in 2015.[3)] Its current prevalence rate in the Korean population is between 0.6% and 0.8%, and the major HCV genotypes (GTs) found in Korean patients are GT 1b and 2.[4)]

Pegylated interferon (pegIFN) and ribavirin (RBV) have

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been primarily used for HCV treatments; however, the uses of these agents have been restricted due to low efficacy and frequent adverse events (AEs).[5] Thus, treatments for HCV infections are shifting to pegIFN-free therapy such as direct-acting antivirals (DAAs).[5,6] The pegIFN-free regimens lead to greater efficacy and better tolerability than the older regimens, providing various treatment options for patients who experience therapeutic failure or have been contraindicated with pegIFN+RBV.[6,7] In addition, these regimens not only shorten the duration of treatment to 12-24 weeks, but also improve HCV cure rates to greater than 90%.[2,6]

The recent WHO clinical practice guideline also recommends DAA regimens for the treatment of HCV infection as to regimens with pegIFN+RBV.[2] Specifically recommended are different combinations of sofosbuvir (SOF) and other DAAs (e.g., daclatasvir [DCV] and ledipasvir [LDV]) with or without RBV, depending on cirrhosis status and HCV GT.[2] In addition, additional studies have been conducted to provide improved therapeutic outcomes and shorter treatment courses.[8-11] According to the clinical trial conducted by Zeuzem et al., glecaprevir (GLE)/pibrentasvir (PIB) for 8 or 12 weeks showed high rates of sustained virologic response (SVR) ranging from 95 to 100% in non-cirrhotic patients with GT 1 or 3, 12 weeks post-treatment (sustained virological response 12 weeks post-treatment [SVR12]).[8] Other studies have also showed that SOF/velpatasvir (VEL)/voxilaprevir (VOX) for 8 or 12 weeks resulted in high rates of SVR12 ranging from 95 to 100% in treatment-naive (TN) and treatment-experienced (TE) patients with GT 1, 2, or 3.[9,10]

However, the high rates of SVR12 reported in controlled clinical trials may not reflect a real-world setting. In addition, Korean HCV guidelines have changed rapidly according to the timing of DAA approval in Korea.[12,13] The aims of this study were to investigate the effectiveness and safety of DAA treatment for Korean patients infected with HCV GT 1b or 2 at a tertiary care hospital under a real-world setting.

Methods

Ethics

The Institutional Review Board (IRB) of Jeonbuk National University Hospital (JBUH) granted ethical approval for this study (CUH-2018-03-008). The IRB waived the requirement for informed consent from the study participants since their data were de-identified and encoded anonymously before starting analysis.

Patients and treatment

This retrospective study was conducted with the following patients who had visited JBUH, located at Jeonju in South Korea, between August 2015 and August 2019: 1) patients aged ≥18 years old; 2) patients diagnosed with HCV infection; and 3) patients who had received DAAs for the treatment of HCV infection. The following patients were excluded: 1) patients with HCV GTs other than GT 1b or 2; 2) patients who had received only pegIFN+RBV; and 3) patients who did not complete the antiviral therapy during the study period. In cases of DAA re-treatment, only information about the first treatment was considered in the analysis. The available DAA regimens were DCV/ASV, SOF, LDV/SOF, elbasvir (EBR)/grazoprevir (GZR), ombitasvir/paritaprevir/ritonavir plus dasabuvir (OPr-D), and GLE/PIB. The choice of regimens and the use of RBV were determined by physicians, depending on the practice guidelines and clinical indications in real-world settings.[12,13]

Measurements

A retrospective chart review of the electronic medical records of selected HCV-infected patients were conducted. A trained hospital pharmacist collected the following information: demographic characteristics, prior history of HCV treatment, baseline disease features such as chronic kidney disease (CKD), co-infection with hepatitis B or human immunodeficiency virus, liver cirrhosis, HCC, and other comorbidity and laboratory values. HCV RNA was analyzed using COBAS® HCV Test (Roche Diagnostics Corporation, Indianapolis, IN, United States). Unquantifiable HCV RNA was defined as less than the lower limit of detection of 15 IU/mL. Among cirrhotic patients, Child-Turcotte-Pugh (CTP) class and Model for End-Stage Liver Disease (MELD) were calculated at baseline.[14] Glomerular filtration rate estimation (eGFR) was performed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15]

Assessment and analysis

The primary effectiveness endpoint was SVR12; defined as the unquantifiable HCV RNA level 12 weeks post-treatment. However, SVR12 has also been defined as the undetectable HCV RNA level between 12 and 16 weeks after the completion of treatment in the clinical practice setting. Thus,

HCV RNA levels between 12 and 16 weeks post-treatment were measured to assess SVR12 in this study. Virological failure was considered when SVR12 was not reached due to one of the following cases: 1) no response (unable to achieve undetectable HCV RNA levels during treatment); 2) virological breakthrough (redetection of HCV RNA during treatment after virological response); or 3) relapse (redetection of HCV RNA after treatment was discontinued).[12] Non-virological failure also included discontinuation of treatment due to AEs, treatment interruption due to patient's decision, or missing HCV RNA level measurements due to lack of follow-up (including SVR12 follow-up loss due to HCC incidence or death).[16,17] Primary analysis was an intention-to-treat (ITT) assessment based on the initial treatment assignment, considering all patients who received at least one dose of the treatment medicine. The secondary analysis was a modified intention-to-treat (mITT) assessment where patients who did not achieve SVR12 due to non-virologic reasons (such as AEs and loss to follow-up) were excluded.[16,17]

The yearly use patterns of various DAA regimens were also evaluated during the study period. Referring to previous studies, clinical laboratory values performed in JBUH were compared before and after DAA treatments according to HCV GTs.[9,10,16] Safety was evaluated with spontaneous AE reporting obtained via clinical assessment and laboratory data based on the types of HCV treatment regimens. Anemia was defined as hemoglobin (Hgb) levels below 10 g/dL. Decompensated liver cirrhosis was defined according to the occurrence of varix bleeding, ascites, hepatic encephalopathy, or any other liver-related clinical event requiring hospitalization. The incidences of HCC during or after DAA treatments were also monitored during the study period.

Statistical analyses

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). The mean and standard deviation (SD) were used for continuous variables, whereas frequencies (n) and percentages (%) were used to present categorical variables. The Wilcoxon rank sum test or two sample t-test was utilized to compare the differences in means of continuous variables, and the Wilcoxon signed rank test or paired t-test was used to evaluate the differences in the means of the laboratory values before and after DAA treatments. The Chi-square test or Fisher's exact test was also applied to compare the differences in the proportions of the categorical variables. P-value <0.05 was considered statistically significant.

Results

Characteristics of patients

During the study period, 297 patients were diagnosed with chronic HCV infections and treated with antivirals. Of those, 270 met our criteria and were included in our analysis (Fig. 1). The baseline characteristics of the patients are summarized in Table 1. The mean age of all patients was 61.2±11.5 years, and 161 (59.6%) were females. Liver cirrhosis were found in 73 (27%) of the patients, and most of the cirrhotic patients were categorized as CTP class A. pegIFN+RBV was administered to 49 (18.1%) of the patients prior to DAA initiation. Two (0.7%) received liver transplants and 12 (4.4%) had a history of HCC.

Use patterns of DAAs

The use patterns of DAA regimens are presented according to HCV GTs and year of prescription in Table 2. Of the 127 patients with GT 1b, DCV+ASV were prescribed to 61 (48%) of the patients. EBR/GZR were prescribed to 35 (27.6%) of the patients, and LDV/SOF were prescribed to 23 (18.1%) of the patients. GLE/PIB and OPr-D were prescribed to 6 (4.7%), and 2 (1.6%) of the patients respectively. Looking at the year-to-year treatment patterns from 2015, when DAA treatments first started at JBUH, all 21 patients received DCV+ASV in 2015. However, DCV+ASV has gradually decreased over the years and has not been prescribed since 2018. EBR/GZR was utilized since 2017 and has the highest prescription rate of 66.7% in 2018. This prescription rate has decreased in 2019. LDV/SOF (±RBV) was used since 2016 and was prescribed for 8, 12, and 24 weeks depending on cirrhotic status or prior PR treatments. In the treatment for GT 2, SOF+RBV has been used since 2016 and prescribed to 132 (92.3%) of 143 patients over the entire study period. However, with the introduction of GLE/PIB in 2019, GLE/PIB was prescribed more often (66.6%) than the SOF+RBV.

Virological effectiveness (SVR12)

The results of SVR12 and treatment failure are summarized according to HCV GTs and treatment regimens in Table 3. ITT analysis showed 213 (78.9%) out of 270 patients achieved SVR12. Of the 57 (21.1%) patients who did not achieve SVR12, virologic failure occurred in 4 (1.4%) patients, and

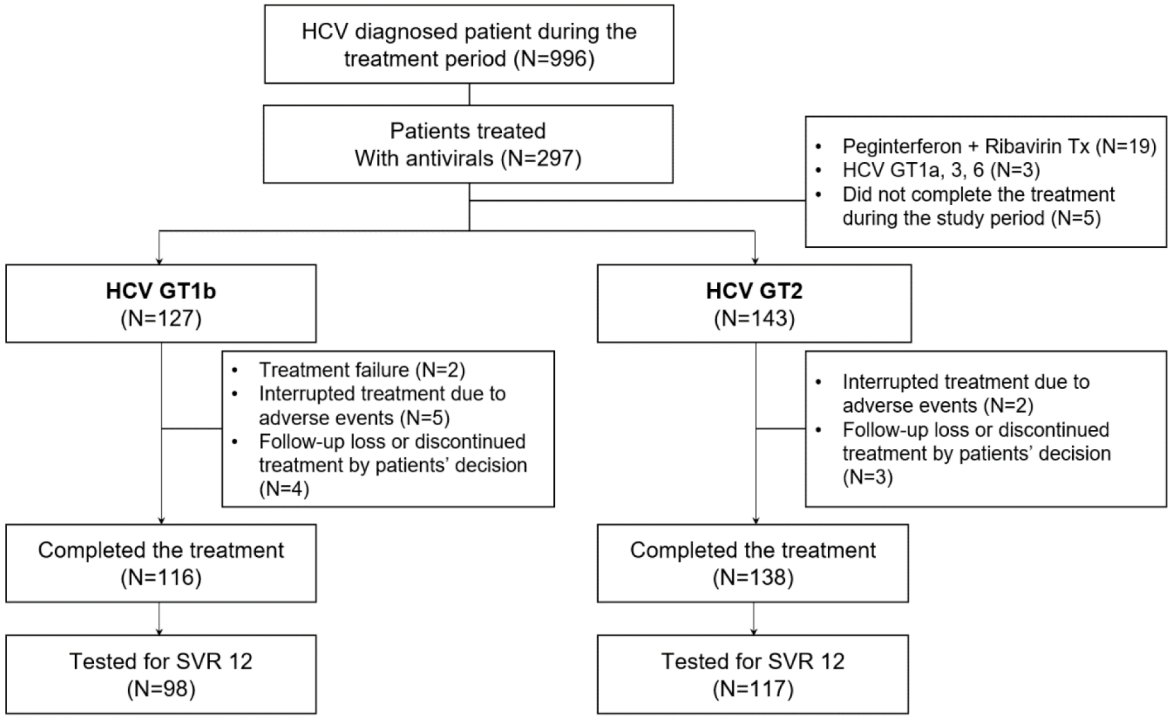

Fig. 1. Flow diagram of steps in the selection of study subjects.
HCV, hepatitis C virus; GT, genotype; SVR, sustained virological response; Tx, treatment

non-virologic failure took place in 53 (19.7%) patients. As a result, 213 (98.2%) out of 217 patients achieved SVR12 in the mITT analysis. Among the 127 patients with GT 1b, non-response occurred in 2 (1.6%) patients, and 27 (21.3%) patients experienced non-virologic failure. SVR12 was achieved in 77.2% of patients in the ITT analysis and in 98.0% of patient in the mITT analysis. Out of 143 patients with GT 2, 2 (1.4%) experienced relapse after completing the treatment, and 26 (18.2%) had non-virologic failure. SVR12 was achieved in 80.4% of patients in the ITT analysis and in 98.3% of patients in the mITT analysis. A subset of patients (39) completed the treatment but achieved SVR at other weeks (range: week 4-136). All the patients achieved SVR; however, end-of-treatment response (ETR) was measured in 20 of the patients.

Biochemical responses

The differences in the laboratory values between pre- and post-treatment are summarized in Table 4. After the DAA treatments, the mean levels of Hgb, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were significantly decreased. Meanwhile, the mean levels of platelets, international normalized ratio (INR), total bilirubin, albumin, and total cholesterol were significantly increased. In addition, significant changes were shown in white blood cell (WBC), AST, ALT, albumin, and total cholesterol in patients with GT 1b. Patients with GT 2 showed significantly decreased levels of WBC, Hgb, ALP, AST, and ALT, while platelet, INR and total bilirubin levels were significantly increased.

Safety assessment

The safety assessment results are illustrated in Table 5. A total of 117 (43.3%) patients experienced one or more AEs during treatment. Seven (2.6%) of the patients had AEs that lead to premature discontinuation of the scheduled treatment. When analyzing the data according to DAA regimens, AEs most frequently occurred in patients receiving LDV/SOF+RBV (83.3%), followed by SOF+RBV (51.5%), DCV+ASV (49.2%), LDV/SOF (27.8%), GLE/PIB (18.8%), and EBR/GZR (17.1%). The most common AE was anemia which occurred in 33.3% and 25.8% of patients receiving LDV/SOF+RBV and SOF+RBV respectively. Results with regard to the incidence of HCC after DAA-based treatments are summarized in Table 6.

Table 1. Baseline characteristics of the patients included in the study

Characteristics	Total patients (n=270)	GT 1b (n=127)	GT 2 (n=143)	*p*-value
Age (year)	61.2±11.5	59.6±10.1	62.6±11.8	0.011
Sex, n (%)				
Male	109 (40.4)	51 (40.2)	58 (40.6)	0.946
Female	161 (59.6)	76 (59.8)	85 (59.4)	
BMI (kg/m^2)	23.6±3.3	23.4±3.3	23.8±3.3	0.458
Drinking, n (%)				
Yes	60 (22.2)	25 (19.7)	35 (24.5)	0.403
No	131 (48.5)	67 (52.8)	64 (44.8)	
Unknown	79 (29.3)	35 (27.6)	44 (30.8)	
Comorbidity, n (%)				
Hypertension	79 (29.3)	37 (29.1)	42 (29.4)	0.966
Diabetes mellitus	59 (21.9)	34 (26.8)	25 (17.5)	0.065
Gastritis, GERD	33 (12.2)	17 (13.4)	16 (11.2)	0.582
Dyslipidemia	15 (5.6)	11 (8.7)	4 (2.8)	0.036
CKD (eGFR <30 mL/min per 1.73 m^2)	9 (3.3)	9 (7.1)	0 (0.0)	0.001
Thyroid dysfunction	9 (3.3)	6 (4.7)	3 (2.1)	0.314
BPH	7 (2.6)	6 (4.7)	1 (0.7)	0.054
Stroke	7 (2.6)	2 (1.6)	5 (3.5)	0.452
Ischemic heart disease	6 (2.2)	2 (1.6)	4 (2.8)	0.687
Anemia	4 (1.5)	4 (3.1)	0 (0.0)	0.048
CHC treatment experienced, n (%)				
Naïve	221 (81.9)	96 (75.6)	125 (87.4)	0.012
PR Experienced	49 (18.1)	31 (24.4)	18 (12.6)	
Liver cirrhosis, n (%)	73 (27.0)	35 (27.6)	38 (26.6)	
Child-Turcotte-Pugh A	67 (24.8)	32 (25.2)	35 (24.5)	1.000
Child-Turcotte-Pugh B	6 (2.2)	3 (2.4)	3 (2.1)	
Child-Turcotte-Pugh C	0 (0.0)	0 (0.0)	0 (0.0)	
MELD	9.3±2.7	10.0±3.6	8.8±1.6	0.387
Liver transplantation, n (%)	2 (0.7)	1 (0.8)	1 (0.7)	1.000
Previous history of HCC	12 (4.4)	5 (3.9)	7 (4.9)	0.703
HCV RNA ($\log_{10}$ IU/ml)	5.8±1.1	6.0±0.8	5.6±1.2	0.003
NS5A mutation, n (%)				
Yes	20 (7.4)	20 (15.7)	0 (0.0)	<0.001
No	65 (24.1)	61 (48.0)	4 (2.8)	
Unknown	185 (68.5)	46 (36.2)	139 (97.2)	
Baseline lab data				
WBC (10^3 /μL)	5.6±2.0	5.5±1.8	5.6±2.2	0.858
Hemoglobin (g/dL)	13.6±1.5	13.6±1.7	13.6±1.4	0.842
Platelet (10^3/μL)	174.2±69.8	168.4±71.6	179.2±68.1	0.132
INR	1.1±0.2	1.1±0.2	1.1±0.2	0.122

Table 1. Continued

Characteristics	Total patients (n=270)	GT 1b (n=127)	GT 2 (n=143)	*p*-value
ALP (IU/L)	84.5±33.0	84.7±33.5	84.3±32.7	0.778
AST (IU/L)	57.8±41.4	57.7±45.5	57.8±37.5	0.589
ALT (IU/L)	45.7±37.3	40.3±24.9	50.5±45.1	0.328
Total bilirubin (mg/dL)	0.9±0.4	0.9±0.5	0.8±0.4	0.527
Albumin (mg/dL)	4.1±0.4	4.1±0.4	4.2±0.4	0.565
Creatinine (mg/dL)	0.9±1.1	1.1±1.6	0.7±0.2	0.924
eGFR (ml/min/1.73m^2)	93.3±20.8	92.5±26.4	94.1±14.2	0.112
Total cholesterol (mg/dL)	163.4±36.4	162.2±39.1	164.5±34.1	0.235
α-fetoprotein (ng/ml)	12.8±33.1	13.6±34.2	12.2±32.2	0.096

Data presented as mean and standard deviation (SD), unless otherwise noted.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BPH, benign prostatic hyperplasia; CHC, chronic hepatitis C; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate calculated by CKD-EPI equation; GERD, gastroesophageal reflux disease; GT, genotype; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; PR, peg-interferon+ribavirin; WBC, white blood cell.

Table 2. Use patterns of DAA regimens in HCV-infected patients with GT 1b and 2 according to year

DAA regimens	Total (n=127)	2015 (n=21)	2016 (n=38)	2017 (n=38)	2018 (n=18)	2019 (n=12)
GT 1b, n (%)						
DCV+ASV						
24 wk	61 (48.0)	21 (100.0)	26 (68.4)	14 (36.8)	-	-
EBR/GZR						
12 wk	35 (27.6)	-	-	19 (50.0)	12 (66.7)	4 (33.3)
LDV/SOF						
8 wk	1 (0.8)	-	-	-	-	1 (8.3)
12 wk	15 (11.8)	-	6 (15.8)	3 (7.9)	5 (27.8)	1 (8.3)
12 wk+RBV	6 (4.7)	-	5 (13.2)	-	1 (5.6)	-
24 wk	1 (0.8)	-	1 (2.6)	-	-	-
GLE/PIB						
8 wk	6 (4.7)	-	-	-	-	6 (50.0)
OPr-D						
12 wk	2 (1.6)	-	-	2 (5.3)	-	-
DAA regimens	Total (n=143)	2015 (n=0)	2016 (n=56)	2017 (n=31)	2018 (n=41)	2019 (n=15)
GT 2, n (%)						
SOF+RBV						
12 wk	107 (74.8)	-	45 (80.4)	26 (83.9)	34 (82.9)	2 (13.3)
16 wk	25 (17.5)	-	11 (19.6)	5 (16.1)	7 (17.1)	2 (13.3)
GLE/PIB						
8 wk	5 (3.5)	-	-	-	-	5 (33.3)
12 wk	5 (3.5)	-	-	-	-	5 (33.3)
LDV/SOF						
8 wk	-	-	-	-	-	-
12 wk	1 (0.7)	-	-	-	-	1 (6.7)

ASV, asunaprevir; DAA, direct acting antiviral; DCV, daclatasvir; EBR/GZR, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; OPr-D, ombitasvir/paritaprevir/ritonavir plus dasabuvir; RBV, ribavirin; SOF, sofosbuvir; wk, week.

Table 3. Rates of SVR12 and treatment failure after DAA treatments in HCV-infected patients with GT 1b and 2

	Total (n=270)	GT 1b							GT 2			
		Total (n=127)	DCV+ASV (n=61)	EBR/GZR (n=35)	LDV/SOF (n=17)	LDV/ SOF+RBV (n=6)	GLE/PIB (n=6)	OPr-D (n=2)	Total (n=143)	SOF+RBV (n=132)	GLE/PIB (n=10)	LDV/SOF (n=1)
SVR12												
ITT	213 (78.9)	98 (77.2)	45 (73.8)	29 (82.9)	14 (82.4)	3 (50.0)	5 (83.3)	2 (100.0)	115 (80.4)	108 (81.8)	7 (70.0)	-
Virologic failure												
Non-response	2 (0.7)	2 (1.6)	2 (3.3)	-	-	-	-	-	-	-	-	-
Relapse	2 (0.7)	-	-	-	-	-	-	-	2 (1.4)	1 (0.8)	1 (10.0)	-
Non-virologic failure												
AEs	7 (2.6)	5 (3.9)	4 (6.6)	-	-	-	-	-	2 (1.4)	2 (1.5)	-	-
Self-discontinuation	7 (2.6)	4 (3.1)	3 (4.9)	1 (2.9)	1 (5.9)	-	-	-	3 (2.1)	2 (1.5)	-	1 (100.0)
SVR12 follow-up loss	39 (14.4)	18 (14.2)	7 (11.5)	5 (14.3)	2 (11.8)	3 (50.0)	1 (16.7)	-	21 (14.7)	19 (14.4)	2 (20.0)	-
	Total (n=217)	GT 1b							GT 2			
		Total (n=100)	DCV+ASV (n=47)	EBR/GZR (n=29)	LDV/SOF (n=14)	LDV/ SOF+RBV (n=3)	GLE/PIB (n=5)	OPr-D (n=2)	Total (n=117)	SOF+RBV (n=109)	GLE/PIB (n=8)	LDV/SOF (n=0)
SVR12												
mITT	213 (98.2)	98 (98.0)	45 (95.7)	29 (100.0)	14 (100.0)	3 (100.0)	5 (100.0)	2 (100.0)	115 (98.3)	108 (99.1)	7 (87.5)	-

AE, adverse event; ASV, asunaprevir; DCV, daclatasvir; EBR/GZR, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; ITT, intent-to-treat; LDV, ledipasvir; mITT, modified intent-to-treat (excludes non-virologic failures); OPr-D, ombitasvir/paritaprevir/ritonavir plus dasabuvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after the end of treatment.

Table 4. Comparison of clinical laboratory parameters between baseline and end of treatment

Lab parameters	Total			GT 1b			GT 2		
	Baseline	End of treatment	*p*-value	Baseline	End of treatment	*p*-value	Baseline	End of treatment	*p*-value
WBC (10^3/μL)	5.6±2.0	5.3±1.9	0.123	5.5±1.8	5.6±1.9	0.013	5.6±2.2	5.1±1.8	<0.001
Hemoglobin (g/dL)	13.6±1.5	12.5 ±1.8	<0.001	13.6±1.7	13.5±1.7	0.154	13.6±1.4	11.8±1.6	<0.001
Platelet (10^3/μL)	174.2±69.8	193.6±75.3	<0.001	168.4±71.6	173.5±63.1	0.368	179.2±68.1	209.9±80.5	<0.001
INR	1.1±0.2	1.1±0.3	<0.001	1.1±0.2	1.1±0.1	0.957	1.1±0.2	1.2±0.4	<0.001
ALP (IU/L)	84.5±33.0	76.9±25.8	<0.001	84.7±33.5	80.0±27.6	0.380	84.3±32.7	74.3±24.1	<0.001
AST (IU/L)	57.8±41.4	28.5±15.9	<0.001	57.7±45.5	28.5±17.6	<0.001	57.8±37.5	28.4±14.4	<0.001
ALT (IU/L)	45.7±37.3	24.3±16.3	<0.001	40.3±24.9	24.8±15.3	<0.001	50.5±45.1	23.9±17.1	<0.001
Total bilirubin (mg/dL)	0.9±0.4	1.0±0.5	<0.001	0.9±0.5	0.9±0.4	0.058	0.8±0.4	1.0±0.5	<0.001
Albumin (mg/dL)	4.1±0.4	4.2±0.3	0.008	4.1±0.4	4.3±0.3	<0.001	4.2±0.4	4.2±0.3	0.704
Creatinine (mg/dL)	0.9±1.1	0.8±0.9	0.834	1.1±1.5	1.0±1.3	0.401	0.7±0.2	0.7±0.2	0.518
eGFR (mL/min/1.73 m^2)	93.3±20.8	92.8±19.8	0.438	92.5±26.4	90.3±25.8	0.191	94.1±14.2	94.9±12.5	0.897
Total cholesterol (mg/dL)	163.4±36.4	169.5±39.3	0.028	162.2±39.1	179.6±42.6	<0.001	164.5±34.1	161.0±34.1	0.485

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate calculated by CKD-EPI equation; GT, genotype; INR, International normalized ratio; WBC, white blood cell.

Table 5. Adverse events and laboratory abnormalities by DAA regimens

Adverse events	Total (n=270)	DAA regimens						
		SOF+RBV (n=132)	DCV+ASV (n=61)	EBR/GZR (n=35)	LDV/SOF (n=18)	GLE/PIB (n=16)	LDV/SOF+RBV (n=6)	OPr-D (n=2)
Any AE, n (%)	117 (43.3)	68 (51.5)	30 (49.2)	6 (17.1)	5 (27.8)	3 (18.8)	5 (83.3)	-
AE leading to discontinuation, n (%)	7 (2.6)	2 (1.5)	4 (6.6)	-	1 (5.6)	-	-	-
Decompensated LC, n (%)	1 (0.4)	-	1 (1.6)	-	-	-	-	-
AE occurring in ≥1% total patients, n (%)								
Anemia[#]	45 (16.7)	34 (25.8)	3 (4.9)	4 (11.4)	1 (5.6)	1 (6.3)	2 (33.3)	-
Dizziness	15 (5.6)	11 (8.3)	2 (3.3)	1 (2.9)	1 (5.6)	-	-	-
Headache	12 (4.4)	6 (4.5)	6 (9.8)	-	-	-	-	-
Fatigue	11 (4.1)	10 (7.6)	-	-	-	-	1 (16.7)	-
Abdominal pain/discomfort	10 (3.7)	6 (4.5)	3 (4.9)	1 (2.9)	-	-	-	-
Decreased appetite	9 (3.3)	7 (5.3)	2 (3.3)	-	-	-	-	-
Pruritus/itching	8 (3.0)	2 (1.5)	5 (8.2)	-	-	-	1 (16.7)	-
Nausea	5 (1.9)	5 (3.8)	-	-	-	-	-	-
Constipation	4 (1.5)	4 (3.0)	-	-	-	-	-	-
Weakness	4 (1.5)	1 (0.8)	2 (3.3)	-	1 (5.6)	-	-	-
Diarrhea	3 (1.1)	2 (1.5)	-	-	-	1 (6.3)	-	-

AE, adverse event; ASV, asunaprevir; DAA, direct acting antiviral; DCV, daclatasvir; EBR/GZR, elbasvir/grazoprevir; GLE/PIB, glecaprevir/pibrentasvir; LC, liver cirrhosis; LDV, ledipasvir; OPr-D, ombitasvir/paritaprevir/ritonavir plus dasabuvir; RBV, ribavirin; SOF, sofosbuvir.
[#]Anemic patients at baseline were included: 1 in DCV+ASV, 2 in EBR/GZR, and 1 in GLE/PIB.

Table 6. Incidence of HCC after DAA treatments in HCV-infected patients with GT 1b and 2

No	Age	Sex	GT	Prior HCV Tx	Liver Cirrhosis (Y/N)	CTP class	MELD score	AFP (ng/mL)	HCC Treatment Maneuver	Treatment regimen	Time to HCC incidence after end of treatment
HCC occurrence											
1	75	M	2	-	N	-	-	3.9	-	SOF+R, relapse ETR (+) after GLE/PIB	1 month after GLE/PIB
2	76	M	1b	-	N	-	-	66.1	-	DCV+ASV SVR12 (+)	21 months
3	65	M	1b	PR	Y	A	8	12.5	-	LDV/SOF+RBV SVR12 (+)	26 months
4	74	M	2	PR	Y	A	10	3.7	-	SOF+RBV Incomplete, AE	22 months
5	58	M	2	-	Y	A	7	51.5	-	SOF+RBV SVR12 (+)	20 months
6	66	M	1b	-	Y	A	12	42.7	-	DCV+ASV Incomplete, F/U loss	15 months
7	66	F	2	-	Y	A	9	11.1	-	SOF+RBV ETR (+)	1 months
HCC recurrence											
1	68	M	1b	PR	Y	A	14	10.3	Surgical resection	LDV/SOF+RBV SVR12 (+)	16 months
2	74	M	1b	-	Y	A	7	5.9	TACE	DCV+ASV SVR12 (+)	17 months
3	56	M	2	-	N	-	-	2.2	Surgical resection	SOF+RBV ETR (+)	2 months
4	75	F	2	-	Y	A	8	5.4	TACE	SOF+RBV ETR (+)	At the end of treatment
5	74	M	2	-	Y	B	13	85.6	RFA	SOF+RBV SVR12 (+)	2 months
6	73	M	1b	-	Y	B	14	2.4	Surgical resection, TACE, RFA	LDV/SOF+RBV ETR (+)	On treatment

AE, adverse event; AFP, α-fetoprotein; ASV, asunaprevir; CTP, Child-Turcotte-Pugh; DAA, direct acting antiviral; DCV, daclatasvir; ETR, end-of-treatment response; F, female; GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; M, male; MELD, model for end stage liver disease; N, no; PR, peg-interferon+ribavirin; RBV, ribavirin; RFA, radio-frequency ablation; SOF, sofosbuvir; SVR12, sustained virological response at 12 week; TACE, transarterial chemoembolization; Tx, treatment; Y, yes.

Discussion

In this study, the effectiveness and safety of DAA treatments were evaluated for Korean patients infected with HCV GT 1b or 2 in a real-life setting. The results showed the SVR12 rate for all patients to be 78.9% and 98.2% in the ITT and mITT analyses, respectively. Similar results were reported when the data was analyzed based on HCV GTs. Most treatment failures resulted from non-virologic reasons such as premature treatment discontinuations, due to AEs, or missing SVR12. One or more AEs occurred in 43.3% of patients during treatment, and 2.6% prematurely discontinued treatment due to the AEs. The most prevalent AE was anemia that occurred in 33.3 and 25.8% of patients who were receiving LDV/SOF+RBV and SOF+RBV, respectively. Although this study was conducted in a single hospital in Korea, its results reassure the effectiveness and safety of various DAA treatments in the real-world settings of Asia where results from controlled clinical trials are still rare.[16)]

DCV+ASV for 24 weeks was a preferred choice for the treatment of patients with HCV GT 1b in 2015 and 2016. However, its prescription rate dropped by almost half in 2017, and has not been prescribed since 2018. This trend may be due to a number of reasons. EBR/GZR was introduced to the institution in 2017, and allowed for a shortened duration of treatment from 24 to 12 weeks and had enhanced efficacy and safety outcomes. Thus EBR/GZR not only improved DAA therapy but also reduced the costs of HCV infection treatments. Similar results were reported in a previous study, wherein Chen and colleagues reported EBR/GZR to be more cost-effective, compared to DCV+ASV, in the treatment of Chinese patients infected with HCV GT 1b.[18)] GLE/PIB was first added to the hospital formulary in December 2018 and was prescribed to half of the patients infected with HCV GT 1b in 2019. This attributed to its pan-genotypic property and shortening of treatment duration from 12 to 8 weeks.[19)] SOF+RBV were mostly prescribed to patients infected with HCV GT 2 between 2016 and 2018. However, GLE/PIB was predominantly prescribed in 2019, probably due to its advantages for broad coverage against all GTs and treatment duration.[19)]

Overall, the proportion of the patients who achieved SVR12 were lower when evaluated via ITT analysis (78.9%) than via mITT analysis, where non-virologic failures were excluded to calculate SVR12. Based on the mITT analysis, 98.2% of all patients achieved SVR12, which is similar to results reported in other real-life studies and clinical trials.[8,11,16,17,20)] Fifty-three (19.6%) of all patients showed treatment failures secondary to non-virologic reasons. Considering 39 (14.4%) SVR12 follow-up loss patients, 20 (7.4%) patients with ETR reported SVR at various points (week 4-136), instead of week 12, during the follow-up period. Therefore, 26 (9.6%) patients (self-discontinuation, 7 [2.6%]; SVR12 follow-up loss, 19 [7.0%]) could be considered as actual follow-up loss. This loss of follow-up rate is similar to that reported by Darvishian and colleagues (10.1%).[21)] SVR rates in real-world studies are lower due to an inability to follow-up with all patients, as shown in this study, than in well-planned clinical trials. Managing patient adherence to DAAs and monitoring SVR during an extended period after treatment is crucial to achieve a satisfactory SVR rate. Monitoring could be conducted through an interdisciplinary collaboration between healthcare providers including physicians, pharmacists, and nurses.[22,23)]

In spite of DAA's high rate of efficacy in viral clearance; additional host and virus factors (such as liver cirrhosis, prior negative HCV therapy, and resistance associated-substitutions [RASs]) related with virologic failure can induce poor efficacy of DAAs.[24)] In this study, 4 patients experienced treatment failure due to secondary virologic reasons (i.e., non-response and relapse). Two HCV GT 1b-infected patients who were receiving a DCV+ASV regimen for 24 weeks discontinued their treatments at week 12 due to non-response. One of them had a mutation in the non-structural protein 5A (NS5A) gene (L31/Y93H), a prior HCV treatment with pegIFN+RBV, and liver cirrhosis (CTP class A). All of the above is believed to have contributed to treatment failure. Specifically due to the NS5A genetic variant at the L31 or Y93 amino acids, which has shown to reduce the efficacy of DCV+ASV.[25)] After the first treatment failure, she received LDV/SOF+RBV for 12 weeks, but relapse occurred. Thereafter, SOF/VEL/VOX was administered for 12 weeks, and finally resulted in SVR12 achievement. The other GT 1b-infected patient had liver cirrhosis, but had no mutation, or previous HCV treatment. This patient was unreachable after discontinuing the first treatment. The other 2 HCV GT 2-infected patients experienced relapses. One of them, who had prior pegIFN+RBV therapy, achieved ETR after the 8-week treatment with GLE/PIB, but showed relapse at week 16 after treatment. The other patient did not have an underlying disease or previous pegIFN+RBV therapy. He received SOF+RBV for 12 weeks and showed

relapse at week 12 after treatment. Since then, he had received GLE/PIB for 8 weeks and achieved ETR; however, he developed HCC at week 4 after treatment.

The safety assessment results were satisfactory. Although a total of 117 (43.3%) patients experienced at least one AE during treatment, only 7 (2.6%) had AEs leading to premature discontinuation of the scheduled treatment. Specifically, 4 (6.6%) patients, all treated with DCV+ASV, discontinued treatment, due to severe vomiting, headache, fatigue, and decompensated liver cirrhosis, respectively. Two (1.5%) patients, treated with SOF+RBV, discontinued treatment due to nausea and vomiting, and 1 (5.6%) patient, undergoing LDV/SOF treatment, discontinued treatment due to worsening of existing CKD symptoms. The most common AE among all patients was anemia, which occurred in 33.3% of patients undergoing LDV/SOF+RBV and 25.8% of patients with SOF+RBV. Patients with anemia during the RBV treatment reduced their dose or temporarily discontinued it. There were grades 3 or 4 of anemia in 3 patients, of whom 1 were hospitalized due to it. It is thus necessary to pay more attention to patients containing RBV in their DAA regimen. As shown in previous studies,[26] pharmacists may be well-suited to HCV medication counseling regarding AEs due to their knowledge on the pharmacokinetic and pharmacodynamic profiles of the drugs associated with AEs.

In this study, HCC occurred or re-occurred in 13 patients during the follow-up period [median: 14.5 months (range: 0-46)]. Seven out of 258 (2.7%) patients experienced de novo HCC after a median follow-up of 15 months after treatment. This rate was lower than those in previous studies. Conti and colleagues reported that de novo HCC was detected in 9 out of 285 patients (3.2%) with cirrhosis after DAA treatments during the 24-week post-treatment follow-up.[27] In a study conducted by Ravi and colleagues, 6 out of 66 patients (9.1%) with cirrhosis developed de novo HCC within 6 months after completing DAA therapy.[28] However, considering only 73 patients with cirrhosis at baseline, its incidence rate could be approximately 6.8% (5/73). Meanwhile, 12 patients with a history of HCC initiated DAAs after completing HCC treatment (e.g., surgical resection and radiofrequency catheter ablation), of whom 6 (50.0%) had HCC recurrence after a median follow-up of 2 months after treatment. This rate was much higher than those from previous studies. Reig and colleagues reported that 16 out of 58 patients (27.8%), with a history of HCC treatment, experienced recurrent tumor formation after a median follow-up of 6 months from DAA treatment initiation.[29] Another study by Conti and colleagues also reported recurrent HCC in 17 out of 59 patients (28.8%) after a median follow-up of 6 months from DAA treatment completion.[27] This trend can be explained by the following: The sample size of patients in this study was relatively smaller than that of other studies, which was likely to exaggerate the effect of DAAs on recurrent HCC. In addition, the different characteristics of patients in terms of HCC status (i.e., non-early stage HCC and non-curative locoregional therapy) would also be expected to result in higher recurrent rate.[30]

This study has some limitations which should be kept in mind when interpreting the results. The first limitation is the patient representation in this study. Most of the patients are most likely current residents of North Jeolla Province in South Korea where the hospital is situated; thus, it is likely that the patient population underrepresent other areas of South Korea. To overcome this shortcoming, collaborations with other hospitals will be necessary for future studies. Secondly, some patient subgroups had small sample sizes (e.g., patients treated with LDV/SOF and OPr-D); therefore, results from these subgroups should be interpreted with caution. Lastly, information on the DDIs between DAAs and concomitant drugs could not be tried due to limited patient data. In the future study, this issue should be investigated.

In this study, we discuss the change in pattern in DAA regimen use over the years, including DAAs with broad coverage against all GTs (e.g., GLE/PIB). The DAA-based treatment regimens for HCV-infected patients showed high effectiveness and safety. Non-virological factors, such as premature DAA discontinuation due to AEs or a loss to follow-up, were the major causes for preventing achievement of SVR12. Therefore, managing patient compliance to DAAs is required through interdisciplinary collaboration between healthcare providers. The most prevalent AE was anemia, which occurred mainly in patients receiving regimens containing RBV. It is also crucial to identify and manage potential DDIs before initiating DAA-based therapies in order to optimize the efficacy of the treatment and minimize the frequency of AEs due to DDIs.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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