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Original Article

Real-Life Effectiveness and Safety of Glecaprevir/Pibrentasvir for Korean Patients with Chronic Hepatitis C at a Single Institution

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Background/Aims: Glecaprevir/pibrentasvir (G/P) is a combination of direct-acting antiviral agents that is an approved treatment for chronic infections by all six hepatitis C virus (HCV) genotypes. However, there are limited data on the effect of G/P in Korean patients in actual real-world settings. We evaluated the real-life effectiveness and safety of G/P at a single institution in Korea.

Methods: This retrospective, observational, cohort study used sustained virologic response at 12 weeks after treatment completion (SVR12) as the primary effectiveness endpoint. Safety and tolerability were also determined.

Results: We examined 267 individuals who received G/P for chronic HCV infections. There were 148 females (55.4%), and the overall median age was 63.0 years (range, 25 to 87 years). Eighty-three patients (31.1%) had HCV genotype-1 and 182 (68.2%) had HCV-2. A total of 212 patients (79.4%) were HCV treatment-naïve, 200 (74.9%) received the 8-week treatment, 13 (4.9%) had received prior treatment for hepatocellular carcinoma, 37 (13.7%) had chronic kidney disease stage 3 or higher, and 10 (3.7%) were receiving dialysis. Intention to treat (ITT) analysis indicated that 256 (95.9%) achieved SVR12. A modified ITT analysis indicated that SVR12 was 97.7% (256/262). Six patients failed therapy because of posttreatment relapse. SVR12 was significantly lower in those who received prior sofosbuvir treatment (p=0.002) and those with detectable HCV RNA at week 4 (p=0.027). Seventy patients (26.2%) experienced one or more adverse events, and most of them were mild.

Conclusions: These real-life data indicated that G/P treatment was highly effective and well tolerated, regardless of viral genotype or patient comorbidities. **(Gut Liver 2021;15:440-450)**

Key Words: Hepatitis C, chronic; Glecaprevir; Pibrentasvir; Sustained virologic response

INTRODUCTION

There have been recent changes in the treatment of chronic hepatitis C virus (HCV) infections. In particular, there are now several oral direct-acting antiviral (DAA) therapies that do not contain interferon (IFN).[1] More specifically, there are now three pangenotypic DAA regimens (sofosbuvir [SOF]/velpatasvir, SOF/velpatasvir/voxilaprevir, and glecaprevir/pibrentasvir [G/P]) approved for use in Europe and the United States. These regimens are recommended by international guidelines[2,3] because they are highly effective and have favorable safety profiles for patients with all HCV genotypes (GTs).[4-6] An increased availability of a pangenotypic DAA therapy would simplify HCV treatment, but access to some of these treatments is limited in Asia.

G/P is the only one of these regimens that is currently approved in Korea and covered by the Korean National Health Insurance Service.[7] This ribavirin-free medication consist of two pangenotypic DAAs: glecaprevir (which inhibits HCV NS3/4A protease) and pibrentasvir (which inhibits HCV NS5A) and is given as 3 oral doses per day

(100/40 mg per tablet) with food for 8 to 16 weeks, depending on the GT, prior treatment, and the presence of cirrhosis.[6]

Phase II and III registration trials indicated that this treatment provided excellent sustained virologic response at post-treatment week 12 (SVR12, 97.5%) in patients infected with any of the 6 GTs.[8-15] Before this G/P regimen, the only IFN-free DAA regimen for GT2 in South Korea was SOF plus ribavirin. The SOF plus ribavirin regimen had an SVR12 of about 90 to 95%, was associated with adverse events (AEs) and discontinuation due to ribavirin, and could not be administered to individuals who had chronic kidney disease (CKD).[16-18] Notably, the G/P regimen provides a high virologic response, less than 0.1% of patients permanently discontinued treatment because of adverse reactions, and CKD patients, even those undergoing dialysis, can use the G/P regimen.[6]

Although the G/P regimen had excellent efficacy and safety in trials, there are limited data regarding the efficacy of the G/P regimen in the treatment of Korean patients in non-clinical trial settings. In fact, patients treated in everyday practice tend to be older, have more severe hepatic fibrosis, have more comorbidities, often take multiple drugs, and have variable economic status, all of which can affect treatment efficacy and tolerability.[19-21] The present study investigated the efficacy and safety of G/P in a non-clinical trial setting in South Korean, and determined the clinical factors associated with SVR12.

MATERIALS AND METHODS

This retrospective, observational cohort study evaluated the efficacy of the G/P regimen in a non-clinical trial setting at a single institution. The analysis examined all consecutive patients with HCV infections who started this regimen from January 2016 to July 2019 at Pusan National University Hospital. All patients provided informed consent. The Pusan National University Hospital Institutional Review Board approved the protocol (IRB number: H-1910-012-084) and all procedures were according to the most recent guidelines of the Declaration of Helsinki.

All included individuals were adults who had chronic HCV infections with viral replication (detectable HCV RNA) and received 1 or more doses of G/P. The treatment duration was according to the Korean Association for the Study of the Liver-approved label (Supplementary Table 1). Thus, treatment duration depended on the specific GT, prior HCV treatment regimen (IFN or pegylated interferon [pegIFN] with or without ribavirin, SOF plus ribavirin with or without pegIFN), and the presence of cirrhosis.[22] None of the patients had decompensated cirrhosis or had hepatocellular carcinoma (HCC) with a remaining viable portion of the liver.

1. Assessments

The demographic and clinical characteristics of all patients were assessed at baseline, and the virologic effectiveness and safety were recorded throughout and after treatment. Cirrhosis was diagnosed by use of a liver stiffness measurement (transient elastography score ≥13 kPa), ultrasound, and/or clinical findings, such as esophageal varices.[2,23,24]

Real-time polymerase chain reaction was used to determine serum HCV-RNA levels (COBAS TaqMan Analyzer; Roche Molecular Systems Inc., Pleasanton, CA, USA). This instrument had a detection limit of 15 IU/mL. Unquantifiable HCV-RNA was defined as "detected" but below the lower limit of quantitation (LLOQ) or as "not detected" (ND) and reported separately.

The Kidney Disease: Improving Global Outcomes system was used to assign CKD stage: stage 1 (normal, estimated glomerular filtration rate [eGFR] of at least 90 mL/min/1.73 m^2); stage 2 (mild damage, eGFR of 60 to 89 mL/min/1.73 m^2); stage 3 (moderate damage, eGFR of 46 to 59 [3a] or 30 to 45 [3b] mL/min/1.73 m^2); stage 4 (severe damage, eGFR of 15 to 29 mL/min/1.73 m^2); and stage 5 (end-stage renal disease, eGFR below 15 mL/min/1.73 m^2).[25]

2. Viral sequencing

Sequence analysis was conducted using serum samples collected from patients with virologic failure at baseline, during treatment (when available), and at the time of relapse. Deep sequencing of the NS3, NS5A, and NS5B genes was performed by the DDL Diagnostic Laboratory (Rijswijk, The Netherlands) using the Illumina MiSeq deep sequencing platform (Illumina, San Diego, CA, USA). Internally developed software (Gilead Sciences Inc., Foster City, CA, USA) was used to process and align sequences and identify resistance-associated substitutions (RASs) using 15% cutoffs. The presence of baseline RASs was established by comparison with wild-type reference sequences (JFH1 AB047639 for GT2a, MD2b10 AY232748 for GT2b).

3. Study endpoints

The SVR12 was the primary effectiveness endpoint and was defined as an HCV-RNA level below the LLOQ or ND at 12 weeks after treatment completion.[2] The two secondary endpoints were: (1) response (HCV-RNA <LLOQ or ND) at 4 weeks after onset of treatment and (2) response (HCV-RNA <LLOQ or ND) at the end of treatment (EOT).

Records were made of all patients who discontinued treatment due to a drug-related AE and/or a drug-related death. All treatment-related AEs and clinical laboratory abnormalities were recorded in the medical records.

4. Statistical analysis

An intention to treat (ITT) procedure was used for all analyses, in that patients who discontinued treatment or were lost to follow-up were included. Virologic response was assessed using ITT analysis and a modified ITT (mITT) analysis, in that patients who discontinued treat-

Table 1. Baseline Characteristics of All Patients (ITT Analysis)

Characteristic	All patients (n=267)	8-Week group (n=200)	12-Week group (n=67)	p-value
Age, yr	61.7±11.8	60.8±11.7	64.3±11.9	0.033*
Male sex	119 (44.6)	90 (45.0)	29 (43.3)	0.807
BMI, kg/m^{2}†	23.8±3.2	23.7±3.2	24.0±3.3	0.473
Prior treatment				0.210
IFN or pegIFN±RBV	51 (19.1)	33 (16.5)	18 (26.9)	
SOF+RBV	2 (0.7)	2 (1.0)	0	
SOF+RBV after pegIFN+RBV	2 (0.7)	2 (1.0)	0	
LSM, kPa‡	9.9±6.7	6.7±2.3	16.2±8.1	0.000*
Liver cirrhosis	56 (21.0)	2 (1.0)	54 (80.6)	0.000*
HCV genotype				0.197
1	83 (31.1)	66 (33.3)	17 (25.4)	
2	182 (68.2)	133 (66.5)	49 (73.1)	
3	1 (0.4)	0	1 (1.5)	
4	1 (0.4)	1 (0.5)	0	
HCV RNA, IU/mL	4,088,428.1±7,390,041.9	4,665,276.5±8,211,753.2	2,366,492.5±3,573,107.3	0.002*
ALT, U/L	39.9±36.4	40.2±36.2	38.8±37.5	0.791
Platelet, ×10^{3}/mm^{3}	186,348.3±69,255.5	201,295.0±65,679.0	141,731.3±60,218.4	0.000*
Albumin, g/dL	4.4±0.4	4.5±0.3	4.2±0.4	0.000*
Creatinine, mg/dL	1.1±1.6	1.1±1.5	1.1±1.7	0.984
HBsAg positivity	10 (3.7)	7 (3.5)	3 (4.5)	0.715
CKD stage				0.759
Stage 3	23 (8.6)	20 (10.0)	3 (4.5)	
Stage 4	2 (0.7)	2 (1.0)	0	
Stage 5	12 (4.5)	9 (4.5)	3 (4.5)	
History of HCC	13 (4.9)	3 (1.5)	10 (14.9)	0.000*
Concomitant disease				
More than one comorbidity	197 (73.8)	147 (73.5)	50 (74.6)	0.856
Diabetes	65 (24.3)	43 (21.5)	22 (32.8)	0.061
Hypertension	91 (34.1)	65 (32.5)	26 (38.8)	0.346
Extrahepatic malignancy	35 (13.1)	30 (15.0)	5 (7.5)	0.114
Psychiatric disease	30 (11.2)	26 (13.0)	4 (6.0)	0.115
Alcoholic abuse/dependency	4 (1.5)	4 (2.0)	0	0.575
Pulmonary disease	16 (6.0)	9 (4.5)	7 (10.4)	0.132
Co-medication	140 (52.4)	101 (50.5)	39 (58.2)	0.274
ACE inhibitor/ARB	50 (18.7)	36 (18.0)	14 (20.9)	0.599
Ca-channel blocker	48 (18.0)	35 (17.5)	13 (19.4)	0.726
Beta blocker	24 (9.0)	16 (8.0)	8 (11.9)	0.329
Thyroid hormone	10 (3.7)	7 (3.5)	3 (4.5)	0.715
Diabetes medication	47 (17.6)	29 (14.5)	18 (26.9)	0.021*
Proton pump inhibitor	8 (3.0)	5 (2.5)	3 (4.5)	0.418
Psychiatric medication	22 (8.2)	18 (9.0)	4 (6.0)	0.435
Antiplatelet/anticoagulant drug	28 (10.5)	21 (10.5)	7 (10.4)	0.990
No co-medication	127 (47.6)	99 (49.5)	28 (41.8)	

Data are presented as mean±SD or number (%).

ITT, intention to treat; BMI, body mass index; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; LSM, liver stiffness measurement; HCV, hepatitis C virus; ALT, alanine transaminase; HBsAg, hepatitis B surface antigen; CKD, chronic kidney disease; HCC, hepatocellular carcinoma; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

*p<0.05 is considered statistically significant; †BMI was measured in 237 patients: 174 in the 8-week group and 63 in the 12-week group; ‡LSM was measured in 129 patients: 86 in the 8-week group and 43 in the 12-week group.

ment and did not achieve SVR12, or were lost to follow-up were excluded. Factors associated with SVR12 were assessed using mITT analysis.

All categorical variables were reported as counts and percentages and compared using the Pearson chi-square test or Fisher exact test. All continuous variables were reported as medians and ranges and compared using the Mann-Whitney U-test. Univariate and multivariate logistic regression analyses were used to identify factors significantly associated with SVR12. All statistical tests were two-sided and p-values below 0.05 were considered significant. Statistical analyses were conducted with SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Study population

We administered the G/P regimen to 267 consecutive patients who were diagnosed with HCV (Table 1). Among these patients, 55.4% were females, the median age was 63.0 years (range, 25 to 87 years), and 79.4% were HCV treatment-naïve. A total of 56 patients (21.0%) had cirrhosis, and all of these cases were compensated cirrhosis (Child-Pugh score A). Patients were most frequently infected with HCV GT2 (68.2%), followed by GT1 (31.1%). Thirteen patients previously received HCC therapy, and all of them had complete remission. Ten patients had hepatitis B virus (HBV) co-infections, and four of them took an antiviral agent for this infection. At pretreatment, the median level of HCV-RNA was 1,830,000 IU/mL (range, 758 to 88,900,000 IU/mL), and 162 patients (60.7%) had a level above 1,000,000 IU/mL. There were also 37 patients (13.8%) with CKD stage 3 or higher (eGFR <59 mL/min/1.73 m^2), and 10 patients (3.7%) were undergoing dialysis. Fifty-five patients (20.5%) received previous treatment for HCV; 14 received IFN with ribavirin, one received IFN only, 31 received pegIFN with ribavirin, one received pegIFN only, two received SOF with ribavirin, two received SOF with ribavirin after pegIFN with ribavirin, and four received pegIFN with ribavirin after IFN with ribavirin.

Two hundred and fifty-two patients received G/P treatment according to the current guideline. Fifteen patients received treatment that deviated from the current guideline. More specifically, 13 patients initially classified as non-cirrhotic received treatment for 12 weeks because of advanced fibrosis (stage F3) based on transient elastography and low platelet count thus indicating the presence of cirrhosis. Among these 13 patients, 10 had GT2 and 3 had GT1b; six received prior IFN treatment for HCV (two received IFN with ribavirin, two received pegIFN with ribavirin, and two received pegIFN with ribavirin after IFN with ribavirin); and all 13 achieved SVR12. There were also two cirrhosis patients who received only 8 weeks of treatment; one patient stopped treatment because of high drug costs, and the other (who had CKD stage 5) did not tolerate the medication owing to a lack of appetite and poor oral intake. Nonetheless, each of these two patients achieved an SVR12.

Two hundred patients (74.9%) took G/P for 8 weeks, and 67 (25.1%) took G/P for 12 weeks. Comparison of these two groups indicated that the 8-week group was younger (p=0.033) and had less-severe liver disease (p<0.001); had higher levels of HCV RNA (p=0.002), platelets (p<0.001), and albumin (p<0.001); had a lower prevalence of HCC (p<0.001); and had a lower prevalence of treatment for diabetes mellitus (p=0.021) (Table 1). Five patients were lost to follow-up during or after treatment; therefore, mITT efficacy analysis has been carried out on 262 patients (98.1%), including 197 treated for 8 weeks and 65 treated for 12 weeks.

2. Effectiveness

Analysis of factors associated with the virologic response at week-4 (Supplementary Table 2) indicated that 203 patients (203/249, 81.5%) achieved a virologic response at that time, and this was independent of final treatment duration (8 weeks vs 12 weeks: 79.8% [150/188] vs 86.9% [53/61], p=0.218). Thirty-seven patients had HCV

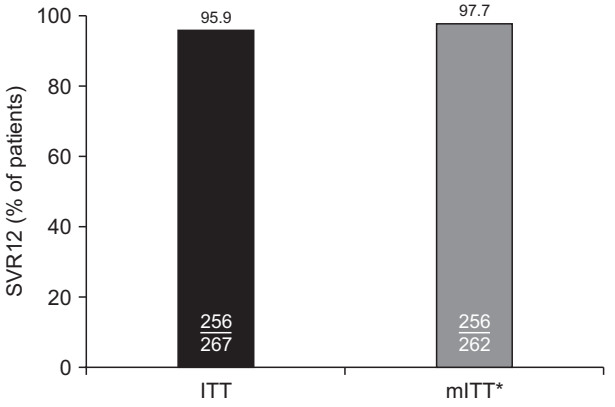

Fig. 1. SVR12 following glecaprevir/pibrentasvir treatment in overall population. SVR12 was defined as an HCV-RNA level below the lower limit of quantitation or not detected at 12 weeks after treatment completion.
SVR12, sustained virologic response at 12 weeks after treatment completion; HCV, hepatitis C virus; ITT, intention to treat; mITT, modified intention to treat. *mITT analysis excluded patients who discontinued treatment early and did not achieve SVR12 or patients who were lost to follow-up.

levels below the LLOQ. Among the nine patients who had detectable HCV-RNA, the mean level was 52.3 IU/mL (range, 16.8 to 180 IU/mL). A higher level of HCV-RNA at baseline was the only factor significantly associated with lack of response at week-4 (p=0.034).

Four patients were lost to follow-up during the treatment and one after the treatment but before testing at EOT so that no SVR12 data were available. Therefore, ITT analysis indicated that 262 out of 267 patients (98.1%) achieved EOT response, and mITT analysis indicated that 262 out of 262 patients (100.0%) achieved EOT response. Overall, the HCV-RNA level was below the LLOQ in five patients and ND in 257 patients.

ITT analysis of the primary effectiveness endpoint indicated the overall SVR12 was 95.9% (256/267) and mITT analysis indicated the overall SVR12 was 97.7% (256/262) (Fig. 1). Univariate analysis indicated the SVR12 was significantly lower in patients who previously received SOF treatment (p<0.001), had higher baseline HCV RNA titer (p=0.030), and had detectable HCV RNA at week-4 (p=0.010) (Table 2). Multivariate analysis indicated that prior SOF treatment and detectable HCV RNA at week-4 were significantly and independently associated with SVR12 (p=0.002 and p=0.027, respectively).

The SVR12 in treatment-naïve patients who did not have cirrhosis and who received 8 weeks of G/P was 95.7%

Table 2. Factors Associated with SVR12 in the Overall Population (n=262, mITT Analysis†)

Characteristic	SVR12 (n=256)	Non-SVR (n=6)	Univariate p-value‡	Multivariate p-value‡
Age, yr	61.6±11.9	62.3±6.5	0.874	
Age above 65 yr	110 (43.0)	2 (33.3)	0.639	
Male sex	112 (43.8)	5 (83.3)	0.092	
BMI, kg/m^2§	23.8±3.2	24.3±2.9	0.732	
Prior treatment				
IFN or pegIFN±RBV	51 (19.9)	0	0.997	
SOF+RBV	1 (0.4)	1 (16.7)	0.000*	0.002*
SOF+RBV after pegIFN+RBV	1 (0.4)	1 (16.7)		
LSM, kPa‖	9.9±6.7	4.3±0.0	0.265	
Liver cirrhosis	54 (21.1)	0	0.997	
HCV genotype			1.000	
1	82 (32.0)	0		
2	172 (67.2)	6 (100.0)		
3	1 (0.4)	0		
4	1 (0.4)	0		
HCV RNA, IU/mL	3,735,884.0±5,223,365.6	21,433,333.3±33,726,427.4	0.030*	0.157
ALT, U/L	39.3±34.9	42.0±62.4	0.855	
Platelet, ×10^3/mm^3	186,726.6±69,710.4	187,000.0±35,417.5	0.992	
Albumin, g/dL	4.4±0.4	4.5±0.4	0.384	
Creatinine, mg/dL	1.1±1.6	1.1±0.2	0.922	
CKD stage			0.448	
Stage 3	20 (7.8)	2 (33.4)		
Stage 4	2 (0.8)	0		
Stage 5	11 (3.5)	0		
HBsAg positivity	10 (3.9)	0	0.999	
History of HCC	13 (5.1)	0	0.999	
Co-medication	135 (52.7)	3 (50.0)	0.895	
Diabetes	60 (23.4)	3 (50.0)	0.154	
Concomitant disease	189 (73.8)	4 (66.7)	0.695	
Treatment duration, wk			0.997	
8	191 (74.6)	6 (100.0)		
12	65 (25.4)	0		
Detectable HCV RNA at wk 4	41 (17.1)	4 (66.7)	0.010*	0.027*

Data are presented as the mean±SD or number (%).

SVR12, sustained virologic response at 12 weeks after treatment completion; mITT, modified intention to treat; BMI, body mass index; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; LSM, liver stiffness measurement; HCV, hepatitis C virus; ALT, alanine transaminase; CKD, chronic kidney disease; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

*p<0.05 is considered statistically significant; †Analysis was performed on the mITT population. Five patients without SVR12 because they were lost to follow-up during (n=4) or after (n=1) treatment were excluded from the analysis; ‡Logistic regression was performed for comparison; §BMI was measured in 233 patients: 228 in the SVR12 group and five in the non-SVR12 group; ‖LSM was measured in 129 patients: 128 in the SVR group and one in the non-SVR group.

(154/161) in the ITT analysis and 97.5% (154/158) in the mITT analysis (Table 3). Each of the cirrhosis patients achieved an SVR12. Among those with or without cirrhosis who received previous treatment for HCV, the SVR12 was 96.4% (53/55), but this was based on a small number of patients.

There were six documented cases of virologic relapse after achievement of EOT response. All six patients had HCV GT2 infections, had no cirrhosis, and received 8 weeks of treatment (Supplementary Table 3). Two pa-

Table 3. SVR12 in Different Subgroups Following Glecaprevir/Pibrentasvir Treatment

Characteristic	SVR12 (n=267)*	SVR12 (n=262)†
Sex		
Male	94.1 (112/119)	95.7 (112/117)
Female	97.3 (144/148)	99.3 (144/145)
Age, yr		
≤65	96.1 (146/152)	97.3 (146/150)
>65	95.7 (110/115)	98.2 (110/112)
BMI, kg/m^2‡		
≤30	96.1 (220/229)	97.8 (220/225)
>30	100.0 (8/8)	100.0 (8/8)
Prior treatment		
None	95.8 (203/212)	98.1 (203/207)
IFN or pegIFN±RBV	100.0 (51/51)	100.0 (51/51)
SOF+RBV	50.0 (1/2)	50.0 (1/2)
SOF+RBV after pegIFN+RBV	50.0 (1/2)	50.0 (1/2)
Liver cirrhosis	96.4 (54/56)	100.0 (54/54)
HCV genotype		
1	98.8 (82/83)	100.0 (82/82)
2	94.5 (172/182)	96.6 (172/178)
3	100.0 (1/1)	100.0 (1/1)
4	100.0 (1/1)	100.0 (1/1)
HCV RNA, IU/mL		
<3,500,000	96.5 (167/173)	98.8 (167/169)
≥3,500,000	94.7 (89/94)	95.7 (89/93)
CKD stage		
Stage 3	87.0 (20/23)	90.9 (20/22)
Stage 4	100.0 (2/2)	100.0 (2/2)
Stage 5	91.7 (11/12)	100.0 (11/11)
History of HCC	100.0 (13/13)	100.0 (13/13)
Treatment duration, wk		
8	95.5 (191/200)	97.0 (191/197)
12	97.0 (65/67)	100.0 (65/65)
Detectable HCV RNA at wk 4§	91.1 (41/45)	91.1 (41/45)
History of alcohol abuse/dependency		
Yes	75.0 (3/4)	100.0 (3/3)
No	96.2 (253/263)	97.7 (253/259)
History of psychiatric disease		
Yes	96.7 (29/30)	100.0 (29/29)
No	95.8 (227/237)	97.4 (227/233)
Proton pump inhibitor use		
Yes	100.0 (8/8)	100.0 (8/8)
No	95.8 (248/259)	97.6 (248/254)
Diabetes mellitus		
Yes	92.3 (60/65)	95.2 (60/63)
No	97.0 (196/202)	98.5 (196/199)

Data are presented as percent (number/number).

SVR12, sustained virologic response at 12 weeks after treatment completion; BMI, body mass index; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; HCV, hepatitis C virus; CKD, chronic kidney disease; HCC, hepatocellular carcinoma.

*SVR12 was analyzed in the intention to treat (ITT) population (n=267); †SVR12 was analyzed in the modified ITT (mITT) population (n=262). Five patients without SVR12 because they were lost to follow-up during (n=4) or after (n=1) treatment were excluded; ‡BMI was measured by ITT analysis in 237 patients and by mITT analysis in 233 patients; §HCV RNA at week 4 was measured by ITT analysis in 249 patients and by mITT analysis in 246 patients.

tients received prior HCV treatment; one used SOF with ribavirin and one used SOF with ribavirin after pegIFN with ribavirin. We performed viral sequencing to identify the RASs associated with virologic failure and also reexamined the HCV GTs in patients with virologic failure. Baseline samples were available for two of six subjects and samples after 12 weeks of treatment were available for all six patients with virologic relapse. Sequencing of the eight samples indicated the GT at the time of virologic relapse was same as the GT at baseline in all patients with virologic failure. Therefore, we considered these virologic failures as virologic relapses not reinfections. All viruses had the NS5A L31M substitution and one virus also has the NS5A T24S substitution. No NS3 or NS5B RASs were detected. Thus, analysis of the two subjects with baseline and post-treatment data indicated no evidence of a new emergence of NS3 or NS5A class RASs.

Univariate analysis of patients who received 8-weeks of G/P indicated that treatment failure was more common in those who received prior SOF treatment (p=0.001), had higher baseline HCV RNA titers (p=0.037), and had detectable HCV RNA at week 4 (p=0.013) (Table 4). The results of the subsequent multivariate analysis showed that prior SOF treatment and detectable HCV RNA at week-4 remained significantly associated with a low SVR12 (p=0.004 and p=0.032, respectively).

Thirteen patients received therapy for HCC before G/P treatment. Four patients received surgery, four received transarterial chemoembolization, four received percutaneous radiofrequency ablation, and one received transarterial chemoembolization after surgery. These 13 patients started G/P for an average of 420.5 days (range, 91 to 1,984 days)

Table 4. Clinical Factors Associated with SVR12 in Patients Who Received 8 Weeks of Glecaprevir/Pibrentasvir (n=197, mITT analysis†)

Characteristic	SVR12 (n=191)	Non-SVR (n=6)	Univariate p-value‡	Multivariate p-value‡
Age, yr	60.7±11.8	62.3±6.5	0.742	
Age above 65 yr	76 (39.8)	2 (33.3)	0.751	
Male sex	83 (43.5)	5 (83.3)	0.090	
BMI, kg/m^2§	23.7±3.2	24.3±2.9	0.683	
Prior treatment				
IFN or pegIFN±RBV	33 (17.8)	0	0.998	
SOF+RBV	1 (0.5)	1 (16.7)	0.001*	0.004*
SOF+RBV after pegIFN+RBV	1 (0.5)	1 (16.7)		
LSM, kPa‖	6.7±2.2	4.3±0.0	0.271	
Liver cirrhosis	2 (1.0)	0	1.000	
HCV genotype			1.000	
1	65 (34.0)	0		
2	125 (65.4)	6 (100.0)		
4	1 (0.5)	0		
HCV RNA, IU/mL	4,188,724.1±5,602,553.0	21,433,333.3±33,726,427.4	0.037*	0.246
ALT, U/L	39.4±33.9	42.0±62.4	0.859	
Platelet, ×10^3/mm^3	201,408.4±66,818.6	187,000.0±35,417.5	0.598	
Albumin, g/dL	4.5±0.3	4.5±0.4	0.621	
Creatinine, mg/dL	1.1±1.5	1.1±0.2	0.898	
CKD stage			0.501	
Stage 3	18 (9.4)	2 (33.4)		
Stage 4	2 (1.0)	0		
Stage 5	9 (4.7)	0		
HBsAg positivity	7 (3.7)	0	0.999	
History of HCC	3 (1.6)	0	0.999	
Co-medication	98 (51.3)	3 (50.0)	0.950	
Diabetes	39 (20.4)	3 (50.0)	0.104	
Concomitant disease	141 (73.8)	4 (66.7)	0.697	
Detectable HCV RNA at wk 4	33 (18.2)	4 (66.7)	0.013*	0.032*

Data are presented as the mean±SD or number (%).

SVR12, sustained virologic response at 12 weeks after treatment completion; mITT, modified intention to treat; BMI, body mass index; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; LSM, liver stiffness measurement; HCV, hepatitis C virus; ALT, alanine transaminase; CKD, chronic kidney disease; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

*p<0.05 is considered statistically significant; †Analysis was performed on the mITT population (n=197). Three patients without SVR12 because they were lost to follow-up during (n=2) or after (n=1) treatment were excluded from the analysis; ‡Logistic regression was performed for comparison; §BMI was measured in 171 patients: 166 in the SVR group and five in the non-SVR group; ‖LSM was measured in 86 patients: 85 in the SVR group and one in the non-SVR group.

after the last HCC treatment, and five of them developed recurrence of HCC at an average of 65 days (range, 0 to 129 days) after G/P treatment.

3. Safety

Seventy patients (26.2%) experienced one or more AEs, most of which were mild (Table 5). The most common AEs were gastrointestinal discomfort (9.7%), upper respiratory infection symptoms (9.4%), and pruritus (6.4%). There was one premature discontinuation of treatment related to AEs. This male patient had an HCV GT2 infection, was cirrhotic, and therapy naïve. He completed only 8 weeks of the planned 12-week treatment because of lack of appetite and poor oral intake. The patient also had diabetes, hypertension, and CKD stage 5. Despite these many comorbidities and short treatment, this patient achieved an SVR.

DISCUSSION

There have only been limited real-world studies of the effect of the G/P regimen on chronic HCV infection, especially in Asian populations.[21] We studied patients at a single institution in South Korea who had chronic HCV infections. This is the first real-world study to demonstrate that 8 to 12 weeks of the G/P regimen provided an excellent SVR12 and is well tolerated by Korean patients.

There were twice as many patients with GT2 infections as GT1 infections in our cohort. HCV GT2-infected chronic hepatitis C patients account for about 20% to 45% of all HCV infections in East Asia.[26,27] This is probably because more patients with GT1 received previous treatment with a DAA. Among our patients, the most common comorbidity was hypertension (34.1%) and the most common co-medication was an anti-hypertensive drug. This is because HCV in South Korea and other regions of Asia is mainly transmitted in healthcare and cosmetology settings. In contrast, the most common comorbidity among patients in Western Europe is opioid substitution therapy and most transmission is due to intravenous drug use.[20,28,29] In fact, none of our patients self-reported active use of intravenous drugs. However, active drug use is forbidden by law in South Korea, so this might have been under-reported in our cohort. The data presented here suggest that this patient cohort provides an accurate reflection of the general HCV patient population in South Korea.

Furthermore, only 4.9% of our patients had a history of HCC. The reason for the low rate of HCC in our population was because the National Health Insurance of Korea does not cover the costs of HCV treatment for patients with viable HCC. In addition, 13.8% of our study population had CKD and 3.7% were on dialysis. This study also included HBV co-infected patients (3.7% of total cohort). These populations are generally excluded in clinical trials. The SVR12 was 100% in all these sub-populations. Therefore, this study showed that 8 to 12 weeks of G/P treatment was effective and well tolerated by patients with CKD, HCC, or HBV co-infection, the types of patients that everyday clinical practitioners often encounter.

The overall SVR12 for our patients was 95.9% (ITT) and 97.7% (mITT). In addition, 94.4% of all patients followed the treatment guideline, and the 15 patients who received treatment that deviated from the guideline all achieved SVR12. The SVR12 in patients who were treatment-naïve, did not have cirrhosis, and received treatment for 8 weeks (60.3% of the patients in this cohort) was 95.7% (154/161; ITT) and 97.5% (154/158; mITT). The 55 patients who received prior HCV treatment, regardless of cirrhosis, had an SVR12 of 96.4%. Most of this cohort (74.9%) received 8 weeks of treatment, and the SVR12 was 95.5% (ITT) and 97.0% (mITT). Compared to other HCV treatment regimens that last at least 12 weeks, the G/P regimen achieved similar efficacy and safety after 8 weeks in most patients. A small number of our patients had cirrhosis, but each of them nonetheless achieved an SVR12. Our results are similar to those of major clinical trials and real-world studies of G/P in other countries.[19,20,30-32] Most of the AEs associated with G/P treatment were mild, and only one of our patients had a serious AE that required discontinuation of treatment. No hepatic decompensation occurred, even in patients with cirrhosis or HCC, and HBV reactivation did not occur in patients with HBV co-infections.

The phase 3 EXPEDITION-8 trial of patients with HCV reported that those who received no prior HCV treatment and had compensated cirrhosis achieved an SVR12 of 97.9% (274/280) after 8 weeks, and that no patients expe-

Table 5. Prevalence of AEs Overall and in Patients Who Received Treatment for 8 Weeks and 12 Weeks

Adverse event	8 Weeks (n=200)	12 Weeks (n=67)	Overall (n=267)
Any AE	49 (24.5)	21 (31.3)	70 (26.2)
Specific AEs			
Fatigue	8 (4.0)	0	8 (3.0)
GI discomfort	18 (9.0)	8 (11.9)	26 (9.7)
Pruritus	14 (7.0)	3 (4.5)	17 (6.4)
URI	17 (8.5)	8 (11.9)	25 (9.4)
AEs leading to discontinuation	1 (0.5)	0	1 (0.4)
Deaths	0	0	0

Data are presented as number (%).
AE, adverse event; GI, gastrointestinal; URI, upper respiratory infection.

rienced virologic failure.[33] Based on this trial, the Ministry of Food and Drug Safety (Korea Food & Drug Administration) approved an 8 week G/P regimen for treatment of patients who received no prior HCV treatment, with or without cirrhosis, but were not infected with HCV GT3. This regimen has reduced medical costs, is simpler, and has better patient compliance. In the present study, two patients with cirrhosis received 8 weeks of G/P treatment and achieved SVR12. However, all six patients who failed to achieve SVR12 in our study received 8 weeks of G/P treatment because they did not have cirrhosis. Although the number of treatment failures was small, further real-world data are needed to verify the effectiveness of an 8-week G/P regimen in everyday clinical practice. A retreatment regimen following G/P failure is not yet available in Korea, and its efficacy has not yet been verified in the general population.

For this reason, it is important to identify factors associated with treatment failure. Six of our patients developed post-treatment relapse. Interestingly, all but one of these six patients were male, all had HCV GT2 infections, all received 8 weeks of treatment, and two of them received prior SOF treatment. Our analysis also indicated that the SVR12 was significantly reduced in patients received prior SOF treatment and had detectable HCV RNA at week-4. Moreover, the viral load at baseline also affected the on-treatment viral kinetics; more specifically, a high response at week-4 occurred in patients who had low levels of baseline HCV-RNA. Therefore, high viral load at baseline and slow change of viral load during treatment seem to be associated with treatment failure. However, in contrast to our observations, a previous study[18] reported that SVR12 was independent of previous HCV treatment, HCV viral load at baseline, and on-treatment viral kinetics in groups that received treatment for different durations. These researchers attributed this result to a high genetic barrier to resistance. The reason for these different results is uncertain, but might be due to racial differences, lower compliance in a real-world setting, or drug-drug interactions. It is uncertain if this is because of the lower effectiveness of the G/P regimen in different patient subgroups.

Similarly, it is also unclear whether previous SOF treatment contributed to failure of the G/P regimen. A previous study in Japan showed that the SVR12 was 100% with the G/P regimen in patients with GT2 who failed previous SOF treatment.[31] In both studies, the number of patients who had previously been treated with SOF was limited, so examination of a larger number of patients is necessary to resolve this issue. Patients are unlikely to develop SOF resistance[34] because of the catalytic site where this synthetic nucleotide binds is highly conserved. A RAS in NS5B is uncommon (1%), even in patients who fail to respond to a DAA regimen with a nucleotide inhibitor and does not last long after treatment.[35,36] In fact, we detected no NS5B RASs in patients with previous SOF failure.

We identified the L31M polymorphism in NS5A in all patients with virologic failure (possibly present from baseline), which is very common in GT2. T24S was present in one patient at the time of virologic failure, and it is not clear whether this was a baseline polymorphism or selected during the treatment because there was no baseline sample for this patient. L31M and T24S are well known polymorphisms of NS5A in GT2, and L31M has a prevalence of 92.3% in GT2a and 83.8% in GT2b.[37] The L31M polymorphism reduces susceptibility to first-generation NS5A inhibitors, such as daclatasvir (>1,000-fold) or ledipasvir (12-fold) and also reduces the barrier for resistance for ombitasvir.[38-40] However, *in vitro* and clinical research reported that G/P had potent antiviral activity irrespective of the presence of common polymorphisms and had a higher barrier of resistance than the first-generation protease inhibitors or NS5A inhibitors.[41,42] Therefore, whether a baseline L31M polymorphism, with or without another polymorphism in NS5A, contributed to treatment failure needs further investigation.

The present study has several limitations. In contrast to a clinical trial, a real-world study may be associated with certain biases due to incomplete, inconsistent, or incorrect data. Because of this, some minor AEs may not be reported. These biases could be worse in multicenter real-world studies. However, all of our patients were from a single institution, the population was mostly homogeneous, and data collection techniques were uniform. These advantages are difficult to achieve in a multicenter study. Another limitation is that some of our subgroup analyses only examined small numbers of patients, so we cannot make confident conclusions from these analyses. Similarly, we did not have on-treatment kinetic data for some patients because the Korean national insurance made changes in the requirements for on-treatment testing. Lastly, loss of patients to follow-up may occur in study conducted in a non-clinical trial setting, although we lost very few patients to follow-up and this probably did not significantly affect our results.

In conclusion, this study, which was conducted in a real-world setting, indicated that the 8- to 12-week G/P regimen had high efficacy and was well-tolerated in most Korean patients who had chronic HCV infections regardless of HCV GT and patient comorbidities.

CONFLICTS OF INTEREST

G.H.K. is an editorial board member of the journal but did not involve in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: H.Y.W., J.H. Data curation: H.Y.W., Y.J.P., J.H. Formal analysis: H.Y.W., Y.J.P., J.H. Funding acquisition: J.H., M.C. Methodology: Y.J.P., H.Y.W., J.H., S,G.P., Y.M.H., K.T.Y., D.U.K., G.H.K., H.H.K., G.A.S., M.C. Project administration: H.Y.W., Y.J.P., J.H. Visualization: H.Y.W., Y.J.P., J.H. Writing-original draft: H.Y.W., Y.J.P., J.H. Writing-review & editing: H.Y.W., Y.J.P., J.H. Approval of final manuscript: all authors.

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