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Original article

Efficacy and safety of glecaprevir and pibrentasvir combination therapy in old-aged patients with chronic hepatitis C virus infection

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Abstract

Objective: Combination therapy with glecaprevir and pibrentasvir (G/P) has been shown to provide a sustained virologic response (SVR) rate of >97% in patients with chronic hepatitis C virus (HCV) infection in the first published real-world Japanese data. However, a recently published study showed that the treatment was often discontinued in patients ≥75 years old, resulting in low SVR in intention-to-treat (ITT) analysis. Thus, our aim was to evaluate real-world data for G/P therapy in patients ≥75 years of age, the population density of which is high in "rural" regions.

Patients and Methods: We conducted a multicenter study to assess the efficacy and safety of G/P therapy for chronic HCV infection, in the North Kanto area in Japan.

Results: Of the 308 patients enrolled, 294 (95.5%) completed the treatment according to the protocol. In ITT and per-protocol analyses, the overall SVR12 rate was 97.1% and 99.7%, respectively. The old-aged patients group consisted of 59 participants, 56 of whom (94.9%) completed the scheduled protocol. Although old-aged patients tended to have non-SVR factors such as liver cirrhosis, history of HCC, and prior DAA therapies, the SVR12 rates in old-aged patients were 98.3% and 100% in the ITT and PP analyses, respectively. Of 308 patients enrolled, adverse events were observed in 74 patients (24.0%), with grade ≥3 events in 8 patients (2.6%). There was no significant difference in any grade and grade ≥3 adverse events between the old-aged group and the rest of the study participants. Only one patient discontinued the treatment because of adverse events.

Conclusion: G/P therapy is effective and safe for old-aged patients.

Key words: age disparities, chronic hepatitis C, glecaprevir, pibrentasvir

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Introduction

Chronic hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) in Japan[1, 2] and results in heavy health-care burden. Interferon (IFN)-based therapy was used to treat HCV infection until 2014. The issues of IFN-based treatment were the high rate of adverse events and long duration of treatment. Hence, it was difficult for elderly patients to achieve sustained virologic response (SVR) due to dropout from treatment[3, 4]. As a result, 1–1.5 million patients still have HCV infection in Japan[5] despite the nationwide campaign to promote the treatment of chronic HCV infection.

In 2014, an interferon (IFN)-free direct-acting antiviral (DAA) treatment regimen was approved for patients with chronic HCV infection in Japan. Because IFN-free DAA treatments were associated with low rates of adverse events and short duration of treatment in comparison to IFN-based therapy, IFN-free DAA treatments provided SVR rate >95%, as observed in many studies[6–8]. In addition, SVR achieved by IFN-free DAA treatment improved health-related quality of life in patients with chronic HCV infection[9]. Furthermore, SVR achieved by IFN-free DAA treatment suppressed recurrence of HCC and improved overall survival[10]. Thus, increased SVR can provide a lot of benefits for patients with chronic HCV infection, including old-aged patients.

In 2017, the combination of glecaprevir and pibrentasvir (G/P) was approved in Japan that showed potent anti-viral effects for pan-genotype HCV including GT1-6. A phase-3 Japanese study showed that SVR12 rates in GT1 and GT2 increased to 99.2–100%[11] and 97.8–100%[12], respectively. In addition, G/P therapy showed favorable results in "difficult-to-treat patients" from previous DAA treatments, including GT2-infected patients with severe renal failure, GT3-6, and prior DAA-treated patients[13–15]. Currently, several studies using G/P therapy have published real-world data from the general as well as special populations with HCV infection in Japan, and have demonstrated extremely high SVR rates[16, 17].

Although previous studies included many patients ≥65 years of age, little information is available on another "special population", patients ≥75 years of age. These old-aged patients tend to have non-SVR factors, including liver cirrhosis[18], history of HCC[6, 19], and prior DAA treatment[6, 8]. In addition, adverse events are of concern in this population. Indeed, patients ≥75 years of age tended to discontinue the treatment[20]. Furthermore, the population of these old-aged patients is increasing in Japan; their population density is high in "rural" regions (https://www8.cao.go.jp/kourei/whitepaper/w-2018/html/zenbun/s1_1_4.html). We therefore performed a multicenter study to evaluate the efficacy and safety of G/P therapy in patients ≥75 years of age.

Patients and Methods

Patients with chronic HCV infection were enrolled in this retrospective study, which was conducted at 16 institutions in the North Kanto area in Japan between December 2017 and October 2018. The following institutions participated in this study: Jichi Medical University, Dokkyo Medical University, Saiseikai Utsunomiya Hospital, Nasu Red Cross Hospital, Shin-Oyama City Hospital, Nasu Minami Hospital, Sano Kousei General Hospital, Tochigi Medical Center Shimotsuga, Haga Red Cross Hospital, Tochigi Medical Center, Koga Red Cross Hospital, JCHO Utsunomiya Hospital, Utsunomiya Higashi Hospital, Ashikaga Red Cross Hospital, Kamitsuga General Hospital, and Yuai Memorial Hospital.

Patients with compensated liver cirrhosis, GT3-6, and previously DAA-treated patients were scheduled to undergo 12 weeks of the G/P combination (Maviret®, Abbvie, Tokyo, Japan) treatment. The remaining patients were scheduled to receive 8 weeks of treatment. In all patients, treatment was initiated with 3 tablets of Maviret®, which contains 300 mg of glecaprevir and 120 mg of pibrentasvir. The main exclusion criteria were 1) decompensated liver cirrhosis (Child-Pugh grade B or C), 2) the presence of HCC, and 3) other contraindications for treatment. The old-aged group was determined as ≥75 years old in the present study. No upper-limit age was imposed on this study.

The study consisted of 308 consecutive patients; 10 patients (3.2%) deviated from the protocol. Four patients (1.3%) dropped out during or after the end of treatment. Thus, ITT and per protocol (PP) analyses were performed for 308 and 294 patients, respectively. We recorded the age, gender, history of HCC, previous DAA treatments, liver status (chronic hepatitis or liver cirrhosis), and GT or serotype (ST). The HCV GT was available for 260 patients (84.4%). In the present study, ST1 and ST2 were counted in GT1 and GT2, respectively. The diagnosis of liver cirrhosis was made by chief doctors based on laboratory and imaging examinations. Alcohol users were determined by consuming 60 g/day of ethanol for men and 40 g/day for women for over 5 years, including the patients who stopped drinking before the entry to the present study. The FIB-4 index, a marker for liver fibrosis, was determined using the following formula: (age × AST[U/L])/ (Plt [10^9/L] × ALT[U/L]$^{1/2}$). Serum HCV-RNA was measured by quantitative real-time polymerase chain reaction (COBAS® TaqMan® HCV Test, version 2.0; Roche Diagnostics, Tokyo, Japan, or AccuGENE® m-HCV RNA quantitative assay; Abbott Japan, Tokyo, Japan). HCV ST and GT were examined at SRL (Tokyo, Japan). The severity of chronic kidney disease (CKD) was determined according to the guidelines of the Japanese Society of Nephrology. In the present study, severe CKD was defined as grade 4, grade 5, and grade 5D based on the estimated glomerular-filtration rate (eGFR) being 15-30 min/mL/1.73m^2,

<15 min/mL/1.73 m^2, and dialysis-dependent, respectively. Achievement of SVR at 12 weeks post-treatment (SVR12) was used for the evaluation of the virologic response. Adverse events were recorded according to the Common Terminology Criteria for Adverse Events v4.0.

This study was approved by the Institutional Review Board of Jichi Medical University (A18-091) as well as independent ethics committees at all participating sites, and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective nature of this study, written informed consent was waived except in case of Jichi Medical University. However, opt-out consent documents were shown on the website of Jichi Medical University for patients who reconsidered participation even after agreeing to the study.

Analysis of resistance-associated substitutions (RASs)

RASs in previously DAA-treated patients were determined by direct sequencing (SRL Laboratory, Tokyo, Japan or LSI Laboratory, Tokyo, Japan)[21], or Cycleave polymerase chain reaction (SRL Laboratory). An RAS was considered present when it exceeded 10% and 1% by direct sequencing and Cycleave polymerase chain reaction, respectively.

Statistical analyses

Statistical analyses were performed using the SPSS Statistics (version 23.0, IBM Corp., Armonk, NY, USA) and EZR Statistics (Saitama Medical Center, Jichi Medical University, Japan) software programs. Continuous variables were expressed as the median. Fisher's exact test and the Mann-Whitney U test were performed as appropriate. *P*-values of <0.05 were considered to indicate statistical significance.

Results

Characteristics of patients

Table 1 shows the characteristics of the 308 patients enrolled in the present study. The median age was 65 years; the number of patients was 59 (19.2%) in the old-aged group (age ≥75 years old). Patients with GT4-GT6 were not enrolled, and all patients with GT3 were <75 years of age. The prevalence of cirrhotic and previously DAA-treated patients tended to be higher in the old-aged group. As a result, the proportion of 12 weeks of G/P therapy was larger in the old-aged group because a 12-week protocol is required for cirrhotic and previously DAA-treated patients. The prevalence of patients with

Table 1 Characteristics of 308 patients enrolled in the present study

	Overall (n=308)	Age <75 (n=249)	Age ≥75 (n=59)	*P*-value
Age (years) [Range]	65 [26–96]	61 [26–74]	80 [75–96]	<0.001
Male	176 (57.1%)	148 (59.4%)	28 (47.5%)	0.108
Genotype 1/2/3	147/156/5	117/127/5	30/29/0	0.701
Liver cirrhosis	68 (22.1%)	50 (20.1%)	18 (30.5%)	0.115
DAA-experienced	46 (14.9%)	36 (14.5%)	10 (16.8%)	0.685
12 w of treatment	112 (36.4%)	85 (34.1%)	27 (45.8%)	0.100
Severe CKD	32 (10.4%)	26 (10.4%)	6 (10.2%)	1.000
Hemodialysis	24 (7.8%)	21 (8.4%)	3 (10.2%)	0.589
History of HCC	22 (7.1%)	14 (5.6%)	8 (13.6%)	0.047
Alcohol	49 (15.9%)	45 (18.1%)	4 (6.8%)	0.031
Diabetes mellitus	63 (20.5%)	53 (21.3%)	10 (16.9%)	0.590
HCV-RNA (LogIU/mL)	6.3 [2.7–8.1]	6.3 [2.7–8.1]	6.1 [3.3–7.3]	0.360
WBC (/μL)	5,100 [1,600–10,800]	5,300 [1,600–10,800]	4,600 [2,580–8,900]	0.009
Hemoglobin (g/dL)	13.6 [8.4–17.4]	13.8 [8.4–17.4]	12.5 [9.6–15.4]	<0.001
Platelet (×10^4 /μL)	17.7 [1.9–98.5]	18.1 [1.9–98.5]	16.1 [6.2–46.0]	0.011
AST (U/L)	36 [10–359]	36 [10–359]	35 [15–193]	0.682
ALT (U/L)	34 [4–519]	38 [8–519]	28 [4–137]	0.004
Albumin (mg/dL)	4.1 [2.1–5.2]	4.1 [2.1–5.2]	3.9 [2.8–4.8]	<0.001
Total bilirubin (mg/dL)	0.6 [0.2–4.5]	0.6 [0.2–4.5]	0.7 [0.2–1.7]	0.631
Creatinine (mg/dL)	0.76 [0.39–9.66]	0.76 [0.39–9.66]	0.80 [0.5–9.15]	0.040
eGFR (mL/min/1.73m^3)	71.0 [3.7–152.8]	74.1 [4.5–152.8]	57.7 [3.7–119.5]	<0.001
α-fetoprotein (ng/mL)	4.0 [0.7–146]	4.0 [1.0–146.0]	3.8 [0.7–22.0]	0.106
PIVKA-II (mAU/mL)	18.9 [1.79–200]	19.0 [1.79–200]	18.0 [8.2–30.0]	0.017
Fib-4 index	2.4 [0.29–23.3]	2.07 [0.29–23.33]	3.92 [1.56–17.91]	<0.001
M2BPGi	2.3 [0.27–14.79]	2.01 [0.27–14.79]	2.77 [0.93–14.70]	0.002

CKD: chronic kidney disease, DAA: direct acting antivirals, HCC: hepatocellular carcinoma, HCV: hepatitis C virus, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, eGFR: estimated glomerular-filtration rate, PIVKA-II: protein induced by vitamin K absence or antagonist II, M2BPGi: Mac-2 binding protein glycosylated isomers.

severe CKD was similar between the old-aged and the other group. The old-aged group had a higher proportion of HCC history but a smaller proportion with alcohol use. Patients in the old-aged group were also characterized by low levels of white blood cells, hemoglobin, platelet, ALT, albumin, eGFR, and PIVKA-II but high Fib4-index and M2BPGi in comparison to the other, non-old-aged group.

Virologic response to G/P therapy

We next evaluated the virologic responses. The overall SVR12 rate was 97.1% (299/308) and 99.7% (293/294) in the ITT and PP analyses, respectively (Figure 1a). The SVR12 rate of the old-aged group was similar to that of non-old-aged group in both ITT and PP analyses (Figure 1a). The SVR12 rates in patients with GT1, GT2 and GT3 were 97.3%, 96.8%, and 100% in the ITT analysis, respectively (Figure 1b). The SVR12 rates of the old-aged group in GT1 and GT2 were similar to those of non-old-aged group (Figure 1b).

Further, we compared the SVR12 rates for the old-aged group and non-old-aged group using several parameters including liver status, prior DAA treatment, duration of treatment, gender, presence of severe CKD, history of HCC, FIB4 index >3.25, and M2BPGi >3.15. We found that the SVR12 rate was not significantly influenced by these parameters in the old-aged group (Figures 1c–1h, data not shown). In 32 patients with severe CKD, the SVR rate of 6 patients from the old-aged group was 100%, with 4 and 2 patients being of the GT1 and GT2 status, respectively. GT3-infected patients with severe CKD were not enrolled in the present study. Among 46 previously DAA-treated patients, 32 and 14 were GT1- and GT2-infected patients, respectively. The SVR12 rate of 10 previously DAA-treated patients in the old-aged group was 100%, with 6 GT1- and 4 GT2-infected patients, respectively. Patients with p32 deletion (NS5A) were not enrolled in the present study. HCV relapsed in a 61-year-old man with liver cirrhosis and a history of DAA treatments including simeprevir, Daclatasvir + asunaprevir, and sofosbuvir/ledipasvir for GT1b infection. A detailed analysis showed that HCV had P29del, C85C/Y, and T95A/T in NS5A, S122G in NS3, and C316N in NS5B but not L31, A92, Y93, and p32 deletion in NS5A.

Treatment safety and adherence

We next evaluated safety and adherence of G/P therapy. Of the 308 patients initially enrolled, 74 patients (24.0%) showed adverse events, with eczema/pruritus (n=38, 12.3%) and malaise (n=11, 3.6%) being the most frequent (Table 2). Although the frequency of eczema/pruritus was higher in the old-aged group, the rates of grade ≥3 adverse events as well as other adverse events were not significantly different between the old-aged group and non-old-aged group (Table 2). All grade-3 adverse events in the old-aged group were observed at the end of treatment. Among the 74 patients with adverse events, 64 completed the scheduled protocol since the adverse events were managed. However, 5 patients discontinued treatment and the other 5 deviated from the protocol because of the adverse events (Table 3). Among these 10 patients, 3 were old-aged patients. Patients who received ≥75% of the scheduled dose achieved an SVR (Table 3).

Discussion

In the present study, the overall SVR12 rates in the ITT and PP analyses were 97.1% and 99.7%, respectively. Although the old-aged group tended to have non-SVR factors, including liver cirrhosis, history of HCC, and experience of DAA therapies, the SVR12 rates were 98.3% and 100% in the ITT and PP analyses, respectively. There were no significant differences in grade ≥3 adverse events between the old-aged and non-old-aged group. Only one patient in the old-aged group did not achieve SVR due to adverse events. Thus, G/P therapy was effective and safe for old-aged patients.

G/P therapy showed high SVR12 rate in many studies[13, 14, 16, 17], in which half of the enrolled patients were ≥65 years of age. Thus, the age disparities in the IFN-free DAA therapy seemed to disappear with high adherence to the treatment. Indeed, Ogawa *et al.* reported that the SVR rate in patients ≥75 years old was 100%, in PP analysis[16]. However, they did not show SVR rate in ITT analysis, which could potentially include the patients who discontinued the treatment. We showed extremely high rates of SVR with ITT analysis in the old-aged group, which suggests that only a small number of patients discontinued the treatment. In addition, the present study did not include patients with p32 deletion in NS5A who are highly resistant to DAAs, including G/P therapy[22]. Because RASs is a non-SVR factor regardless of age[6, 8], it is important to examine RAS before G/P treatment. Thus, G/P therapy is effective for old-aged patients as well as "difficult-to-treat patients" under appropriate entry to the treatment.

In general, although hepatologists select patients expecting that they would complete the G/P therapy, old-aged patients sometimes unexpectedly discontinue the treatment. In a study performed in metropolitan areas, the frequency of dropout from G/P therapy was 7.1%[20] while the rate in the present study was 1.3%. The major reason for dropout in the metropolitan areas was transfer to other hospitals. Because patients can choose any medical resources in Japan, patients may transfer to other medical facilities when experiencing unexpected events during the DAA treatment. Tamori *et al.* reported that patients ≥75 years of age tended to drop out from the treatment owing to other diseases that occurred during G/P therapy[20]. In the present study, no patients in the old-aged group dropped out from the treatment. In Tochigi Prefecture, a part of North Kanto (https://www.mhlw.go.jp/toukei/saikin/hw/iryosd/m18/is1802.html), alternative medical resources are not readily available, resulting in no transfer

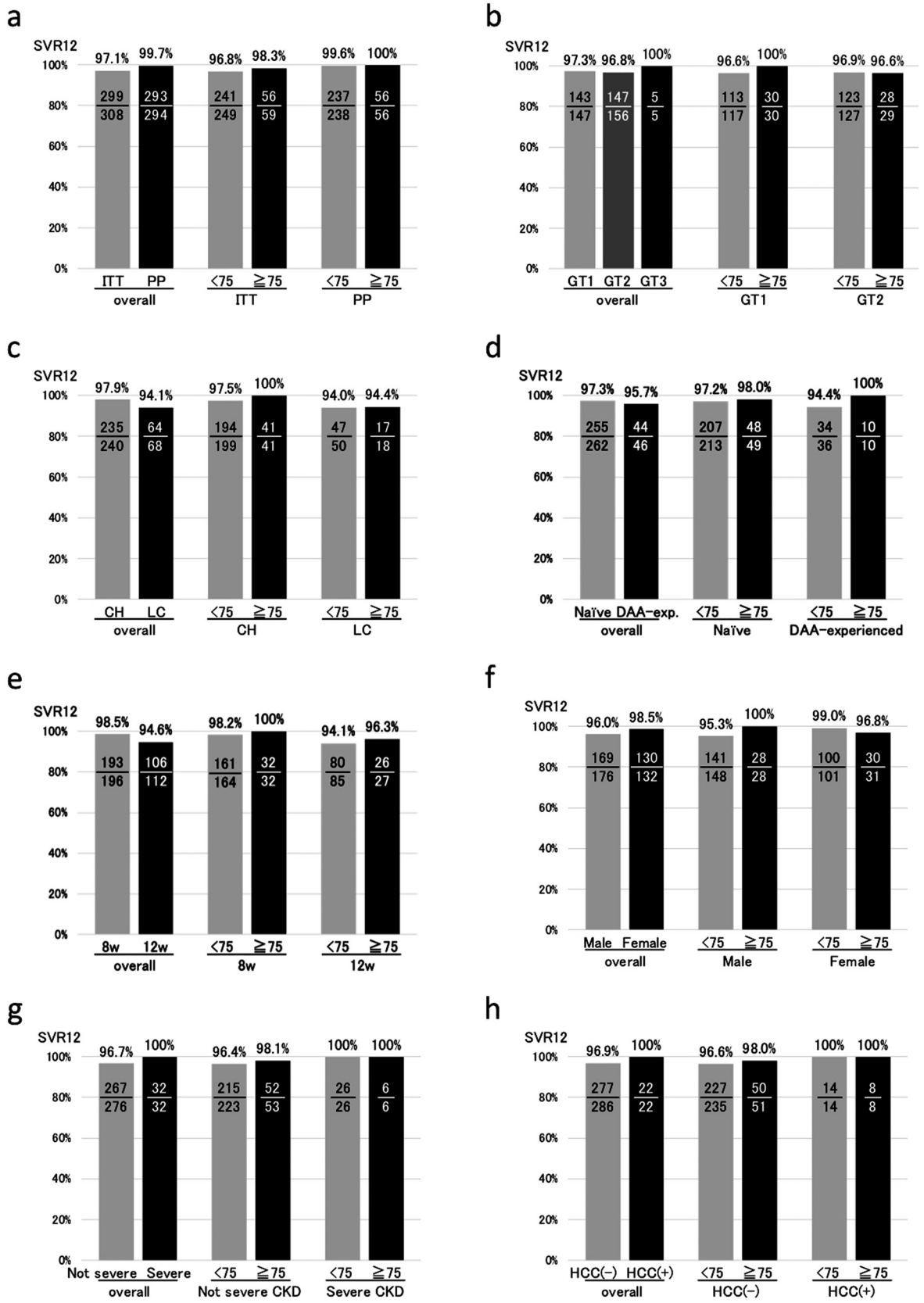

Figure 1 SVR12 rates in each parameter and comparison between the old-aged group and non-old-aged group. (a) ITT and PP analyses. (b) Each genotype. (c) Status of the liver. (d) Prior DAA treatment. (e) Duration of treatment. (f) Gender. (g) Presence of severe CKD. (h) History of HCC. SVR12 rates in the ITT analysis are shown from (b) to (h).

Table 2 Adverse events

Events	Overall (n=308)		Age <75 (n=249)		Age ≥75 (n=59)		*P*-value	
	Any grade	≥ Grade 3	Any grade	≥ Grade 3	Any grade	≥ Grade 3	Any grade	≥ Grade 3
Any	74 (24.0%)	8 (2.6%)	55 (22.1%)	6 (2.4%)	19 (32.2%)	2 (3.4%)	0.127	0.652
Eczema/Pruritus	38 (12.3%)	2 (0.6%)	26 (10.4%)	1 (0.4%)	12 (20.3%)	1 (1.7%)	0.047	0.347
Malaise	11 (3.6%)		8 (3.2%)		3 (5.1%)		0.446	
Headache/Myalgia	6 (1.9%)		5 (2.0%)		1 (1.7%)		1.000	
Bilirubin increased	5 (1.6%)	2 (0.6%)	5 (2.0%)	2 (0.8%)				
Constipation	3 (1.0%)		3 (1.2%)					
Nausea	3 (1.0%)		1 (0.4%)		2 (3.4%)		0.095	
Lung infection	2 (0.6%)	1 (0.3%)	2 (0.8%)	1 (0.4%)				
ALT increased	2 (0.6%)	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (1.7%)		0.347	
Dizziness	2 (0.6%)		2 (0.8%)					
Heart failure	2 (0.6%)	2 (0.6%)	1 (0.4%)	1 (0.4%)	1 (1.7%)	1 (1.7%)	0.347	0.347
Cough	1 (0.3%)		1 (0.4%)					
Others	4 (1.3%)		4 (1.6%)					

ALT: alanine aminotransferase.

Table 3 Characteristics and outcome in patients who discontinued or deviated from the protocol

Patient	Age / sex	GT	CH/LC	CKD grade	AEs	AE grade	Drug adherence	Outcome
#1	40 / F	2	CH	1	Eczema	1	12.5% (1W/8W)	Non SVR
#2	77 / F	2b	LC	3b	Nausea	1	16.7% (2W/12W)	Non SVR
#3	72 / M	1b	CH	3a	Cough	1	41.7% (5W/12W)	Non SVR
#4	65 / M	1b	CH	1	Lung infection	2	50.0% (4W/8W)	Non SVR
#5	66 / M	2b	LC	HD	Eczema	3	75.0% (9W/12W)	SVR
#6	65 / M	1b	CH	4	Lung infection	3	100% (8W/8W)	SVR
#7	76 / F	2a	CH	2	Malaise	2	100% (12W/12W)	SVR
#8	87 / M	2	LC	4	ALT increased	2	100% (12W/12W)	SVR
#9	70 / F	2	LC	2	Malaise	2	100% (12W/12W)	SVR
#10	41 / F	3a	CH	1	ALT increased	3	100% (12W/12W)	SVR

Case #3 is a prior DAA-treated patient. Cases #1–5 are patients who did not resume the G/P therapy after discontinuation. Cases #6–10 are patients who deviated from the protocol. Cases #6 and #7 completed the scheduled dose but temporally discontinued G/P therapy. Cases #8–10 completed the scheduled dose by reducing daily dose. GT: genotype, CH: chronic hepatitis, LC: liver cirrhosis, CKD: chronic kidney disease, AEs: adverse events, ALT: alanine aminotransferase, SVR: sustained virologic response, HD: hemodialysis.

to other hospitals during G/P therapy. In addition, we made efforts to communicate with hospitals during the G/P therapy by having several meetings to exchange information on the present study. These efforts might have helped to decrease the number of patients who dropped out from the treatment.

The G/P therapy accomplished a high SVR rate, as observed in other DAA treatments. Indeed, modified ITT analysis demonstrated high SVR rates despite low SVR rates in ITT analysis[20]. In our study, 5 patients achieved an SVR with modification of the protocol to receive 100% of the scheduled dose; 2 were old-aged patients. Of note, the duration of treatment was extended for 3 patients by reducing the daily dose due to adverse events. We believe that this modification of the treatment protocol is acceptable because a 16-week regimen is approved in other countries[23]. However, 5 patients discontinued treatment due to adverse events. Our study showed that a patient who received ≥75% of the scheduled dose achieved an SVR, while this was not observed in patients who received 50% or less. These data indicate that receiving the scheduled dose as possible is important for achieving an SVR. In addition, successful management of adverse events is essential for achieving an SVR.

Although we demonstrated that G/P therapy was effective and safe in old-aged patients, a couple of patient selection and condition need to be mentioned. First, some patients with severe comorbidities were not enrolled in the present study. Second, we did not enter some patients who might have had difficulties in visiting medical resources every 2 weeks during the treatment. Old-aged patients may have such problems, though age is not a restriction for entry into IFN-free DAA treatments such as G/P therapy. Interestingly, the proportion of alcohol use was low in old-aged

patients. Alcohol use may have progressed to decompensated liver cirrhosis and/or HCC in old-aged patients with chronic HCV infection, which were excluded from the present study. Thus, patients who enrolled in the present study might have presented favorable conditions. These results also indicate that close attention needs to be given to who should be treated, i.e., to the patients' selection.

Conclusion

G/P therapy is effective and safe in patients ≥75 years of age. While the accomplishment of G/P therapy yields a high SVR rate, appropriate management is required to achieve SVR in patients ≥75 years of age.

Conflict of interest: N.M., T.M., Y.O., N.I., and H.Y. received lecture fees from AbbVie. T.M., N.I., and H.Y. received research fees from AbbVie. The other authors have no conflicts of interest associated with this study.

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