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ABOUT COVER

Editorial board member of *World Journal of Hepatology*, Dr. Genco Gencdal is an Associate Professor at Uskudar University, School of Medicine in Istanbul, Turkey. Dr. Gencdal graduated from Ankara University, School of Medicine (2001) and specialized in internal medicine at the Okmeydanı Training and Research Hospital (2008) and in Gastroenterohepatology at Ege University School of Medicine (2012). He has worked as clinician and teaching staff in the Department of Gastroenterology at Yeni Yuzyl University, School of Medicine in Istanbul. Throughout his career, Dr. Gencdal has published several national and international articles. His ongoing research interests involve liver transplantation, hepatic encephalopathy, sleep disorders in liver cirrhosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatitis C, hepatitis B, autoimmune hepatitis, primary biliary cholangitis. (L-Editor: Filipodia)

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Prospective Study

Sofosbuvir plus ribavirin is tolerable and effective even in elderly patients 75-years-old and over

Hideyuki Tamai, Naoki Shingaki, Yoshiyuki Ida, Ryo Shimizu, Shuya Maeshima, Junpei Okamura, Akira Kawashima, Taisei Nakao, Takeshi Hara, Hiroyoshi Matsutani, Izumi Nishikawa, Katsuhiko Higashi

ORCID number: Hideyuki Tamai 0000-0003-4511-4573; Naoki Shingaki 0000-0002-1798-4080; Yoshiyuki Ida 0000-0001-9698-9439; Ryo Shimizu 0000-0001-9745-7215; Shuya Maeshima 0000-0002-7316-3260; Junpei Okamura 0000-0002-3312-4128; Akira Kawashima 0000-0001-5345-0732; Taisei Nakao 0000-0003-4823-3703; Takeshi Hara 0000-0002-9682-8974; Hiroyoshi Matsutani 0000-0002-1587-8540; Izumi Nishikawa 0000-0001-5799-8930; Katsuhiko Higashi 0000-0001-5931-706X.

Author contributions: Tamai H drafted the manuscript, provided oversight of the study, and performed data analysis; Shingaki N, Ida Y, Shimizu R, Maeshima S, Okamura J, Kawashima A, Nakao T, Hara T, Matsutani H, Nishikawa I, and Higashi K participated in the design and were involved with data collection; all authors read and approved the final manuscript.

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Hideyuki Tamai, Naoki Shingaki, Department of Hepatology, Wakayama Rosai Hospital, Wakayama 6408505, Japan

Yoshiyuki Ida, Ryo Shimizu, Shuya Maeshima, Second Department of Internal Medicine, Wakayama Medical University, Wakayama 6418509, Japan

Junpei Okamura, Akira Kawashima, Taisei Nakao, Department of Internal Medicine, Naga Municipal Hospital, Wakayama 6496414, Japan

Takeshi Hara, Department of Gastroenterology, Wakayama Rosai Hospital, Wakayama 6408505, Japan

Hiroyoshi Matsutani, Izumi Nishikawa, Katsuhiko Higashi, First Department of Internal Medicine, Hidaka General Hospital, Wakayama 6440002, Japan

Corresponding author: Hideyuki Tamai, MD, PhD, Director, Department of Hepatology, Wakayama Rosai Hospital, 93-1 Kinomoto, Wakayama 6408505, Japan. hdy-tamai@wakayamah.johas.go.jp

Abstract

BACKGROUND

Although clinical use of sofosbuvir plus ribavirin has been approved for patients infected with genotype 2 hepatitis C virus, patients ≥ 75 -years-old have not been included in previous clinical trials.

AIM

To evaluate the real-world safety and efficacy of sofosbuvir plus ribavirin for elderly patients (≥ 75 -years-old) compared to nonelderly patients, we conducted a post-marketing prospective cohort study.

METHODS

We treated 265 patients with genotype 2 hepatitis C virus using standard approved doses of sofosbuvir (400 mg/d) plus ribavirin adjusted by body weight, administered orally for 12 wk.

RESULTS

Sustained virological response rates for the overall cohort, patients < 65 -years-old, ≥ 65 -years-old but < 75 -years-old, and ≥ 75 -years-old were 97% (258/265), 98%

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(93/95), 97% (84/87), and 98% (81/83), respectively ($P = 0.842$). Logistic regression analyses identified history of hepatocellular carcinoma treatment and alpha-fetoprotein as factors significantly associated with sustained virological response. Alpha-fetoprotein was the only independent factor identified. Sustained virological response rate was significantly lower for patients with hepatocellular carcinoma treatment (91%) than for patients without history of hepatocellular carcinoma treatment (98%, $P = 0.004$). One patient (0.4%) discontinued treatment due to drug-induced pneumonia. Dose reduction or interruption of ribavirin was required for 12.1% (32/265) of patients because of anemia, including 7.7% (14/182) of patients < 75-years-old and 21.7% (18/83) of patients \geq 75-years-old ($P = 0.002$).

CONCLUSION

Although ribavirin dose reduction or interruption was required with advanced age, sofosbuvir plus ribavirin appears tolerable and highly effective even in patients \geq 75-years-old.

Key Words: Hepatitis C virus; Genotype 2; Sofosbuvir; Ribavirin; Elderly patients; Cirrhosis

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Core Tip: This was a multicenter post-marketing prospective cohort study of sofosbuvir plus ribavirin therapy for patients with genotype 2 hepatitis C virus in a real-world clinical setting. Combination therapy using sofosbuvir plus ribavirin was tolerable and highly effective even in elderly patients \geq 75-years-old.

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INTRODUCTION

Although interferon (IFN)-based therapy was standard for hepatitis C virus (HCV) infection for many years, clinical trials of IFN-free direct-acting antiviral agent (DAA) regimens using sofosbuvir and ribavirin for patients with genotype 2 HCV have been reported from Western countries since 2013^[1-3]. Those clinical trials demonstrated higher viral eradication rates and lower discontinuation rates than IFN-based therapies, and treatment-related health-related quality of life impairment during treatment was reportedly mild in these clinical trials^[4]. However, patients \geq 75-years-old were not included in the sofosbuvir plus ribavirin regimen of those clinical trials. In May 2015, clinical use of combination therapy comprising sofosbuvir and ribavirin was approved as the first IFN-free therapy for patients infected with genotype 2 HCV in Japan^[5]. This therapy was well tolerated and achieved a high sustained virological response (SVR) rate of 96% in a Japanese Phase III trial. However, patients \geq 75-years-old were again not included in that trial. The safety and effectiveness of sofosbuvir plus ribavirin for elderly patients \geq 75-years-old has thus remained unclear.

In real-world settings, elderly patients \geq 75-years-old represent a substantial and growing population and carry a high risk of advanced liver diseases such as cirrhosis and hepatocellular carcinoma (HCC). These patients should be treated as soon as possible. However, ribavirin has various specific side effects that affect tolerability, such as hemolytic anemia, fatigue, cough, depression, and chest pain^[6,7], whereas sofosbuvir is tolerable with minimal adverse effects^[8]. In our previous study of low-dose pegylated IFN plus ribavirin therapy for elderly and/or cirrhotic patients infected with HCV genotype 2, drug dose reduction or interruption rates among nonelderly cirrhotic patients, elderly noncirrhotic patients, and elderly cirrhotic patients were all relatively high (65%, 63%, and 77%, respectively)^[9]. A high risk of

ribavirin dose reduction or interruption and lower effectiveness in elderly patients can thus be expected even with sofosbuvir plus ribavirin therapy. To evaluate the real-world safety and efficacy of sofosbuvir plus ribavirin for elderly patients ≥ 75 -years-old compared to nonelderly patients, we conducted a post-marketing prospective cohort study.

MATERIALS AND METHODS

Patients

This was a multicenter prospective cohort study. Between June 2015 and June 2017, all patients at Wakayama Medical University Hospital, Naga Municipal Hospital, Hidaka General Hospital, and Wakayama Rosai Hospital who were eligible were enrolled in the present study. The inclusion criterion was infection with HCV genotype 2. Exclusion criteria were any of following: (1) Infection with genotypes other than genotype 2; (2) Hemoglobin concentration < 10 g/dL; (3) Estimated glomerular filtration rate < 30 mL/min/1.73 m²; (4) Decompensated cirrhosis (Child-Pugh class B or C); and (5) Any form of cancer. However, patients who had received curative cancer treatments were not excluded from this study. Therefore, patients with HCC who had undergone surgical resection or ablation therapy were included in this study.

Liver cirrhosis was diagnosed clinically from liver biopsy or imaging studies such as ultrasonography, contrast-enhanced computed tomography, and/or magnetic resonance imaging using morphological signs of cirrhosis from portal hypertension, such as portosystemic shunt or hypersplenism. Sample size for the present study was determined by practicability but was planned to exceed the number of patients analyzed in the Japanese phase III trial^[5]. All study protocols were approved by the ethics committees of the participating hospitals. Written informed consent was obtained from all patients included in this study. The present study was registered on the University Hospital Medical Information Network (trial ID: 000023269).

Treatment regimens

Standard approved doses of 400 mg sofosbuvir (Sovardi, Gilead, TKY, Japan) plus ribavirin (Copegus, Chugai Pharmaceutical, TKY, Japan or Rebetol, MSD, TKY, Japan) adjusted by body weight (1000 mg/d for patients weighing > 80 kg, 800 mg/d for patients weighing ≤ 80 but ≥ 60 kg, and 600 mg/d for patients weighing < 60 kg) were orally administered for 12 wk. If hemoglobin level fell to < 10 g/dL, ribavirin dose was reduced to 200 mg/d, and if hemoglobin level fell to < 8.5 g/dL, ribavirin was discontinued. If the attending physician judged this treatment as difficult to continue due to adverse events, both sofosbuvir and ribavirin were discontinued.

Laboratory test

HCV-RNA load was measured using quantitative reverse transcription polymerase chain reaction (COBAS TaqMan PCR assay version 2; Roche Diagnostics, Branchburg, NJ, United States). HCV genotype was determined using the antibody serotyping method (SRL, TKY, Japan). HCV serotypes 1 and 2 correspond to genotypes 1a/1b and 2a/2b, respectively. When HCV serotype could not be determined, genotype was examined using real-time polymerase chain reaction assay (BML, TKY, Japan). HCV-RNA was checked on the day of therapy initiation and every 4 wk during treatment. Biochemical analyses including blood cell counts, C-reactive protein level, blood sugar level, and liver and renal function tests were performed every 2 wk during treatment.

Assessment of effectiveness

Rapid virological response (RVR) was defined as serum HCV-RNA negativity in week 4 after therapy initiation. End-of-treatment response was defined as serum HCV-RNA negativity in week 12 after therapy initiation. SVR was defined as HCV-RNA negativity at 24 wk after the end of therapy. The primary end point of this study was SVR at 24 wk after the end of therapy. Treatment failure was defined as non-SVR.

Assessment of safety and tolerability

Patients were assessed for the safety and tolerability of treatment by attending physicians who monitored adverse events and laboratory parameters such as blood cell counts and liver and renal function tests every 2 wk. Adverse events were assessed according to Common Terminology Criteria for Adverse Events version 4.0. The incidence of and reasons for therapy discontinuation or interruption due to adverse

events were analyzed.

Statistical analysis

Therapeutic efficacy was evaluated using an intention-to-treat analysis. The Mann-Whitney *U* test or the *t*-test was used to analyze continuous variables. Fisher's exact test or the chi-square test was used to analyze categorical variables. Logistic regression analysis for univariate comparisons was performed to investigate factors contributing to SVR. When multiple factors were significant from univariate analyses, multivariate analysis was also performed to identify independent factors. Values of $P < 0.05$ were considered statistically significant. SPSS for Windows version 24J statistical software (SPSS, TKY, Japan) was used for all data analyses.

RESULTS

Baseline characteristics of patients

A total of 265 patients met the inclusion and exclusion criteria and were enrolled in the present study. Although one patient discontinued treatment due to an adverse event, all enrolled patients completed follow-up for evaluation of safety and effectiveness. Patient characteristics are summarized in Table 1. Median age was 68-years-old (range, 17-86 years), and the cohort was comprised of 150 male and 115 female patients. Patients ≥ 75 -years-old, cirrhotic patients, patients with moderate chronic kidney disease (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m²), patients with a history of HCC treatment, and patients with a history of pegylated IFN plus ribavirin therapy accounted for 31%, 34%, 20%, 12%, and 15%, respectively. Median baseline hemoglobin level was 13.6 g/dL (range, 10.2-20.1 g/dL).

Comparison of pre-treatment factors between patients ≥ 75 -years-old and < 75 -years-old

A comparison of pre-treatment factors between patients ≥ 75 -years-old and < 75 -years-old is shown in Table 2. Significant differences were seen in height, weight, body mass index, cirrhosis, chronic kidney disease, history of HCC treatment, white blood cells, hemoglobin, platelets, alanine aminotransferase, γ -glutamyl transferase, alpha-fetoprotein (AFP) levels, and estimated glomerular filtration rate.

Treatment response

SVR rates overall and according to age groups are shown in Figure 1. SVR rates for the overall cohort, patients < 65 -years-old, patients ≥ 65 -years-old but < 75 -years-old, and patients ≥ 75 -years-old were 97% (258/265), 98% (93/95), 97% (84/87), and 98% (81/83), respectively. No significant differences were observed among age groups ($P = 0.842$).

A comparison of the viral negativity rate between patients ≥ 75 -years-old and < 75 -years-old during treatment is shown in Figure 2. RVR rates for patients ≥ 75 -years-old and < 75 -years-old groups were 84% and 89%, respectively. Although RVR rate tended to be higher in patients ≥ 75 -years-old than in patients < 75 -years-old, the difference was not significant ($P = 0.266$). End-of-treatment response rates of patients ≥ 75 -years-old and < 75 -years-old were 99% and 100%, respectively. No significant difference was apparent between groups ($P = 1.000$).

SVR rates according to background factors are summarized in Figure 3. Although no significant difference was seen in comparisons of SVR rates according to sex, cirrhosis, elderly cirrhosis, IFN plus ribavirin therapy, anemia (hemoglobin < 12 g/dL), or chronic kidney disease, a significant difference was seen between patients with and without a history of HCC treatment ($P = 0.004$). In patients ≥ 75 -years-old with a history of IFN plus ribavirin therapy, all patients achieved SVR (100%; 14/14). In patients ≥ 75 -years-old with cirrhosis, the SVR rate was 98% (40/41).

Factors contributing to SVR

Results of logistic regression analysis to investigate factors contributing to SVR are shown in Table 3. On univariate analyses, a history of HCC treatment and AFP were factors significantly contributing to SVR. Multivariate analyses revealed AFP as the only factor independently associated with SVR.

Table 1 Patient characteristics

	n = 265
Age in yr	68 (17-86)
≥ 75 yr	83 (31%)
Sex as male/female	150/115 (57%/43%)
Cirrhosis	91 (34%)
Moderate chronic kidney disease, eGFR < 60 mL/min/1.73 m ²	53 (20%)
History of HCC treatment	33 (12%)
History of pegylated IFN + ribavirin therapy	39 (15%)
Height in cm	160.2 (134.0-182.0)
Weight in kg	58.0 (32.3-99.3)
BMI in kg/m ²	22.6 (15.5-35.0)
Baseline HCV-RNA in logIU/mL	6.0 (1.4-7.4)
WBC as /mm ³	5000 (1810-13260)
Hb in g/dL	13.6 (10.2-20.1)
Platelets as × 10 ⁴ /mm ³	16.2 (4.6-38.9)
AST in IU/L	43 (12-257)
ALT in IU/L	39 (6-394)
γ-GT in IU/L	32 (5-898)
eGFR	73 (31-156)
AFP in ng/mL	4.3 (1.0-88.3)

Values are expressed as median (range) or numbers (percentage). γ-GT: γ-glutamyl transferase; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HCV-RNA: Hepatitis C virus-ribonucleic acid; IFN: Interferon; WBC: White blood cells.

Treatment failure

Non-SVR was shown in seven patients (3%). Factors between patients with and without SVR are compared in Table 4. When drug adherence was defined as a percentage of the actual administered dose to the planned dose, RVR adherence was not identified as significantly related to non-SVR. History of HCC treatment was the only factor significantly related to non-SVR.

Safety and tolerability

The discontinuation rate due to adverse events was 0.4% (1/256). The reason for discontinuation was drug-induced pneumonitis with positive results for sofosbuvir on drug-induced lymphocyte stimulation testing. Adverse event profiles for the overall cohort, patients ≥ 75-years-old, and patients < 75-years-old are shown in Table 5. The most frequent adverse event other than anemia was elevated uric acid level (Grade 1). No severe liver injury or exacerbation of renal dysfunction was seen. A similar safety profile was observed between patients ≥ 75-years-old and < 75-years-old, except for ribavirin dose reduction or interruption due to anemia. Median ribavirin adherence was significantly lower for patients ≥ 75-years-old (96.8%) than for patients < 75-years-old (100%, *P* = 0.001). Ribavirin dose reduction or interruption was required in 12.1% (32/265) of patients because of anemia, and anemia appeared in 7.7% (14/182) of patients < 75-years-old, and 21.7% (18/83) of patients ≥ 75-years-old. A significant difference in ribavirin dose reduction or interruption rate was also seen between groups (*P* = 0.002).

Table 2 Comparison of pre-treatment factors between patients ≥ 75 -years-old and < 75 -years-old

Factors	Patients ≥ 75 -yr-old, n = 83	Patients < 75 -yr-old, n = 182	P value
Age in yr	79 (75-86)	64 (17-74)	< 0.001
Sex as male/female	42/41 (51%/49%)	108/74 (59%/41%)	0.183
Height in cm	156.7 (134.0-170.0)	162.0 (140.0-182.0)	< 0.001
Weight in kg	53.5 (32.3-81.4)	60.0 (37.6-99.3)	< 0.001
BMI in kg/m ²	22.2 (15.5-29.5)	23.1 (16.5-35.0)	0.009
Cirrhosis	41 (49%)	50 (28%)	< 0.001
CKD, eGFR < 60 mL/min/1.73 m ²	28 (34%)	25 (14%)	< 0.001
History of HCC treatment	18 (22%)	15 (8%)	0.002
History of IFN-based therapy	21 (25%)	42 (23%)	0.693
HCV-RNA as logIU/mL	6.1 (2.3-7.3)	5.9 (1.4-7.4)	0.894
WBC in mm ³	4540 (1810-13260)	5200 (2200-11400)	0.004
Hb in g/dL	12.9 (10.2-20.1)	14.1 (10.6-17.6)	< 0.001
Platelets as $\times 10^4$ /mm ³	14.2 (4.9-32.8)	17.4 (4.6-38.9)	< 0.001
AST in IU/L	40 (14-183)	42 (12-252)	0.589
ALT in IU/L	30 (6-139)	44 (6-394)	< 0.001
γ -GT in IU/L	25 (7-361)	37 (5-888)	0.001
AFP in ng/mL	3.9 (1-32.9)	4.8 (1.1-88.3)	0.014
eGFR	66.0 (33.0-106.9)	77.6 (30.9-156.0)	< 0.001

Values are expressed as median (range) or number (percentage). γ -GT: γ -glutamyl transferase; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HCV-RNA: Hepatitis C virus-ribonucleic acid; IFN: Interferon; WBC: White blood cells.

DISCUSSION

This was a multicenter post-marketing prospective cohort study of sofosbuvir plus ribavirin therapy for patients infected with genotype 2 HCV in a real-world clinical setting. In the present study, 31% of patients were ≥ 75 -years-old, and 12% had a history of HCC treatment. Furthermore, 34% of enrolled patients had cirrhosis, and 20% had moderate chronic kidney disease.

Although some real-world data based on post-marketing cohort studies of sofosbuvir plus ribavirin have been reported, few reports have evaluated safety and efficacy for patients ≥ 75 -years-old. Regarding safety, Ogawa *et al*^[10] indicated that the frequency of adverse effects was higher for a ≥ 65 -year-old group (18.9%) than for the < 65 -year-old group (4.3%, $P < 0.001$). However, discontinuation of all drugs was required for only 3 of the 446 patients (0.7%)^[10]. Atsukawa *et al*^[11] indicated that the incidence of anemia increased significantly with age, and ribavirin dose reduction rate increased sharply in patients > 70 -years-old^[11]. Anemia during treatment occurred in 10.6% (23/218) of patients < 75 -years-old, and in 48.1% (25/52) of patients ≥ 75 -years-old^[11]. However, none of those 270 patients discontinued use of either ribavirin or sofosbuvir^[11]. In the present study, although dose reduction or interruption of ribavirin due to anemia was required in 21.7% of patients ≥ 75 -years-old and 7.7% of patients < 75 -years-old, treatment discontinuation was required for only one patient (0.4%). Therefore, although careful monitoring of anemia and ribavirin dose adjustment is necessary to avoid discontinuation of therapy, this treatment appears tolerable even in patients ≥ 75 -years-old.

Regarding efficacy, Nishida *et al*^[12] reported that although the difference was not significant, patients ≥ 75 -years-old tended to show a lower SVR rate than patients < 75 -years-old (81.3%, 13/16 for patients ≥ 75 -years-old; 96.0%, 24/25 for patients < 75 -years-old)^[12]. Atsukawa *et al*^[11] showed SVR rates of 98.1% (51/51) for patients ≥ 75 -years-old and 96.8% (211/218) for patients < 75 -years-old ($P = 0.999$)^[11]. Ogawa *et al*^[10] reported that although SVR12 was achieved by 95% (69/73) of patients > 75 -years-old,

Table 3 Uni- and multivariate analyses of pre-treatment factors contributing to sustained virological response

Factors	Univariate			Multivariate		
	P value	OR	95%CI	P value	OR	95%CI
Age, per 1-yr increase	0.782	0.991	0.931-1.055			
≥ 75 yr	0.874	1.144	0.217-6.022			
Sex, female	0.977	1.023	0.224-4.663			
Height, per 1-cm increase	0.316	0.957	0.879-1.043			
Weight, per 1-kg increase	0.568	0.982	0.924-1.044			
BMI, per 1-kg/m ² increase	0.929	0.990	0.792-1.238			
Cirrhosis	0.214	0.382	0.084-1.743			
CKD, eGFR > 60 mL/min/1.73 m ²	0.569	0.616	0.116-3.266			
History of HCC treatment	0.027	0.175	0.037-0.822	0.072	0.225	0.044-1.145
History of IFN-based therapy	0.763	0.774	0.146-4.091			
HCV-RNA, per 1-logIU/mL increase	0.644	0.831	0.380-1.821			
WBC in mm ³	0.703	1.009	0.963-1.057			
Hb, per 1-g/dL increase	0.196	1.411	0.837-2.380			
Platelets, per 1 × 10 ⁴ /mm ³ increase	0.790	0.984	0.873-1.109			
AST, per 1-IU/L increase	0.552	1.007	0.983-1.033			
ALT, per 1-IU/L increase	0.608	1.005	0.987-1.023			
γ-GT, per 1-IU/L increase	0.490	1.007	0.987-1.027			
AFP, per 1-ng/mL increase	0.004	0.955	0.926-0.985	0.015	0.959	0.926-0.992
eGFR, per 1-mL/min/1.73 m ² increase	0.124	1.036	0.990-1.083			

γ-GT: γ-glutamyl transferase; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CI: Confidence interval; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HCV-RNA: Hepatitis C virus-ribonucleic acid; IFN: Interferon; OR: Odds ratio; WBC: White blood cells.

the SVR12 rate was significantly lower in cirrhotic patients > 75-years-old with a history of IFN treatment (73.3%, 11/15) than in noncirrhotic patients > 75-years-old (100%, 17/17; $P < 0.01$)^[10]. In the present study, the SVR rate of patients ≥ 75-years-old was 98% (81/83). Among patients ≥ 75-years-old with a history of IFN plus ribavirin therapy, the SVR rate was 100% (14/14). Furthermore, the SVR rate of cirrhotic patients ≥ 75-years-old was also extremely high (98%, 40/41). From these results, a high SVR rate (> 95%) would be expected even in patients ≥ 75-years-old, irrespective of cirrhosis or history of IFN treatment.

Discontinuation of pharmacotherapy^[13], history of HCC^[10,13], cirrhosis (advanced fibrosis)^[10,14,15], renal dysfunction^[16], history of IFN-based treatment^[10,15], lower serum albumin, and ribavirin dose at baseline^[14] have all been reported as factors associated with non-SVR of sofosbuvir plus ribavirin. Hirosawa *et al.*^[13] indicated that the risk factor most strongly associated with non-SVR was a history of HCC treatment (odds ratio: 9.29)^[13]. In the present study, a history of HCC treatment and AFP were factors significantly associated with SVR on univariate analysis, and AFP was the only independent factor on multivariate analyses. High serum AFP levels in patients without HCC have been associated with advanced liver fibrosis and a risk of HCC occurrence^[17,18]. Sofosbuvir plus ribavirin might thus be less effective in cases showing advanced liver fibrosis. Patients with a history of HCC treatment or high AFP level should probably be treated using some other ribavirin-free DAA therapy.

In recent HCV treatment guidelines from Western countries, sofosbuvir plus ribavirin therapy is no longer recommended because of the adverse effects of ribavirin and the relatively lower SVR rate compared to other DAA therapies^[14,19,20]. In fact, the

Table 4 Comparison of factors between patients with and without sustained virological response

Factors	SVR, n = 258	Non-SVR, n = 7	P value
Age in yr, n (range)	68 (17-86)	74 (39-79)	0.682
Sex as male/female	146/112	4/3	1.000
Height in cm	160.1 (134.0-182.0)	161.5 (155.0-177.0)	0.350
Body weight in kg	58.0 (32.3-99.3)	63.2 (54.0-66.2)	0.267
BMI in kg/m ²	22.6 (15.5-38.0)	22.6 (20.2-25.9)	0.778
Cirrhosis	87	4	0.237
CKD	51	2	0.630
History of HCC treatment	30	3	0.044
History of IFN-based therapy	61	2	0.672
HCV-RNA as logIU/mL	6.1 (2.7-7.6)	6.3 (3.3-7.0)	0.713
White blood cells as /mm ³	5005 (1810-13260)	4100 (2260-8700)	0.581
Hemoglobin in g/dL	13.6 (10.2-20.1)	12.5 (11.6-14.7)	0.793
Platelets as × 10 ⁴ /mm ³	16.2 (4.6-38.9)	14.9 (9.9-30.3)	0.930
AST in IU/L	42 (12-252)	37 (19-90)	0.789
ALT in IU/L	39 (6-394)	57 (19-79)	0.843
γ-GTP in IU/L	32 (5-888)	36 (13-461)	0.942
AFP in ng/mL	5.2 (1.0-445.0)	10.6 (1.3-29.7)	0.521
eGFR in mL/min/1.73 m ²	73.1 (30-240.2)	72.2 (50.5-105.8)	0.166
Ribavirin adherence in %	100 (28-100)	100 (100-100)	0.323

Values are expressed as median (range) or number of patients. γ-GTP: γ-glutamyl transferase; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CKD: Chronic renal disease; eGFR: Estimated glomerular filtration rate; HCC: hepatocellular carcinoma; HCV: Hepatitis C virus; HCV-RNA: Hepatitis C virus-ribonucleic acid; IFN: Interferon; SVR: Sustained virological response.

real-life SVR rate from nationwide German data was lower compared to SVR rates of clinical trials (83% in intention-to-treat analysis)^[21]. Recently, ribavirin-free DAA therapies such as glecaprevir plus pibrentasvir, and sofosbuvir plus ledipasvir have also been approved for use in patients with HCV genotype 2 in Japan^[22,23]. These therapies have shown no adverse effects due to ribavirin and have thus become first-line treatments. These therapies also represent rescue treatments for patients with sofosbuvir plus ribavirin failure. However, in consensus statements and recommendations on the treatment of hepatitis C from the Asian-Pacific Association for the Study of the Liver, sofosbuvir plus weight-based ribavirin for 12 wk is recommended as a first-line treatment, and ledipasvir and sofosbuvir for 12 wk is recommended for treatment-naïve HCV genotype 2 patients who cannot tolerate ribavirin^[24]. In addition, SVR rates from Asian real-world data were similar to those of the phase III trial^[25]. Sofosbuvir plus ribavirin therapy offers advantages in terms of both cost and real-world evidence.

Some limitations need to be considered for the present study. First, some selection biases would be present. Second, the number of patients may not have been sufficient to reach definitive conclusions regarding safety and effectiveness in patients ≥ 75-years-old. Third, reasons for failure of this therapy could not be clarified by our analysis because the number of patients who did not achieve SVR was too small. Furthermore, sofosbuvir-specific resistance-associated substitutions (RASs) were not tested for in this study. The prevalence of the naturally occurring RAS S282T, as the only known variant conferring sofosbuvir resistance *in vitro*, is reportedly rare in genotype 2 (0.22%)^[26]. However, RAS A150V has recently been found to be associated with reduced response to treatment with sofosbuvir and ribavirin and has appeared in genotype 2a (13.8%) and genotype 2b (1.03%)^[26]. In addition, the naturally occurring nucleoside inhibitor-specific RASs (E237G, M289I/L, L320 F, and V321A/I) are also found in genotype 2^[26]. The influence of these preexisting RASs on SVR should be analyzed using a larger number of cases with treatment failure.

Table 5 Adverse events during treatment

	Total, <i>n</i> = 265	Patients ≥ 75-yr-old, <i>n</i> = 83	Patients < 75-yr-old, <i>n</i> = 182	<i>P</i> value
Treatment discontinuation due to adverse events ¹	1 (0.4%)	1 (1.2%)	0	0.313
Dose reduction or interruption of ribavirin due to anemia ²	32 (13.2%)	18 (21.7%)	14 (7.7%)	0.002
Dermatitis	9 (3.4%)	1 (1.2%)	8 (4.4%)	0.281
Depression	3 (1.1%)	1 (1.2%)	2 (0.5%)	1.000
Headache	4 (1.5%)	0	4 (2.2%)	0.313
Infection	4 (1.5%)	1 (1.2%)	3 (1.6%)	1.000
Other adverse events	11 (4.2%)	5 (6.0%)	6 (3.3%)	0.328
Elevated bilirubin level	2 (0.8%)	1 (1.2%)	1 (0.5%)	0.529
Elevated transaminase level	4 (1.5%)	2 (2.4%)	2 (1.1%)	0.592
Elevated serum ammonia level	5 (1.9%)	2 (2.4%)	3 (1.6%)	0.650
Elevated uric acid level	26 (9.8%)	10 (12.0%)	16 (8.8%)	0.504

¹Drug-induced pneumonitis with positivity to sofosbuvir on drug-induced lymphocyte stimulation test.

²Significant difference between patients ≥ 75-years-old and < 75-years-old (*P* < 0.01).

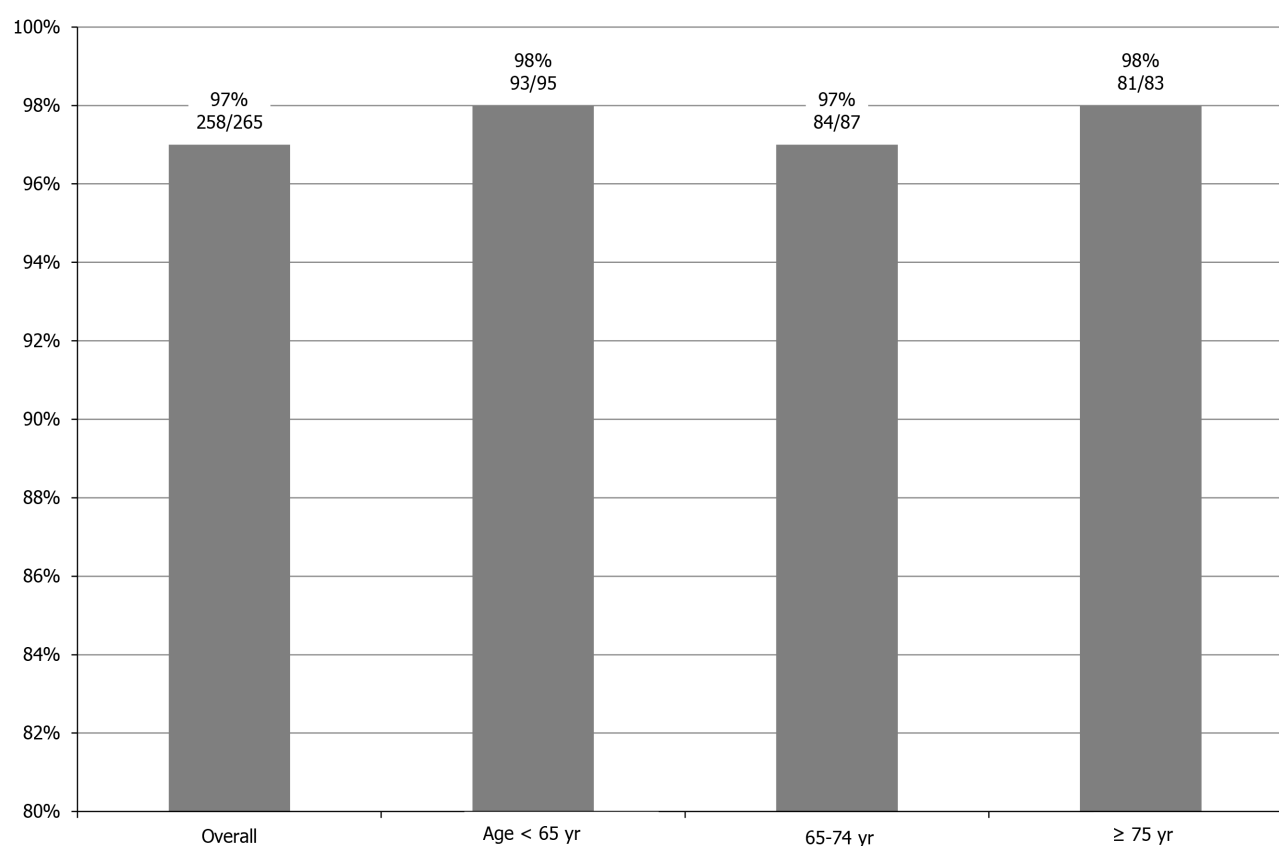


Figure 1 Sustained virological response rates according to age groups. The sustained virological response rates for the overall cohort, patients < 65-years-old, patients ≥ 65-years-old but < 75-years-old, and patients ≥ 75-years-old are 97% (258/265), 98% (93/95), 97% (84/87), and 98% (81/83), respectively. No significant differences are apparent among age groups (*P* = 0.842).

Sofosbuvir and ribavirin represent an acceptable and effective treatment even for patients ≥ 75-years-old in a real-world setting. An extremely high SVR rate can be achieved when adequate management for adverse effects is performed to avoid discontinuation of treatment, irrespective of age.

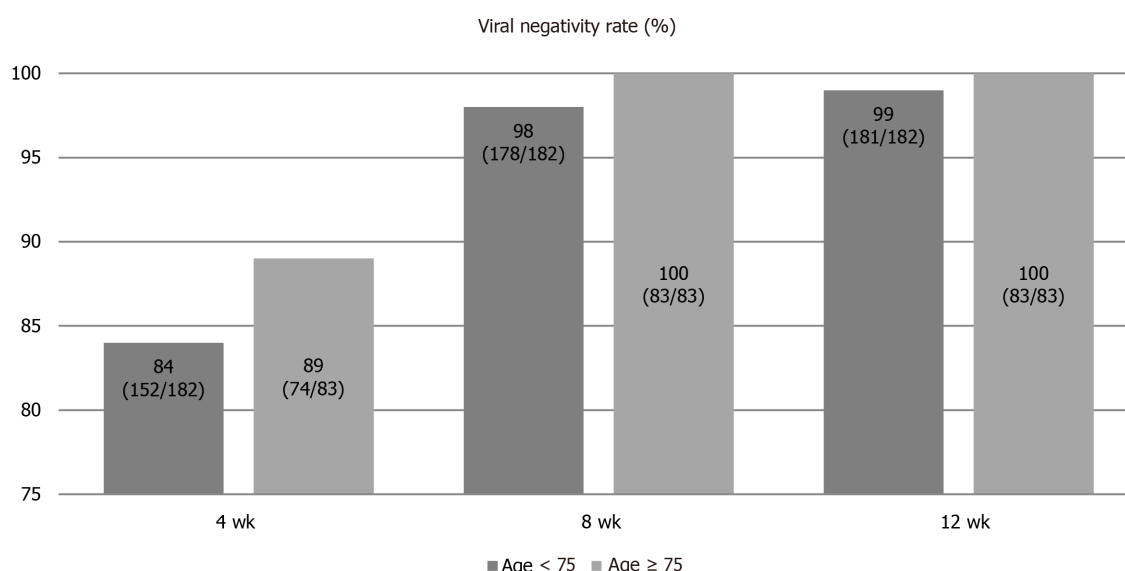


Figure 2 Comparison of viral negativity rates between patients ≥ 75-years-old and < 75-years-old during treatment. Rapid virological response rates of patients ≥ 75-years-old and < 75-years-old are 84% and 89%, respectively. Although rapid virological response rates tend to be higher in patients ≥ 75-years-old than in patients < 75-years-old, the difference is not significant ($P = 0.266$). End-of-treatment response rates for patients ≥ 75-years-old and < 75-years-old are 99% and 100%, respectively. No significant difference is seen between groups ($P = 1.000$).

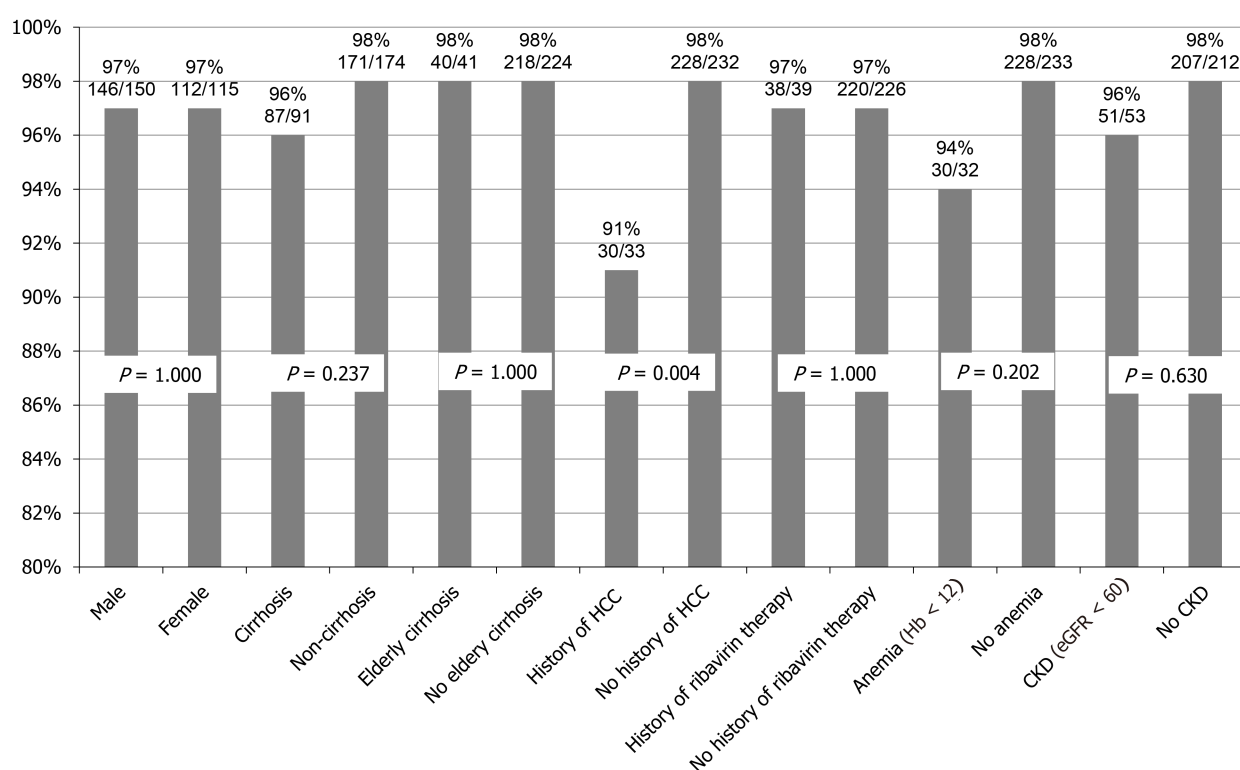


Figure 3 Sustained virological response rates according to background factors. Although no significant differences are seen in comparisons of sustained virological response rates according to sex, cirrhosis, elderly cirrhosis, interferon plus ribavirin therapy, anemia (hemoglobin < 12 g/dL), or chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m²), a significant difference is evident between patients with and without a history of hepatocellular carcinoma treatment ($P = 0.004$). CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HCC: Hepatocellular carcinoma.

ARTICLE HIGHLIGHTS

Research background

In real-world settings, elderly patients infected with hepatitis C virus (HCV) represent a substantial and growing population and carry a high risk of advanced liver diseases such as cirrhosis and hepatocellular carcinoma. Therefore, these patients should be treated as soon as possible. Clinical trials of interferon-free direct-acting antiviral agent regimens using sofosbuvir and ribavirin for patients with genotype 2 HCV have been reported since 2013. However, patients ≥ 75 -years-old were not included in the sofosbuvir plus ribavirin regimen of those clinical trials. The safety and effectiveness of sofosbuvir plus ribavirin for elderly patients ≥ 75 -years-old has thus remained unclear.

Research motivation

In recent HCV treatment guidelines from Western countries, sofosbuvir plus ribavirin therapy is no longer recommended because of the adverse effects of ribavirin and the relatively lower sustained viral response (SVR) rate compared to other direct-acting antiviral agent therapies. However, in consensus statements and recommendations on the treatment of hepatitis C from the Asian-Pacific Association for the Study of the Liver, sofosbuvir plus weight-based ribavirin for 12 wk is recommended as a first-line treatment, and SVR rates from Asian real-world data were similar to those of the phase III trial. Sofosbuvir plus ribavirin therapy also offers advantages in terms of both cost and real-world evidence. The real-world safety and efficacy of sofosbuvir plus ribavirin for elderly patients ≥ 75 -years-old can provide useful information regarding treatment strategy for elderly patients with HCV in the Asia-Pacific region.

Research objectives

The aim of the present study is to evaluate the real-world safety and efficacy of sofosbuvir plus ribavirin for elderly patients ≥ 75 -years-old compared to non-elderly patients

Research methods

This is a multicenter post-marketing prospective cohort study of sofosbuvir plus ribavirin therapy for patients infected with genotype 2 HCV in a real-world clinical setting. We treated 265 patients with genotype 2 HCV using standard approved doses of sofosbuvir (400 mg/d) plus ribavirin adjusted by body weight, administered orally for 12 wk. In the present study, 31% of patients were ≥ 75 -years-old, and 12% had a history of hepatocellular carcinoma (HCC) treatment. Furthermore, 34% of enrolled patients had cirrhosis, and 20% had moderate chronic kidney disease. The primary end point of the present study was SVR at 24 wk after the end of therapy.

Research results

Regarding efficacy, SVR rates for the overall cohort, patients < 65 -years-old, ≥ 65 -years-old but < 75 -years-old, and ≥ 75 -years-old were 97% (258/265), 98% (93/95), 97% (84/87), and 98% (81/83), respectively ($P = 0.842$). Among patients ≥ 75 -years-old with a history of interferon plus ribavirin therapy, the SVR rate was 100% (14/14). Furthermore, the SVR rate of cirrhotic patients ≥ 75 -years-old was also extremely high (98%, 40/41). From these results, a high SVR rate ($> 95\%$) would be expected even in patients ≥ 75 -years-old, irrespective of cirrhosis or history of interferon treatment. Logistic regression analyses identified history of HCC treatment and alpha-fetoprotein as factors significantly associated with SVR. SVR rate was significantly lower for patients with HCC treatment (91%) than for patients without history of HCC treatment (98%, $P = 0.004$). Regarding safety, although dose reduction or interruption of ribavirin due to anemia was required in 21.7% of patients ≥ 75 -years-old and 7.7% of patients < 75 -years-old, treatment discontinuation was required for only one patient (0.4%). Therefore, this treatment appears tolerable even in patients ≥ 75 -years-old.

Research conclusions

Sofosbuvir and ribavirin represent an acceptable and effective treatment even for patients ≥ 75 -years-old in a real-world setting. An extremely high SVR rate can be achieved when adequate management for adverse effects is performed to avoid discontinuation of treatment, irrespective of age.

Research perspectives

Sofosbuvir plus ribavirin might be less effective in patients with a history of HCC treatment or high alpha-fetoprotein level, irrespective of age. These patients should probably be treated using some other ribavirin-free direct-acting antiviral agent therapy.

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