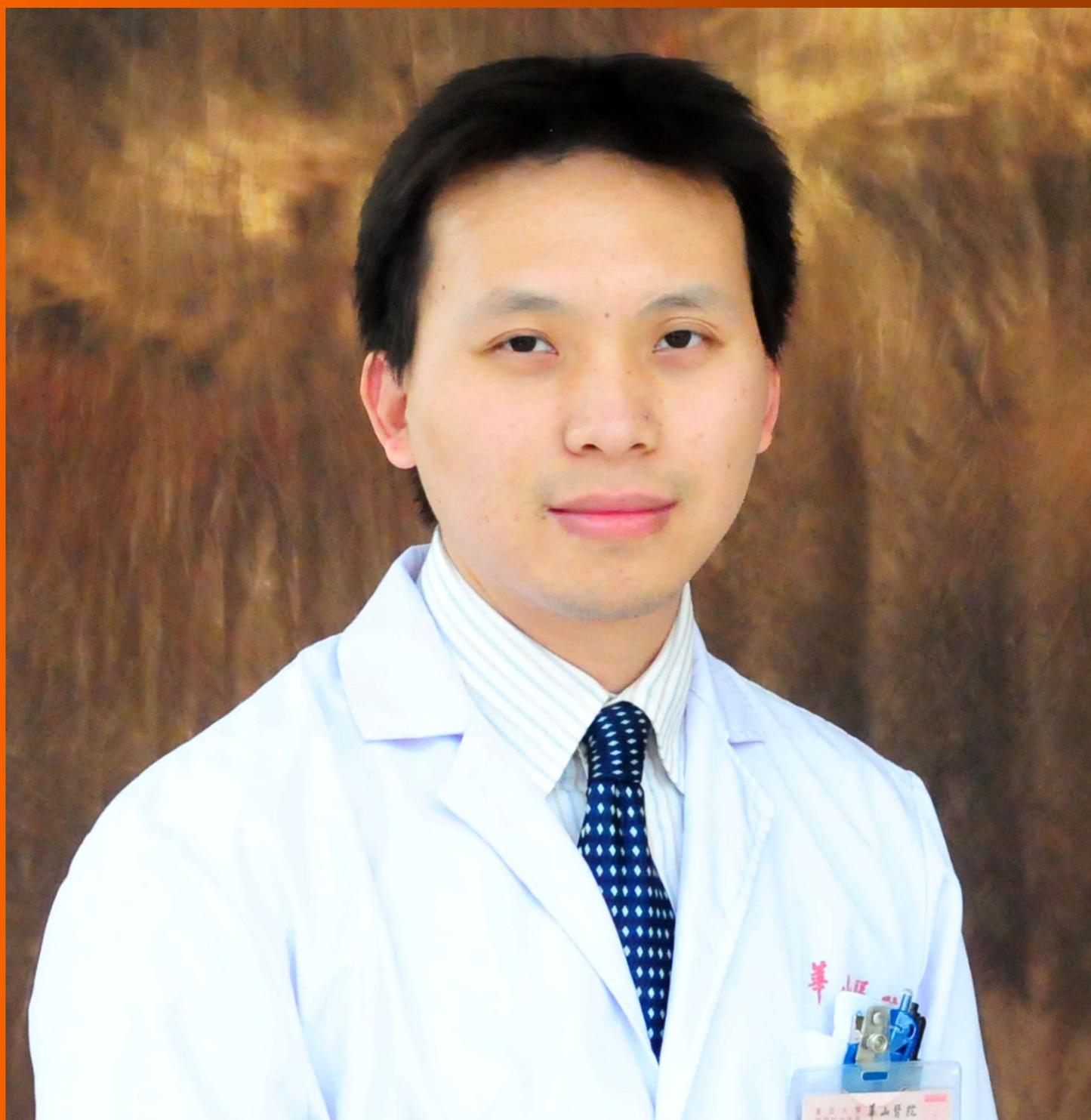


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World J Gastroenterol 2018 April 7; 24(13): 1373-1490



REVIEW

- 1373 Dissecting the molecular pathophysiology of drug-induced liver injury
Ye H, Nelson LJ, Gómez del Moral M, Martínez-Naves E, Cubero FJ

MINIREVIEWS

- 1386 Thrombocytopenia after liver transplantation: Should we care?
Takahashi K, Nagai S, Safwan M, Liang C, Ohkohchi N

ORIGINAL ARTICLE

Basic Study

- 1398 Systems pharmacology approach reveals the antiinflammatory effects of *Ampelopsis grossedentata* on dextran sodium sulfate-induced colitis
Chen YL, Zhang YL, Dai YC, Tang ZP

Retrospective Cohort Study

- 1410 Potential triggering factors of acute liver failure as a first manifestation of autoimmune hepatitis-a single center experience of 52 adult patients
Buechter M, Manka P, Heinemann FM, Lindemann M, Baba HA, Schlattjan M, Canbay A, Gerken G, Kahraman A

- 1419 *Helicobacter pylori* infection in subjects negative for high titer serum antibody
Toyoshima O, Nishizawa T, Arita M, Kataoka Y, Sakitani K, Yoshida S, Yamashita H, Hata K, Watanabe H, Suzuki H

Retrospective Study

- 1429 Impact of postoperative TNM stages after neoadjuvant therapy on prognosis of adenocarcinoma of the gastro-oesophageal junction tumours
Thomaschewski M, Hummel R, Petrova E, Knief J, Wellner UF, Keck T, Bausch D

- 1440 Mild drinking habit is a risk factor for hepatocarcinogenesis in non-alcoholic fatty liver disease with advanced fibrosis
Kimura T, Tanaka N, Fujimori N, Sugiura A, Yamazaki T, Joshita S, Komatsu M, Umemura T, Matsumoto A, Tanaka E

- 1451 Prognostic significance of combined preoperative fibrinogen and CA199 in gallbladder cancer patients
Xu WY, Zhang HH, Yang XB, Bai Y, Lin JZ, Long JY, Xiong JP, Zhang JW, Sang XT, Zhao HT

- 1464 Fecal microbial dysbiosis in Chinese patients with inflammatory bowel disease
Ma HQ, Yu TT, Zhao XJ, Zhang Y, Zhang HJ

Prospective Study

- 1478** Hepatocellular carcinoma or interferon-based therapy history attenuates sofosbuvir/ribavirin for Japanese genotype 2 hepatitis C virus

Yada M, Miyazaki M, Tanaka K, Masumoto A, Motomura K

CASE REPORT

- 1486** Gilbert syndrome combined with prolonged jaundice caused by contrast agent: Case report

Qian JD, Hou FQ, Wang TL, Shao C, Wang GQ

ABOUT COVER

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Prospective Study

Hepatocellular carcinoma or interferon-based therapy history attenuates sofosbuvir/ribavirin for Japanese genotype 2 hepatitis C virus

Masayoshi Yada, Masayuki Miyazaki, Kosuke Tanaka, Akihide Masumoto, Kenta Motomura

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Abstract

AIM

To investigate the real-world efficacy and safety of sofosbuvir/ribavirin (SOF/RBV) therapy for Japanese patients with genotype 2 hepatitis C virus (GT2-HCV).

METHODS

A total of 182 patients with GT2-HCV infection who received SOF/RBV therapy for 12 wk at our hospital were enrolled. The patients comprised 122 men and 60 women (age range: 17-84 years; mean age \pm SD: 60.1 \pm 12.1 years). Relationships between virological response and clinical data were examined by logistic regression analyses.

RESULTS

The proportions of patients with liver cirrhosis and history of hepatocellular carcinoma (HCC) were 29.0% and 17.3%, respectively. The proportion of patients with prior interferon (IFN)-based therapy was 25.6%. SOF/RBV therapy rapidly decreased HCV RNA levels. Several patients required RBV dose reduction because of anemia or fatigue. Four patients discontinued the therapy. The rates of sustained virological response at 12 wk after the end of treatment were 87.9% (intention

to treat: 160/182) and 94.1% (per protocol: 159/169). Multivariate analyses showed that history of HCC or IFN-based therapy independently reduced the efficacy of SOF/RBV therapy.

CONCLUSION

SOF/RBV therapy for GT2-HCV is safe, highly tolerated, and effective. History of HCC or IFN-based therapy independently reduces the efficacy of this treatment.

Key words: Sofosbuvir; Ribavirin; Genotype 2; Hepatitis C virus; Interferon-based therapy; Hepatocellular carcinoma

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Core tip: The real-world efficacy of sofosbuvir/ribavirin therapy for genotype 2 hepatitis C virus infection in Japan is high. Sofosbuvir/ribavirin therapy is safe and highly tolerated. History of hepatocellular carcinoma or interferon-based therapy independently reduces the efficacy of sofosbuvir/ribavirin therapy. Progressive liver fibrosis may attenuate the antiviral effect of sofosbuvir/ribavirin therapy.

Yada M, Miyazaki M, Tanaka K, Masumoto A, Motomura K. Hepatocellular carcinoma or interferon-based therapy history attenuates sofosbuvir/ribavirin for Japanese genotype 2 hepatitis C virus. *World J Gastroenterol* 2018; 24(13): 1478-1485 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i13/1478.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i13.1478>

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis (LC), and hepatocellular carcinoma (HCC). In Global hepatitis report 2017^[1], World Health Organization (WHO) described that 71 million persons were living with chronic HCV infection in 2015 (the global prevalence of HCV infection was 1.0%). Approximately 399000 people died each year from HCV, mostly from LC and HCC. In 2011, Japanese estimated number of persons with chronic HCV infection was 1.25 million containing 64% with genotype 1B and 35% with genotype 2, respectively^[2]. WHO targets 80% of persons with HCV will be treated by 2030^[1]. Combination therapy with peg-interferon (PEG-IFN) and ribavirin (RBV) was the first-line therapy for genotype 2 HCV (GT2-HCV) infection, but only 80% of patients achieved elimination of HCV with this treatment^[3]. The introduction of direct-acting antiviral agents has drastically improved the efficacy of treatments for chronic HCV infection. In Japan, telaprevir (TVR), a first-generation NS3/4A protease inhibitor for GT2-HCV, was approved for clinical use

in 2013. Patients received TVR (750 mg, every 8 h) for 12 wk and PEG-IFN/RBV for 24 wk. The sustained virological response (SVR) rate in patients receiving triple therapy (TVR/PEG-IFN/RBV) was reported to be 85%^[4].

Subsequently, combination therapy with NS5B RNA-dependent RNA polymerase inhibitor sofosbuvir (SOF) and RBV for patients with GT2-HCV infection was approved for clinical use in June 2015. This therapy showed improved efficacy and was well tolerated in a phase 3 trial^[5]. We conducted a prospective study to investigate the efficacy and safety of SOF/RBV therapy for Japanese patients with GT2-HCV infection in a real-world clinical setting.

MATERIALS AND METHODS

Patients

A total of 182 patients with chronic GT2-HCV infection who received SOF/RBV therapy at Iizuka Hospital from September 2015 to January 2017 were enrolled. The patients comprised 122 men and 60 women with an age range of 17-86 years (mean \pm SD: 60.1 \pm 14.1 years). HCV genotype was determined by sequencing the NS5B region of the HCV genome. The results revealed 109 patients with genotype 2A and 70 patients with genotype 2B. Genotype was not determined in 3 patients. Presence of resistance-associated substitution (RAS) was analyzed by sequence determination around S282 in the NS5B region of the HCV genome. Two single nucleotide polymorphisms (SNPs), rs8099917 in the *interleukin-28B* (*IL28B*) locus associated with interferon (IFN) therapy^[6] and rs1127354 in the *inosine triphosphate pyrophosphatase* (*ITPA*) locus associated with RBV-induced hemolytic anemia^[7-9], were analyzed. fibrosis (FIB)-4 index was calculated as a noninvasive marker of liver fibrosis: FIB-4 index = age (years) \times aspartate aminotransferase (IU/L)/[platelet count \times 10⁹/L \times (alanine aminotransferase IU/L)^{1/2}]. FIB-4 index of > 3.25 was defined as progressive fibrosis, based on a previous report^[10].

Treatment regimen

SOF (Sovaldi[®], Gilead Sciences Inc., Durham, NC, United States) was administered orally at a dose of 400 mg once daily, and RBV (Rebetol[®], MSD, Tokyo, Japan or Copegus[®], Chugai, Shizuoka, Japan) was administered orally at a dose of 200-1000 mg for 12 wk. The starting RBV dose was determined by body weight (600 mg for < 60 kg; 800 mg for 60-80 kg; 1000 mg for > 80 kg) (Figure 1).

Evaluation of virological response

HCV RNA levels were measured by a COBAS TaqMan test (Roche Diagnostics, Tokyo, Japan) with a lower limit of quantitation of 1.2 logIU/mL. HCV RNA was measured at screening, at day 1 and weeks 4, 8, and 12 of treatment, and at 12 wk after the end of

Table 1 Pretreatment characteristics of the patients (*n* = 182)

Pretreatment characteristics	Values
Age ¹ , yr	60.1 ± 14.1
Age ≥ 70 yr	27.40%
Sex, M : F	122:60
Body height ¹ , cm	163.0 ± 8.9
Body weight ¹ , kg	62.3 ± 12.1
Liver cirrhosis	26.60%
History of HCC	15.90%
FIB-4 index ²	2.63 (0.45-19.03)
FIB-4 index > 3.25	40.70%
Wisteria floribunda agglutinin+-Mac-2 binding protein ²	1.94 (0.20-18.51)
Hyaluronic acid ² , ng/mL	97.4 (10.0-2750.0)
History of IFN-based therapy	23.60%
<i>IL28B</i> -SNP rs8099917 TT/non TT	136/38/8
<i>ITPA</i> -SNP rs1127354 CC	129/45/8
HCV genotype 2A/2B/ND	109/70/3
HCV RNA ² , logIU/mL	6.1 (1.2-7.6)
HCV RNA > 6 logIU/mL	58.80%
White blood cell count ² , /mm ³	4575 (1700-12010)
Hemoglobin ² , g/dL	13.7 (10.1-17.6)
Platelet count ² , /mm ³	165 (38-389) × 10 ³
Aspartate aminotransferase ² , IU/L	41 (14-336)
Alanine aminotransferase ² , IU/L	40 (5-391)
Albumin ² , g/dL	4.0 (2.6-5.0)
Total bilirubin ² , mg/dL	0.8 (0.3-3.0)
Blood urea nitrogen ² , mg/dL	13 (5-28)
Creatinine ² , mg/dL	0.71 (0.32-1.23)
Estimated glomerular filtration rate ² , mL/min/1.73 m ²	78.9 (42.6-164.2)

¹Mean ± SD; ²Median (range). M: Male; F: Female; HCC: Hepatocellular carcinoma; FIB: Fibrosis; *IL28B*: Interleukin-28B; SNP: Single nucleotide polymorphisms; *ITPA*: Inosine triphosphate pyrophosphatase; HCV: Hepatitis C virus.

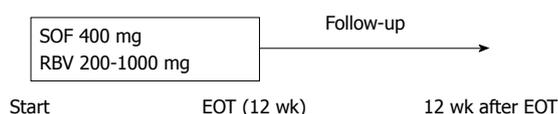


Figure 1 Treatment regimen of sofosbuvir and ribavirin. SOF: Sofosbuvir; RBV: Ribavirin; EOT: End of treatment.

treatment. The primary endpoint was the rate of SVR at 12 wk after the end of treatment (SVR12), defined as undetectable serum HCV RNA at this time point. Relapse and breakthrough were defined based on the guidelines of the American Association for the Study of Liver Diseases^[11].

Safety assessments

Safety evaluations included reported adverse events and serious adverse events, clinical laboratory tests, and physical examinations.

Statistical analysis

Statistical analyses were performed using JMP software version 8.0.2 (SAS Institute Inc., Cary, NC, United States). Hemoglobin levels and estimated glomerular filtration rate were compared by the Tukey honestly significant difference test. Categorical data were

compared by Chi-squared test. To identify independent factors predicting non-SVR, sex, age, liver cirrhosis, and variables with values of *P* < 0.05 in univariate analyses were entered into a multiple logistic regression analysis. Values of *P* < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The pretreatment characteristics of all patients enrolled in the study are presented in Table 1. There were 48 patients (26.4%) with LC, 43 (23.7%) with history of IFN-based therapy, and 28 (15.4%) with history of HCC. Presence of the SNPs in *IL28B* (rs8099917) and *ITPA* (rs1127354) was examined in 174 of 182 patients. HCV RAS of S282 in the NS5B domain was not detected in the 138 patients examined by the RAS test.

Treatment outcomes

Of the 182 patients, 178 (97.8%) completed the treatment. The causes of treatment discontinuation were fatigue (*n* = 1; 0.5%) and self-withdrawal (*n* = 3; 1.6%). The rates of SVR12 were 87.9% [intention to treat (ITT): 160/182] and 94.1% [per protocol (PP): 159/169]. SVR12 was not evaluated in 12 patients (6.7%) because of dropout from the study (Figure 2).

Hemoglobin levels during the treatment period were significantly reduced until 4 wk after the start of administration (Figure 3A). CC of the *ITPA* allele strongly contributed to anemia (Figure 3B). Twenty-nine (15.9%) of 182 patients needed RBV dose reduction because of anemia, but no patients discontinued the treatment for this reason. Although SOF and RBV cannot be used in patients with decreased renal function and we were concerned about SOF/RBV therapy decreasing the renal function of our patients, the estimated glomerular filtration rate did not change significantly during the treatment period (Figure 3C).

Factors contributing to SVR in the PP analysis

In the PP analysis, 13 of 182 patients who discontinued treatment and/or were not evaluated for SVR12 were excluded (Figure 2A). One hundred twenty three of 169 patients (72.8%) achieved rapid virological response (RVR), defined as undetectable serum HCV RNA after 4 wk of treatment. In univariate analyses, history of IFN-based therapy, LC, and history of HCC reduced the virological response, while age (≥ 70 years), sex, FIB-4 index, *IL28B* SNP, *ITPA* SNP, HCV genotype, pretreatment viral load, RBV dose reduction, and RVR had no effect on the treatment efficacy (Figures 4 and 5). The SNPs of *IL28B* and *ITPA* were determined for 161 patients in the PP analysis. The HCV viral genotype was determined in 166 patients. Multivariate analysis showed that history of HCC or IFN-based therapy was independently related to non-

Table 2 Factors contributing to sustained virological response in the per protocol analysis

	Univariate			Multivariate		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age, \geq 70 yr	2.61	0.70, 9.82	0.1494			
Sex, male	4.76	0.85, 88.89	0.0781			
History of IFN-based therapy	5.12	1.39, 20.98	0.0147 ^a	7.05	1.65, 36.08	0.0084 ^a
Liver cirrhosis	6.72	1.78, 32.29	0.0048 ^a	2.13	0.31, 14.34	0.4315
FIB-4 index, $>$ 3.25	2.11	0.58, 8.54	0.2546			
History of HCC	8.87	2.36, 37.04	0.0015 ^a	7.67	1.30, 60.30	0.0233 ^a
<i>IL28B</i> -SNP, non TT	1.21	0.17, 5.55	0.8214			
<i>ITPA</i> -SNP, non CC	0.45	0.02, 2.63	0.4177			
HCV genotype, 2A	2.78	0.67, 18.84	0.1687			
Viral load, \geq 6 logIU/mL	1.53	0.41, 7.31	0.5478			
RBV dose reduction	2.29	0.47, 8.89	0.2757			
Rapid virological response	0.86	0.22, 4.15	0.8401			

^a*P* < 0.05, significant difference. IFN: Interferon; FIB: Fibrosis; HCC: Hepatocellular carcinoma; *IL28B*: Interleukin-28B; SNP: Single nucleotide polymorphisms; *ITPA*: Inosine triphosphate pyrophosphatase; HCV: Hepatitis C virus; RBV: Ribavirin.

Table 3 Assessment of patients with history of hepatitis C virus

	SVR (<i>n</i> = 23)	Non SVR (<i>n</i> = 6)	P value
Alpha fetoprotein	9.6 (1.7-348.9)	5.3 (2.6-65.7)	0.2815
Latest treatment for HCC			0.2558
Surgical resection or Radiofrequency ablation	73.9% (17)	66.6% (6)	
Transcatheter arterial chemoembolization	26.1% (6)	16.7% (1)	
Radiation for bone metastasis	0% (0)	16.7% (1)	
Recurrent HCC within 1 yr from the end of SOF/RBV	65.2% (15)	83.3% (5)	0.6328

SVR: Sustained virological response; HCC: Hepatocellular carcinoma; SOF/RBV: Sofosbuvir/ribavirin.

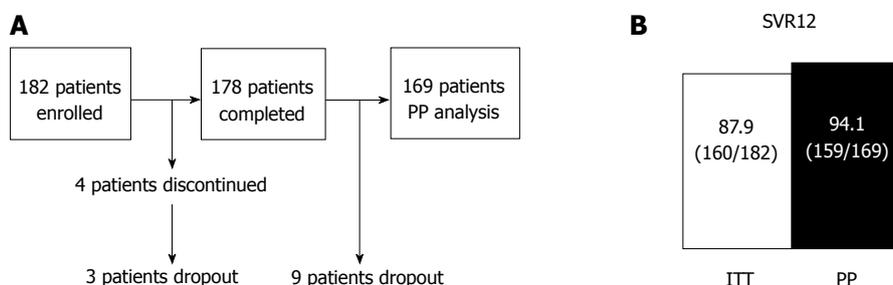


Figure 2 Flow sheet of this study (A) and virological response rates for combination therapy with sofosbuvir and ribavirin (B). The rates of sustained virological response at 12 wk after the end of treatment are shown for intention to treat and per protocol analyses. PP: Per protocol; ITT: Intention to treat; SVR12: Sustained virological response at 12 wk after the end of treatment.

SVR (Table 2).

Assessment of patients with history of HCC

We assessed 29 patients with history of HCC. We ascertained that their HCC was not detected by dynamic computed tomography or dynamic magnetic resonance imaging before initiation of SOF/RBV therapy. We compared alpha fetoprotein (AFP), latest therapy for HCC, and HCC recurrence within 1 year after the end of SOF/RBV therapy according to SVR or non-SVR (Table 3). The AFP level did not differ significantly between the two groups. Patients achieving SVR tended to be treated by surgical resection or radiofrequency ablation,

and also tended to have no HCC recurrence.

DISCUSSION

Combination therapy with SOF/RBV was the first IFN-free therapy for GT2-HCV infection approved for clinical use in Japan. In a phase 3 trial, 97% of patients achieved SVR12 and no patients discontinued the treatment^[5]. Thus, we expected high efficacy and tolerability, and conducted a prospective study in a real-world clinical practice setting to investigate the efficacy and safety of this combination therapy for Japanese patients with GT2-HCV infection.

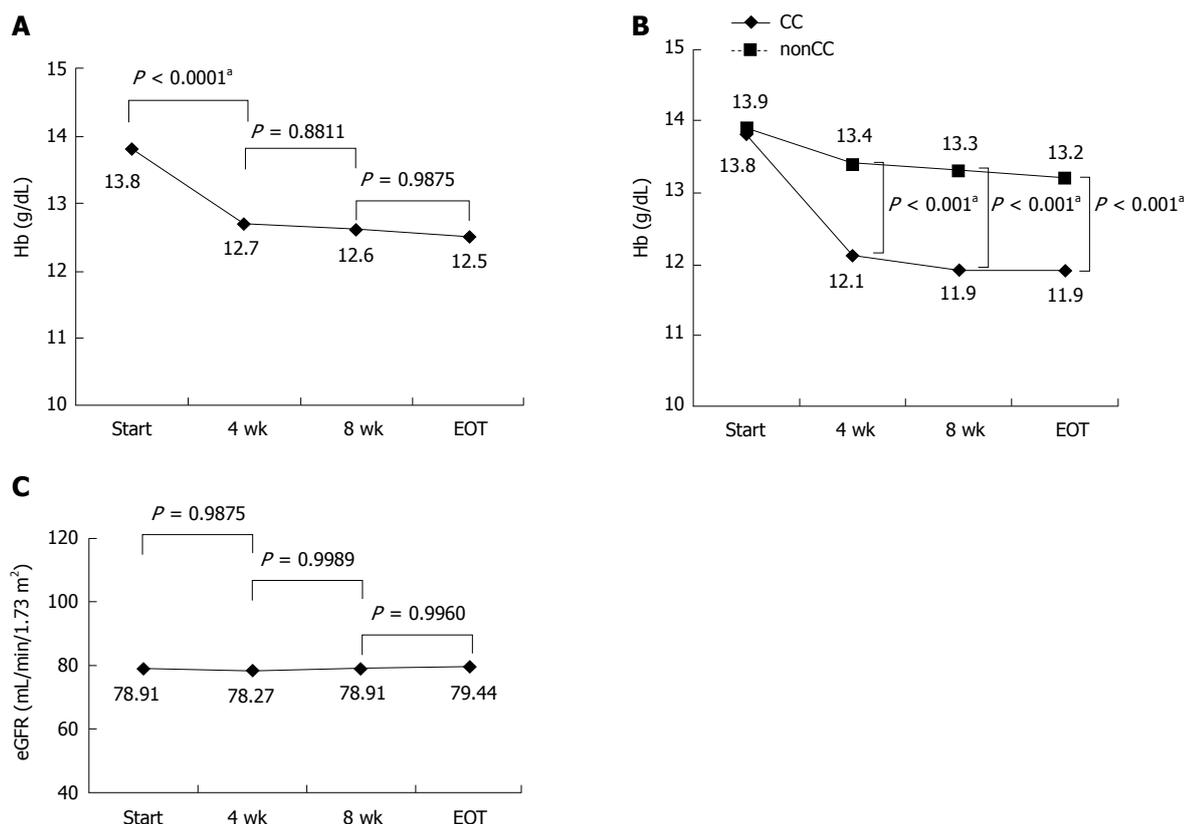


Figure 3 Hemoglobin levels in all patients during combination therapy with sofosbuvir and ribavirin (A), hemoglobin levels in 175 patients categorized by *inosine triphosphate pyrophosphatase* single nucleotide polymorphism rs1127354 (CC or non CC) (B), and estimated glomerular filtration rate levels in all patients during sofosbuvir/ribavirin therapy (C). Hb: Hemoglobin; EOT: End of treatment; eGFR: Estimated glomerular filtration rate. ^a $P < 0.05$, significant difference.

Hemoglobin levels rapidly reduced until 4 wk after the start of treatment. *ITPA* CC allele significantly contributed to anemia in this therapy, similar to the case for combination therapy of PEG-IFN and RBV^[7-9]. Therefore, patients with the *ITPA* CC allele should be monitored frequently for their hemoglobin levels until 4 wk after the start of treatment. Despite our concern that SOF and RBV may decrease renal function of the patients, renal function degeneration was not observed in any of the patients. Many elderly patients (27.4% were aged ≥ 70 years) and cirrhotic patients (26.6% had liver cirrhosis) were enrolled in this study. Thus, the present findings demonstrate that SOF/RBV therapy is safe and highly tolerated regardless of age and LC.

The ITT rate in this study was low compared with the rates in phase 3 clinical trials of SOF/RBV for Japanese^[5] and European^[12] patients with GT2-HCV infection. The reason for the difference was that SVR12 could not be evaluated in 12 patients (6.7%) because of dropout from the study. It is important to monitor carcinogenesis after virus elimination, and it is therefore necessary to provide patients with instructions that promote periodic examinations. Meanwhile, the PP rate was almost equal to the rates in the phase 3 clinical trial of SOF/RBV for Japanese patients with GT2-HCV infection^[5] and in real-world cohorts in North America and Europe^[13].

This finding shows that SOF/RBV therapy for Japanese patients with GT2-HCV infection is highly effective in real-world clinical practice.

In a meta-analysis, Rangnekar *et al.*^[14] reported that *IL28B* SNP was predictor of SVR in Caucasian patients with GT2-HCV infection receiving PEG-IFN/RBV for 24 wk. In contrast, *IL28B* SNP was not associated with SVR in Asian patients with GT2-HCV infection. This study also showed Japanese *IL28B* SNP had no relation to efficacy of SOF/RBV for GT2-HCV infection. Morisco *et al.*^[15] reported RVR was the only independent predictive factor of SVR in triple therapy (TVR/PEG-IFN/RBV) regardless of LC. In the present study, RVR did not affect efficacy of SOF/RBV for GT2-HCV infection. The multivariate regression analysis showed that history of HCC or IFN-based therapy was independently related to non-SVR. LC also reduced the efficacy in univariate analyses. It was previously reported that the efficacy of IFN-based therapy was inferior in LC patients^[16,17]. Furthermore, it was reported that patients with progressive liver fibrosis have a high probability of hepatocellular carcinogenesis^[18-21]. Prenner *et al.*^[22] reported that presence of active HCC at the start of direct acting antivirals, including SOF/RBV therapy, decreased the SVR rate. In our study, the proportion of non-SVR patients treated by surgical resection or radiofrequency ablation tended to be lower than the

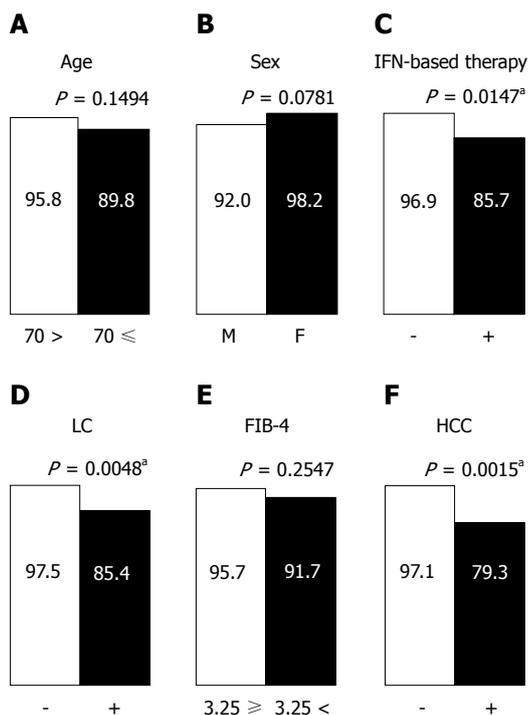


Figure 4 Virological response in patients with sofosbuvir and ribavirin (SOF/RBV) combination therapy categorized by patient characteristics. A: Age (< 70 or ≥ 70 yr); B: Sex (male or female); C: History of interferon-based therapy (- or +); D: Liver cirrhosis (- or +); E: Fibrosis-4 index (≤ 3.25 or > 3.25); F: History of hepatocellular carcinoma (- or +). ^aP < 0.05: Significant difference. M: Male; F: Female; IFN: Interferon; LC: Liver cirrhosis; FIB: Fibrosis; HCC: Hepatocellular carcinoma.

proportion of non-SVR patients treated by transcatheter arterial chemoembolization or radiation for bone metastasis. Meanwhile, the rate of HCC recurrence within 1 year tended to be higher in non-SVR patients than that in SVR patients. These findings show a high probability that active HCC was not detected by dynamic computed tomography or dynamic magnetic resonance imaging at the start of SOF/RBV therapy. Prenner *et al.*^[22] discussed that a putative biological explanation could be inadequate drug delivery by decreased blood flow or local fibrosis arising from HCC treatment. The present results suggested that liver fibrosis attenuated the antiviral effect of SOF/RBV in patients with history of IFN-based therapy or HCC. Although the FIB-4 index, a fibrosis marker^[10], had no effect on efficacy in the present study, the reason was unclear. History of IFN-based therapy and LC had no significant effect on SOF/RBV therapy in the phase 3 clinical trial for European patients with GT2-HCV infection^[12]. However, it was reported that LC and lower serum albumin decreased the SVR rate in the real-world cohorts in North America and Europe^[13]. Treatment-experienced patients tended to have ineffective outcomes in that study. These findings were similar to those in the present study. The real-world studies included larger populations of LC (26.6% in the present study and 26.8% in the North American and European study) than the phase 3 trials (11% in the Japanese trial^[5] and 15% in the European

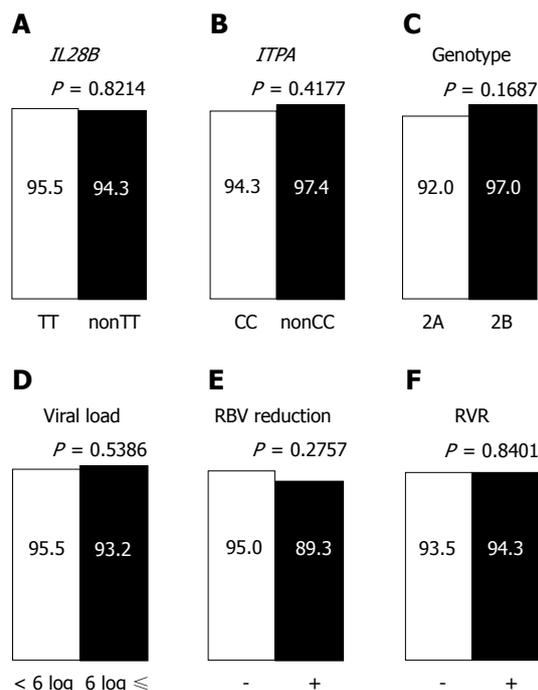


Figure 5 Virological response in patients with sofosbuvir and ribavirin combination therapy categorized by single nucleotide polymorphisms related to anti-hepatitis C virus therapy, pretreatment viral status, ribavirin dose, and rapid virological response. A: *IL28B* single nucleotide polymorphisms rs8099917 (TT or non TT); B: *ITPA* single nucleotide polymorphisms rs1127354 (CC or non CC); C: Hepatitis C virus genotype (2A or 2B); D: Pretreatment viral load (< 6 logIU/mL or ≥ 6 logIU/mL); E: Ribavirin dose reduction (- or +); F: Rapid virological response (- or +). ^aP < 0.05: Significant difference. *IL28B*: Interleukin-28B; *ITPA*: Inosine triphosphate pyrophosphatase; RBV: Ribavirin; RVR: Rapid virological response.

trial^[12]. Our study also enrolled patients with history of HCC (15.9%) and elderly patients aged ≥ 70 years (27.4%). It is suggested that the real-world studies enrolled more patients with severe fibrosis than the phase 3 clinical trials. As viral breakthrough did not occur in any of the non-SVR patients and all of these patients had relapses, it is suggested that SOF/RBV therapy was not ineffective for these patients. Extension of the treatment period for patients with history of IFN-based therapy, HCC, or LC should be considered to increase the efficacy of the therapy. As active HCC not detected by imaging was probably related to non-SVR, monitoring is required for carcinogenesis and recurrence of HCC after the end of SOF/RBV therapy, especially in non-SVR patients.

In conclusion, SOF/RBV therapy for Japanese patients with GT2-HCV infection is safe, highly tolerated, and effective. History of HCC or IFN-based therapy independently reduces the efficacy of the treatment.

ARTICLE HIGHLIGHTS

Research background

Combination therapy with peg-interferon (PEG-IFN) and ribavirin (RBV) was the first-line therapy for genotype 2 hepatitis C virus (HCV) infection, but only 80% of patients achieved elimination of HCV with this treatment. The introduction of direct-acting antiviral agents has drastically improved the efficacy of treatments

for chronic HCV infection. Combination therapy with NS5B RNA-dependent RNA polymerase inhibitor sofosbuvir (SOF) and RBV for patients with genotype 2 hepatitis C virus (GT2-HCV) infection was approved for clinical use in June 2015.

Research motivation

This therapy showed improved efficacy and was well tolerated in a phase 3 trial. However, predictive factor of sustained virological response (SVR) is not unclear.

Research objectives

We conducted a prospective study to investigate the efficacy and safety of sofosbuvir/ribavirin (SOF/RBV) therapy for Japanese patients with GT2-HCV infection in a real-world clinical setting.

Research methods

A total of 182 patients with GT2-HCV infection who received SOF/RBV therapy for 12 wk at our hospital were enrolled. The patients comprised 122 men and 60 women (age range: 17-84 years; mean age \pm SD: 60.1 \pm 12.1 years). One hundred sixty nine of 182 patients completed 12 wk treatment and were examined their virological response. To investigate predictive factors of SVR, we examined the relationships between virological response and clinical data by logistic regression analyses.

Research results

The rates of SVR at 12 wk after the end of treatment were 87.9% (intention to treat: 160/182) and 94.1% (per protocol: 159/169). Multivariate analyses showed that history of hepatocellular carcinoma (HCC) or IFN-based therapy independently reduced the efficacy of SOF/RBV therapy.

Research conclusions

This study showed Japanese *IL28B* single nucleotide polymorphisms had no relation to efficacy of SOF/RBV for GT2-HCV infection. Morisco *et al*^[15] reported rapid virological response (RVR) was the only independent predictive factor of SVR in triple therapy (Telaprevir/PEG-IFN/RBV) regardless of cirrhosis. In the present study, RVR did not affect efficacy of SOF/RBV for GT2-HCV infection. The multivariate regression analysis showed that history of HCC or IFN-based therapy was independently related to non-SVR. In our study, the proportion of non-SVR patients treated by surgical resection or radiofrequency ablation tended to be lower than the proportion of non-SVR patients treated by transcatheter arterial chemoembolization or radiation for bone metastasis. Meanwhile, the rate of HCC recurrence within 1 year tended to be higher in non-SVR patients than that in SVR patients.

Research perspectives

Prenner *et al* reported that presence of active HCC at the start of direct acting antivirals, including SOF/RBV therapy, decreased the SVR rate. As active HCC not detected by imaging was probably related to non-SVR, monitoring is required for carcinogenesis and recurrence of HCC after the end of SOF/RBV therapy, especially in non-SVR patients.

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