EFFICACY AND SAFETY OF TREATMENT WITH SOFOSBUVIR PLUS RIBAVIRIN FOR HEPATITS C VIRUS GENOTYPE2

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Abstract

Objective : We conducted a multicenter study in Akita Prefecture, Japan, to characterize the efficacy and safety of sofosbuvir (SOF) plus ribavirin (RBV) therapy in Japanese patients infected with hepatitis C virus (HCV) genotype 2.

Methods : All of the patients were infected with HCV genotype 2. Patients received 12 weeks of treatment with 400 mg of SOF daily plus weight-based RBV (600-1,000 mg daily).

Results : A total of 170 patients were enrolled in this study, and 167 patients were followed for 12 weeks after its completion. Among our patients, 28.2% (48/170) had liver cirrhosis (LC). Overall, 159 patients achieved a sustained virologic response for 12 weeks (SVR12), while 8 showed virologic failure. There were no significant differences in the rates of SVR12 between the chronic hepatitis (CH) and LC patients. No significant differences were noted between the CH and LC patients in the rates of any adverse events.

Conclusion : We found that SOF plus RBV treatment resulted in high rates of SVR12 with a favorable safety and tolerability profile, including patients with cirrhosis.

Key words : Hepatitis C, genotype2, sofosbuvir, ribavirin

Introduction

Globally, almost 71 million people are infected with the hepatitis C virus (HCV), and more than 399,000 people die from liver disease caused by HCV annually[1)]. A sustained virologic response (SVR) is related to a decreased risk of liver-related morbidity and mortality[2-4)].

Seven HCV genotypes have been isolated thus far[5-7)]. Globally, genotype 2 accounts for only 13%, which is a rate similar to that of genotype 4 but less than that of genotypes 1 and 3[5)]. Interferon (IFN) therapy is recognized as being more effective for genotype 2 patients than genotype 1 patients. This is likely why this new

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therapy was always applied preferentially for the genotype 1 patients.

The first IFN-free therapy, nonstructural protein (NS) 3/4A protease inhibitor asunaprevir (ASV) in combination with the HCV NS5A inhibitor daclatasvir (DCV), was approved in Japan for genotype 1 patients who were null-responders to prior treatment and intolerant or ineligible for IFN. With this therapy, the SVR rates have reached 84.7%[8]. Furthermore, the rates of adverse events with this therapy are much lower than with previous treatments including IFN therapy.

For HCV genotype 2 patients, peg-IFN plus ribavirin (RBV) for 24 weeks was the standard therapy for a long period. However, while this therapy yielded favorable response rates[9], the clinical use of peg-IFN based therapy was limited by its poor tolerability, particularly in patients with liver cirrhosis (LC). Furthermore, these therapies often induced severe adverse events, so more effective therapeutic options with lower adverse event rates were desired.

Sofosbuvir (SOF) plus RBV therapy is the first IFN-free direct-acting antiviral (DAA) therapy for genotype 2 patients in Japan. SOF is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase[10], while RBV is an oral synthetic guanosine analogue with antiviral activities against DNA and RNA viruses[11].

There have been few reports of Japanese real-world studies. We conducted a multicenter study in Akita Prefecture, Japan, with the aim of characterizing the efficacy and safety of SOF plus RBV therapies in Japanese patients infected with HCV genotype 2.

Materials and Methods

Patients

This multicenter study was conducted in the Akita hepatitis C study group (AHC) from 2015 to 2018. The AHC consists of Akita University, seven affiliated hospitals, and six clinics in Akita Prefecture, Japan. A total of 170 patients were enrolled, all infected with HCV genotype 2. The exclusion criteria were as follows : (1) Child-Pugh B or C cirrhosis, (2) severe anemia at baseline, (3) severe renal dysfunction at the baseline, (4) present existence of hepatocellular carcinoma (HCC) and (5) any serious medical condition of any other organ, such as congestive heart failure, or other hepatic diseases. Patients with a history of curative treatment of HCC were enrolled.

All of the patients gave their informed consent to participate in this study. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Akita University, School of Medicine (the number 1450). The data of 170 patients were deemed eligible for the analysis.

Study design

Patients received 12 weeks of treatment with 400 mg of SOF daily (Sovaldi® ; Gilead Sciences, Tokyo, Japan) plus weight-based RBV (600-1,000 mg daily) (Rebetol® ; MSD, Osaka, Japan, or Copegas® ; Chugai Pharma, Tokyo, Japan).

We followed the patients after the end of treatment for 12 weeks and measured their plasma levels of HCV RNA to assess the efficacy of the treatment at 4 weeks (rapid virologic response [RVR]), the end of treatment (end of treatment response [EOTR]) and 12 weeks after the end of treatment (SVR12).

Study assessments

The screening assessments included serum HCV RNA levels, genotyping, standard laboratory and clinical tests. HCV RNA was measured by a COBAS® Taqman HCV assay version 2.0 (Roche Diagnostics, Tokyo, Japan). On-treatment assessments included serum RNA, standard laboratory testing, vital signs and symptom-directed physical examinations. Adverse events (anemia, rash, renal dysfunction) were graded according to the World Health Organization (WHO) toxicity grades. Subjective symptoms were observed during an interview, which was conducted by the treating physician. We measured the aspartate aminotransferase (AST) (IU/L) to platelet count ($\times 10^4/\mu L$) ratio index (APRI) and fibrosis-4 (FIB-4) index to assess liver fibrosis. The FIB-4 index relies on the age, AST levels, alanine aminotransferase (ALT) levels and the platelet count.

Statistical analyses

Data were expressed as the median (interquartile ranges) and frequencies or percentages. Univariate analyses were performed using Student's *t*-test or a chi-squared test. Variables with $P < 0.05$ in the univariate analysis were evaluated using a multivariate logistic regression analysis. Statistical analyses were considered statistically significant. Statistical analyses were conducted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and the Windows Excel 2013 software programs (Microsoft Corporation, Washington D.C., United states of America).

Results

Baseline characteristics

Among our patients, 71.8% (122/170) had chronic hepatitis (CH), and 28.2% (48/170) had LC. The male : female ratio was 79 : 91. There were no significant differences in the HCV-RNA, AST, ALT, creatinine or alpha fetoprotein (AFP) levels between the CH and LC patients. However, the average age, APRI and FIB-4 index were significantly higher in the LC patients than in the CH patients, and the hemoglobin, albumin and platelet levels were significantly lower in the LC patients than in the CH patients. Patients with a history of HCC accounted for 7.6% (13/170) of the total population. The rate of a history of HCC was significantly higher in the LC patients than in the CH patients. Regarding treatment history, 115 patients were naïve, 65 had a history of treatment with IFN or peg-IFN therapy, and 28 had been previously treated with peg-IFN with RBV therapy. The rate of treatment-naïve patients was significantly higher in CH patients than in LC patients (Table 1).

Therapeutic outcomes and details

A total of 170 patients were enrolled in this study, and 167 were followed for 12 weeks after its completion. Of these, 139 patients achieved RVR. Six patients did not

Table 1. Baseline characteristics of the patients

	Total (n=170)	CH (n=122)	LC (n=48)	P value
Sex (male/female)	79/91	58/64	21/27	0.656
Age	67.0±11.9	64.5±12.6	73.3±8.2	<0.01
(range)	(33-88)			
HCV-RNA (logIU/mL)	5.78±0.94	5.82±0.94	5.56±1.24	0.379
Hb (g/dL)	13.4±1.7	13.6±1.7	12.7±1.5	<0.01
Platelet ($\times 10^4/\mu L$)	15.7±5.7	17.5±5.2	10.9±3.9	<0.01
AST (IU/L)	51.2±45.4	49.7±44.7	55.1±47.3	0.487
ALT (IU/L)	55.6±59.1	58.4±65.6	48.6±37.6	0.222
Albumin (g/dL)	4.09±0.38	4.17±0.32	3.88±0.41	<0.01
Creatinine (mg/dL)	0.72±0.16	0.71±0.17	0.73±0.15	0.606
APRI	1.02±1.19	0.82±0.86	1.52±1.67	<0.01
FIB4 index	3.72±3.17	2.76±1.68	6.15±4.53	<0.01
AFP (ng/mL)	6.50±11.60	4.90±4.78	10.7±20.2	0.08
History of hepatocellular carcinoma, n (%)	13 (7.6)	1 (0.8)	12 (25.0)	<0.01
Treatment-naïve, n (%)	115 (67.6)	88 (72.1)	27 (56.3)	<0.05
Treatment-experienced, n (%)	55 (32.4)	34 (27.9)	21 (43.7)	<0.05
PEG-IFN/ribavirin, n (%)	28 (16.5)	18 (14.8)	10 (20.8)	0.336

The date are presented as numbers, average or medians with interquartile ranges. The P values were calculated using the chi-square test or the independent-test for continuous variables. CH : chronic hepatitis, LC : liver cirrhosis, HCV : hepatitis C virus, AST : aspartate aminotransferase, ALT : alanine aminotransferase, APRI : Aspartate aminotransferase to platelet ratio index, FIB4 index : fibrosis-4 index, AFP : alpha-fetoprotein, PEG-IFN : polyethylene glycol-interferon.

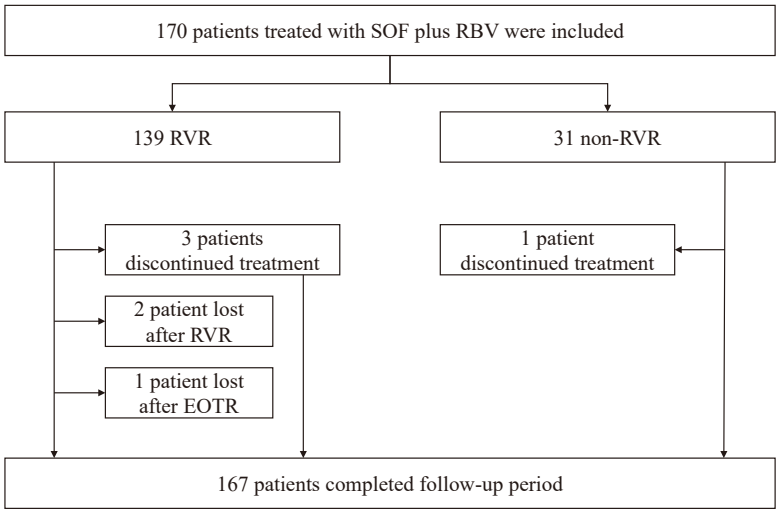

Figure 1. Study profile.
Of 170 patients, 166 completed the combination of sofosbuvir plus ribavirin, and 4 patients discontinued treatment. EOTR : end of treatment response, RBV : ribavirin, RVR : rapid virologic response, SOF : sofosubuvir.

fully complete the therapy, four discontinued therapies due to severe anemia, and two were lost after RVR. One patient was lost after EOTR (Fig. 1).

Efficacy of antiviral therapy

The rates of RVR, EOTR and SVR12 were 81.8%, 99.4% and 95.2% in the per-protocol analysis and 81.8%, 97.6% and 93.5% in the intention-to-treat analysis, respectively. Overall, 159 patients achieved SVR12, and 8 had virologic failure. There were no significant differences in the rates of RVR, EOTR or SVR12 between the CH and LC patients (Fig. 2).

Assessments of the factors associated with SVR

A total 167 patients for whom HCV RNA could be evaluated 12 weeks after stopping treatment were analyzed (Table 2). The univariate analysis showed that high AST, ALT and AFP levels tended to be associated with SVR12. These factors and another two (sex, age) were then analyzed by a multivariate logistic regression analysis, which showed that there were no factors associated with SVR12.

Safety analyses

The most frequently reported adverse event was anemia, which was noted in 25.7% (46/170) of patients. Regarding the degree of anemia, 25.3% (43/170) of patients had grade 1/2, and 1.8% (3/170) had grade 3/4. A total of 15.3% (26/170) of patients had total bilirubin elevation : 11.8% (20/170) had grade 1, and 3.5% (6/170) had grade 2. A total of 5.3% (9/170) of patients had ALT elevation : 4.1% (7/170) had grade 1, and 1.2% (2/170) had grade 2. A total of 3.5% (6/170) of patients had renal failure : 2.9% (5/170) had grade 1, and 0.6% (1/170) had grade 2. A total of 11.8% (20/170) of patients had fatigue, 3.5% (6/170) had headache, 4.1% (7/170) experienced nausea, and 2.4% (4/170) had a fever. A total of 15.3% (26/170) of patients had their RBV dose reduced due to adverse events. No significant differences were noted between the CH and LC patients in the rate of any adverse event (Table 3).

AFP and ALT levels and the FIB-4 index according to the response to treatment and liver condition

We measured the AFP and ALT levels and the FIB-4 index of 167 patients at baseline and 12 weeks after starting treatment. In the 159 patients who achieved SVR, the AFP levels were significantly lower than at baseline ($P<0.05$) (Fig. 3A), as were the ALT levels ($P<0.01$)

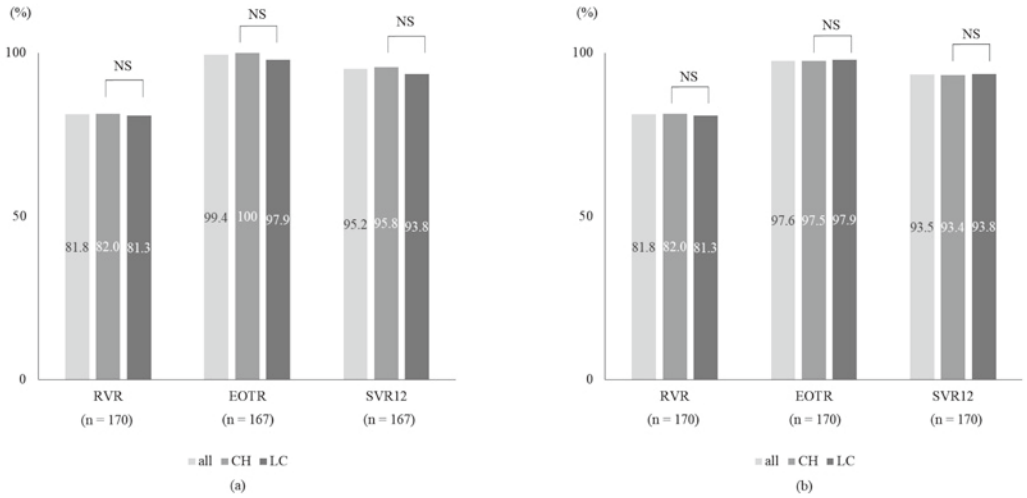

Figure 2. HCV-RNA undetectable rates
Rapid virologic response, end of treatment response and sustained virologic response at 12 weeks with or without cirrhosis. (a) per protocol analysis ; (b) intention to treat analysis. CH : chronic hepatitis, EOTR : end of treatment response, HCV : hepatitis C virus, LC : liver cirrhosis, NS : not significant, RVR : rapid virologic response, SVR12 : sustained virologic response at 12 weeks.

Table 2. Univariate and multivariate logistic regression analysis of predictors of SVR12.

	SVR (n=159)	Non-SVR (n=8)	Univalue	Multivalue
			P value	P value
Sex (male/female)	75/84	4/4	0.876	0.923
Age-median (first-third quiartile)	68 (61-77)	76 (68-79)	0.185	0.593
HCV-RNA low/high	80/79	3/5	0.479	
CH/LC	114/45	5/3	0.575	
Hb (g/dL)	13.2 (12.4-14.5)	12.6 (11.7-13.1)	0.066	
Platelet ($\times 10^4/\mu L$)	15.5 (10.9-18.7)	17.4 (14.7-18.9)	0.661	
AST (IU/L)	33 (24-66)	17 (15-19)	<0.01	0.486
ALT (IU/L)	34 (21-69)	19.5 (17.5-21)	<0.01	0.457
Albumin (g/dL)	4.1 (3.9-4.3)	4.2 (4.0-4.3)	0.780	
Creatinine (mg/dL)	0.69 (0.60-0.81)	0.63 (0.60-0.78)	0.460	
APRI	0.67 (0.38-1.24)	0.30 (0.28-0.52)	0.375	
FIB4 index	2.90 (1.82-4.86)	2.13 (1.77-3.30)	0.828	
AFP (ng/ml)	4.0 (2.4-6.3)	2.6 (1.9-3.2)	<0.01	0.314
History of hepatocellular carcinoma, n (%)	12 (7.5)	1 (12.5)	0.610	
Treatment-naïve, n(%)	107 (67.3)	5 (62.5)	0.778	
Treatment-experienced, n(%)	52 (32.7)	3 (32.5)	0.778	

The date are presented as numbers, average or medians with interquartile ranges. The P values were calculated using the chi-squire test or the independent-test and logistic regression analysis. High and low cut-off value of HCV-RNA is defined as 6 logIU/mL. CH : chronic hepatitis, LC : liver cirrhosis, HCV : hepatitis C virus, AST : aspartate aminotransferase, ALT : alanine aminotransferase, APRI : Aspartate aminotransferase to platelet ratio index, FIB4 index : fibrosis-4 index, AFP : alphafetoprotein.

Table 3. The frequency of adverse event

	Total (n=170)		CH (n=122)		LC (n=48)		P value
Anemia	46	27.1%	30	24.6%	16	33.3%	0.248
Grade 1/2	43	25.3%	29	23.8%	14	29.2%	0.466
Grade 3/4	3	1.8%	1	0.8%	2	4.2%	0.136
Total bilirubin elevation	26	15.3%	18	14.8%	8	16.7%	0.755
Grade 1	20	11.8%	14	11.5%	6	12.5%	0.852
Grade 2	6	3.5%	4	3.3%	2	4.2%	0.778
ALT elevation	9	5.3%	8	6.6%	1	2.1%	0.241
Grade 1	7	4.1%	6	4.9%	1	2.1%	0.402
Grade 2	2	1.2%	2	1.6%	0	0%	0.372
Renal falure	6	3.5%	5	4.1%	1	2.1%	0.522
Grade 1	5	2.9%	4	3.3%	1	2.1%	0.678
Grade 2	1	0.6%	1	0.8%	0	0%	0.529
Fatigue	20	11.8%	12	9.8%	8	16.7%	0.213
Headache	6	3.5%	5	4.1%	1	2.1%	0.522
Nausea	7	4.1%	4	3.3%	3	6.3%	0.380
Fever	4	2.4%	2	1.6%	2	4.2%	0.328
Ribavirin reduction	26	15.3%	16	13.1%	10	20.8%	0.208

The P value were calculated using independent t-test. CH : chronic hepatitis, LC : liver cirrhosis, ALT : alanine aminotransferase.

(Fig. 3B) and FIB-4 index (P<0.01) (Fig. 3C). In the 8 patients who did not achieve SVR, the AFP levels were not significantly different from the baseline (P=0.60) (Fig. 3D), nor were the ALT levels (P=0.28) (Fig. 3E) or FIB-4 index (P=0.71) (Fig. 3F). In the 120 patients who had CH, the AFP levels were significantly lower than at baseline (P<0.05) (Fig. 4A), as were the ALT levels (P<0.01) (Fig. 4B) and FIB-4 index (P<0.01) (Fig. 4C). In the 47 patients who had LC, the AFP levels were not significantly different from the baseline (P=0.19) (Fig. 4D), while the ALT levels and FIB-4 index were significantly lower than at baseline (ALT : P<0.01) (Fig. 4E) (FIB-4 index : P<0.05) (Fig. 4F).

Discussion

The present study characterized the efficacy and safety of SOF plus RBV therapies in Japanese patients infected with HCV genotype 2. In particular, we compared the efficacy and safety between CH and LC patients. SOF plus RBV therapy was the first DAA therapy for genotype 2 patients approved prior to ledipasvir/sofosbuvir therapy for genotype 1 patients.

In this paper, we analyzed 170 HCV genotype 2 patients treated with SOF plus RBV in Akita Prefecture, Japan. Among our patients, 71.8% (122/170) had CH, and 28.2% (48/170) had LC. In our study, mean age and cirrhosis rates tended to be higher than in international and Japanese Phase 3 trials[12-15]. This is probably because Akita Prefecture has the highest aging rate in Japan. In the background analysis, it seems natural that the average age, APRI and FIB-4 index were significantly higher in LC patients than in CH patients, while the hemoglobin, albumin and platelet levels were significantly lower in LC patients than in CH patients (Table 1). Furthermore, the rate of treatment-naïve patients was significant higher in CH patients than in LC patients (Table 1). The overall SVR12 rate was 93.5%, which is almost the same as the value in international and Japanese phase 3 trials[12-15]. We already reported on the efficacy and safety of treatment with DCV and ASV, the first generation of DAAs for HCV genotype 1 in Akita, Japan, and the SVR12 rate was 84.2%[16]. In our study, the SVR12 rate was 93.5%, which is higher than that in the previous

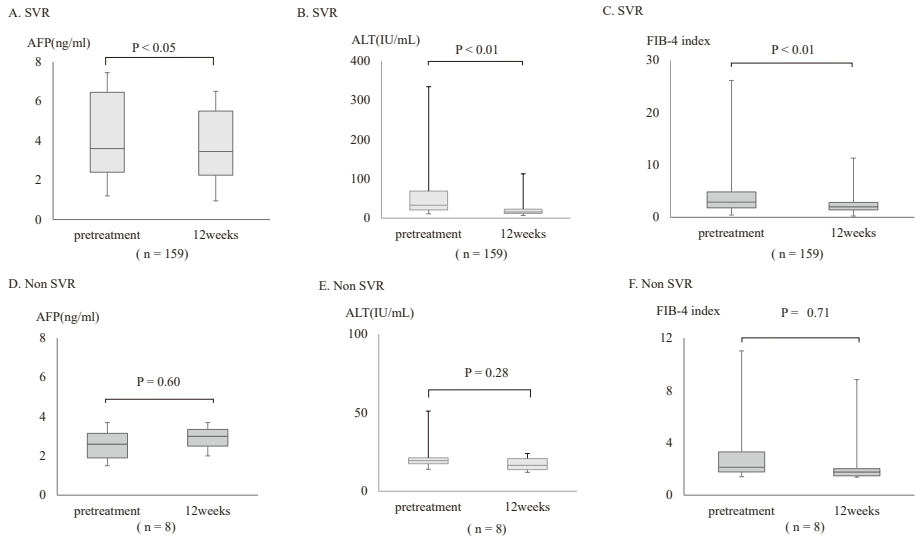

Figure 3. AFP, ALT levels and FIB-4 index of patients who achieved SVR at baseline and 12 weeks.
A. AFP levels of patients who achieved SVR. B. ALT levels of patients who achieved SVR. C. FIB-4 index of patients who achieved SVR. D. AFP levels of patients who achieved non-SVR. E. ALT levels of patients who achieved non-SVR. F. FIB-4 index of patients who achieved non-SVR. The *P* values were calculated using the independent-test. AFP : alpha-fetoprotein, ALT : alanine aminotransferase, FIB-4 index : fibrosis-4 index, SVR : sustained virological response.

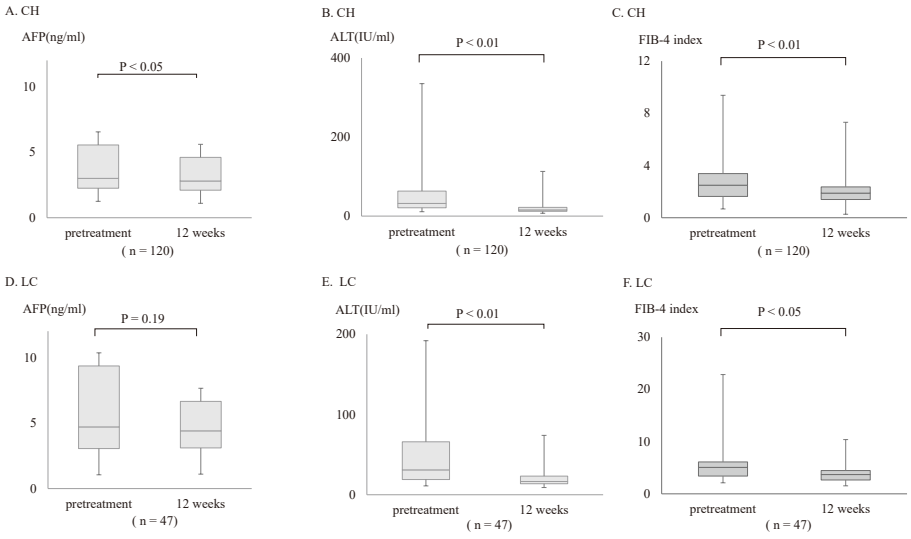

Figure 4. AFP, ALT levels and FIB-4 index of patients with or without cirrhosis at baseline and 12 weeks.
A. AFP levels of patients without cirrhosis. B. ALT levels of patients without cirrhosis. C. FIB-4 index of patients without cirrhosis. D. AFP levels of patients with cirrhosis. E. ALT levels of patients with cirrhosis. F. FIB-4 index of patients with cirrhosis. The *P* values were calculated using the independent-test. AFP : alpha-fetoprotein, ALT : alanine aminotransferase, CH : chronic hepatitis, FIB-4 index : fibrosis-4 index, LC : liver cirrhosis, SVR : sustained virological response.

study, although we can hardly compare this result and that of the previous study simply because the subjects are different, with the previous study involving genotype 1 and our study involving genotype 2. In our study, the SVR12 rates in CH and LC patients were 93.4% and 93.8%, respectively. There were no significant differences in the rates of SVR12 between the CH and LC patients (Fig. 2).

There is no controversy that, in IFN therapy, host factors such as liver fibrosis, age, gender and IL28B SNPs affect the SVR rate[17,18]. However, in our background analysis, while liver fibrosis clearly progressed in LC patients, there were no significant differences in the rates of SVR12 between the CH and LC patients. This suggests that DAA therapy directly affects the HCV virus, regardless of the host status.

We assessed the factors associated with SVR but failed to detect any factors associated with SVR12 in a multivariate analysis. Recent DAA therapy has resulted in a very high SVR rate, so it may be difficult to detect the factors associated with SVR.

In safety analyses, the most frequent adverse event was anemia, noted in 27.1% (46/176) of patients. RBV, which was included in this therapy, may cause hemolytic anemia ; this may be why the next-most frequently observed adverse event was total bilirubin elevation. However, in most cases, bilirubin elevation was slight, and there were no cases with greater than Grade 3 severity. Furthermore, no patients stopped treatment due to bilirubin elevation. In the background analyses, the hemoglobin level was significantly lower in LC patients than in CH patients ; however, in the safety analyses, there was no significant difference in the anemia rate between the two groups. This result suggests that the side effect of this therapy is not strong enough to worsen the LC status.

In our previous study, the rate of anemia, in the IFN+telaprevir+RBV group was 74.1%, while that in the IFN+simeprevir+RBV group was 58.6%[19]. Therefore, compared to those previous therapies, the side effects of the present therapy were very few. Furthermore, flu-like symptoms (fever, headache, nausea, etc.) appear in almost 100% of patients treated with therapy including IFN ; however, with the present regiment, this side effect appeared in only about 3% of cases. Moreover, no significant differences were noted between the CH and LC patients in the rate of any event (Table 3). This therapy is thus considered to be very safe.

We also examined the AFP and ALT level and the FIB-4 index in a time-dependent manner. Among the patients who achieved SVR12, the AFP and ALT level and the FIB-4 index were significantly lower at 12 weeks after starting treatment than at the baseline. However, in the virologic failure patients, there was no significant difference in the AFP or ALT level or the FIB-4 index at 12 weeks after starting treatment and at the baseline. The AFP level may therefore not be related to a reduction in the risk of HCC. However, it may be related to a reduction in hepatic inflammation[20].

We also compared the changes in the AFP and ALT levels and FIB-4 index between CH and LC patients. In the CH patients, the AFP and ALT levels and FIB-4 index were significantly lower at 12 weeks after starting treatment than at the baseline. In the LC patients, the ALT levels and the FIB-4 index were also significantly lower at 12 weeks after starting treatment than at the baseline, although there was no significant difference in the AFP value between these points. The long-term follow-up of patients will be needed to clarify the change in the AFP level related to liver carcinogenesis.

In conclusion, we found that SOF plus RBV treatment resulted in high rates of SVR for 12 weeks with a favorable safety and tolerability profile, including patients with cirrhosis. After this therapy, the new DAAs have been approved in genotype 2 patients one after another. One of these therapies, ledipasvir/sofosbuvir compounding agent, is approved for not only genotype 1 but also genotype 2 patients[21]. RBV is not included in this therapy, so it can be administered safely to anemic patients. Another DAA therapy of glecaprevir/pibrentasvir compounding agent is metabolized in the liver and may thus be used safely for severe renal dysfunction or dialysis patients[22]. Recently, velpatasvir/sofosbuvir compounding agent was shown to be safe for administration to decompensated cirrhosis patients[23]. As such, we now have many DAA therapies to choose from for genotype 2 patients.

We must select the best therapy for each patient as

"tailor-made therapy". Our results suggest that this approach is very effective and safe in LC patients. As the next step, we will consider the usefulness of DAA therapy for improving the prognosis of HCV patients, as we can now achieve impressive SVR rates in LC patients.

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