

# Safety, Tolerability, and Efficacy of Sofosbuvir Plus Ribavirin in Elderly Patients Infected with Hepatitis C Virus Genotype 2

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## Key Words

Sofosbuvir · Ribavirin · Chronic hepatitis C · Genotype 2 · Aged patients

## Abstract

**Background:** An interferon-free regimen including sofosbuvir and ribavirin (RBV) for patients with hepatitis C virus (HCV) genotype 2 (G2) infection leads to a drastic improvement of sustained virological response (SVR). However, the safety, tolerability, and efficacy in patients aged 75 or older have not been completely understood. **Summary:** Fifty-six patients with HCV G2 infection who were treated with sofosbuvir and weight-based dose of RBV were enrolled. Thirty-seven patients aged  $\geq 75$  and 19 patients aged  $\leq 74$  were classified as the aged and non-aged groups, respectively. The aged group was characterized by significantly more number of women, history of hepatocellular carcinoma, low serum albumin (ALB) level, low hemoglobin (Hb) concentration, low estimated glomerular filtration rate (eGFR), and high fibrosis-4 index ( $p = 0.0029$ ). Forty-one patients were evaluated for SVR at 12 weeks after the end of therapy (SVR12); of them, all but one completed the treatment scheduled for 12 weeks. The aged group showed lower SVR12 rate than the non-aged group (81.3% for aged and 96.0% for non-aged groups). Although the Hb concentration and eGFR are significantly

lower in the aged group throughout the clinical course, all patients in the aged group completed the 12-week treatment with a gradual increase of serum ALB level. **Key Messages:** The combination of sofosbuvir plus RBV is tolerable and beneficial in patients aged  $>75$ . However, intensive management of anemia by dose reduction of RBV is necessary, which could lead to a low SVR12 rate compared to that observed in patients younger than 75 years.

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## Introduction

Although progress has been made in the treatment of hepatocellular carcinoma (HCC), it is still one of the leading causes of cancer-related death; chronic infection with hepatitis C virus (HCV) is the major cause of HCC emergence in Japan [1, 2]. Thus far, interferon (IFN)-based regimen has been applied for patients with chronic hepatitis C (CHC); the effectiveness and tolerability of IFN-based treatment have been unsatisfactory, especially for aged patients and those with liver cirrhosis [3]. Recently, an IFN-free regimen for CHC was developed, which led to a drastic improvement in sustained virological response (SVR) [4]. With regard to the treatment of CHC patients infected with HCV genotype 2 (G2), data from a

phase III trial on treatment using combination of nucleotide HCV non-structural protein 5B (NS5B) polymerase inhibitor, sofosbuvir, and ribavirin (RBV) for 12 weeks have been published for different ethnic cohorts including the Japanese population; 93–100% of the patients reportedly achieved SVR at 12 weeks (SVR12) after the end of the treatment (EOT) [5–9]. More importantly, the high SVR12 rate could be achieved regardless of age, gender, background status of liver fibrosis, and history of antiviral therapy [6, 8, 9], which have been known to be associated with failure of IFN-based treatment. In the Japanese phase III trial, pharmacokinetic analysis of sofosbuvir and its nucleoside metabolite, GS-331007 was performed [8]. No difference in pharmacokinetics of sofosbuvir and GS-331007 was observed regardless of age and cirrhosis status. However, although no age limits were set for eligibility in these trials, the majority of the enrolled patients were younger than 75 years and efficacy in patients older than 75 years has not been elucidated properly. In addition, regimens including RBV cause anemia and hyperbilirubinemia, especially in aged patients with impaired renal function [10], and the majority of such patients have liver cirrhosis. Therefore, it is important to clarify the safety and tolerability of sofosbuvir plus RBV combination for aged patients with HCV infection. In this study, we compared the safety, tolerability, and efficacy of sofosbuvir plus RBV treatment between patients aged  $\geq 75$  and those aged  $< 74$ .

## Materials and Methods

### Patients

Between June 2015 and March 2016, 56 patients with CHC caused by HCV G2 who underwent antiviral therapy with sofosbuvir and weight-based dose of RBV were enrolled. The clinical background of the patients before the treatment is as follows; median age (range) was 68 (27–90 years), 29 patients were men and 27 women, 40 patients were treatment-naïve, and 16 had received previous antiviral IFN therapy (5 non-responders, 6 relapsers, and 5 IFN-intolerant). Ten patients had a history of HCC. The median viral load (range) was 6.1 log<sub>10</sub> international unit (IU)/ml (2.9–7.1). The median values and ranges of other blood chemical data of the cohort are as follows: 36 IU/l (17–292) for aspartate aminotransferase, 36 IU/l (6–506) for alanine transaminase, 4.2 g/ml (2.3–5.1) for albumin (ALB),  $170 \times 10^3/\mu\text{l}$  (42–406) for platelet count, 0.7 mg/dl (0.2–2.1) for total bilirubin (T. Bil), 13.95 g/dl (7.7–18.1) for hemoglobin (Hb) concentration, 74.5 (36–188) for estimated glomerular filtration rate (eGFR), and 3 ng/ml (1–72) for serum  $\alpha$ -fetoprotein (AFP) level. The median fibrosis-4 (FIB-4) index was 2.58 (0.545–14.37). Twenty-one patients received a dose reduction of RBV for the management of anemia during treatment. The study was approved by the institutional review boards of the institution involved.

### Assessment of Viral Response and Blood Chemical Analyses among Aged (75 Years or Older) and Non-Aged (Younger Than 75 Years) Patients

We compared the viral response and change of blood chemical data during and after the treatment between aged and non-aged patients. For this purpose, the patients were divided into 2 groups based on their age at the initiation of treatment; 37 patients aged  $\geq 75$  were classified as the aged group and 19 patients aged  $< 74$  comprised the non-aged group. The results for the comparison of the clinical backgrounds between aged and non-aged patients are shown in table 1. The aged group included significantly more female patients (68.4%, 13/19 vs. 37.8%, 14/37,  $p = 0.0301$ ), and was characterized by history of HCC (36.8%, 7/19 vs. 8.1%, 3/37,  $p = 0.0223$ ), lower serum ALB level (median and range 4 g/ml, 3.1–4.5 vs. 4.3, 2.3–5.1,  $p = 0.0165$ ), lower Hb concentration (median and range 13.2 g/dl, 7.7–14.8 vs. 14.4, 9.6–18.1,  $p = 0.0005$ ), lower eGFR (median and range 69, 36–91 vs. 76, 59–188,  $p = 0.0075$ ), and higher FIB-4 index (median and range 3.97, 2.00–9.25 vs. 1.97, 0.56–14.4,  $p = 0.0029$ ) than the non-aged group.

Serum HCV-RNA was quantified at weeks 2, 4, and 12 to evaluate virological response during and at the EOT response (ETR). Similarly, we analyzed viral clearance at weeks 4 and 12 after the EOT (SVR4 and SVR12). Quantification of serum HCV-RNA was performed using the COBAS® TaqMan® HCV Auto Assay System (Roche, USA; lower limit of quantification, 1.2 log<sub>10</sub> IU/ml). Standard laboratory and clinical tests were also performed during the clinical course. For the comparison of viral response between aged and non-aged groups, data were compared in an intention-to-treat manner.

### Statistical Analysis

Pearson's chi-square test or Fisher's exact test was used to compare categorical variables. For comparisons of continuous variables, the Wilcoxon rank-sum test was applied. All  $p$  values were two-sided and  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using JMP version 9.0 software (SAS Institute Inc., Cary, N.C., USA).

## Results

### Clinical Background Associated with the Virological Response at 12 Weeks after the EOT

Of the 56 patients, 41 could evaluate SVR12; 37 achieved SVR12, whereas 4 failed to achieve SVR12 (SVR12 rate = 90.2%, 37/41). RBV dose reduction was performed for 21 (37.5%, 21/56) patients for the management of anemia; 11 of 37 (29.7%) were non-aged patients and 10 of 19 (57.9%) were aged patients. Of the 4 patients who failed to achieve SVR12, 1 who was negative for serum HCV during the treatment, discontinued the treatment at 8 weeks after initiation because of hyperbilirubinemia. Other 3 patients completed the 12-week treatment and showed undetectable serum HCV-RNA at the EOT but failed to achieve SVR12. Of the 4 patients who failed to achieve SVR12, 3 were aged  $\geq 75$ , were men, had previ-

**Table 1.** Difference of background characteristics of non-aged ( $\leq 74$  years of age) and aged patients ( $\geq 75$  years of age) before antiviral treatment

Backgrounds	Non-aged patients (n = 37)	Aged patients (n = 19)	p value
Gender (male/female)	<b>23/14</b>	<b>6/13</b>	<b>0.0301</b>
Previous treatment (with/without)	10/27	6/13	0.7211
History of HCC emergence (with/without)	<b>3/34</b>	<b>7/12</b>	<b>0.0223*</b>
HCV titer, log IU/ml, median (range)	6.1 (3.2–7.1)	6.1 (2.9–6.7)	0.2599
AST, IU/l, median (range)	29 (17–292)	46 (17–68)	0.3648
ALT, IU/l, median (range)	32 (6–506)	38 (8–72)	0.6341
ALB, g/dl, median (range)	<b>4.3 (2.3–5.1)</b>	<b>4 (3.1–4.5)</b>	<b>0.0165</b>
Platelet count, $\times 10^3/\mu\text{l}$ , median (range)	180 (42–406)	161 (77–288)	0.0805
T. Bil level, mg/dl, median (range)	0.7 (0.2–2.1)	0.7 (0.4–1.7)	0.8754
Hb, g/dl, median (range)	<b>14.4 (9.6–18.1)</b>	<b>13.2 (7.7–14.8)</b>	<b>0.0005</b>
eGFR, median (range)	<b>76 (59–188)</b>	<b>69 (36–91)</b>	<b>0.0075</b>
AFP, ng/ml, median (range)	3 (1–72)	3 (1–55)	0.4051
FIB-4 index, median (range)	<b>1.97 (0.56–14.4)</b>	<b>3.97 (2.00–9.45)</b>	<b>0.0029</b>
FIB-4 index ( $>3.25/\leq 3.25$ )	10/27	10/9	0.0583
Reduction of RBV during the treatment (with/without)	11/26	10/9	0.0937

AST = Aspartate transaminase; ALT = alanine transaminase.

p values by were calculated using Pearson's chi-square test for categorical valuables and Wilcoxon rank sum test for contentious variables are shown. \* p values by Fisher's exact test.

Backgrounds showing significant difference between non-aged and aged patients are shown in bold.

ously received antiviral therapy, and had an FIB-4 index  $>3.25$ . Similarly, 2 patients received RBV dose reduction and 1 had a history of HCC. Regarding the association between HCV clearance during clinical course and age, no difference was observed in timing of HCV clearance between aged and non-aged groups in which all patients showed undetectable serum HCV-RNA at EOT regardless of age. Although not statistically significant, aged patients showed lower SVR12 rate than non-aged patients did (81.3%, 13/16 for aged and 96.0%, 24/25 for non-aged groups, respectively; fig. 1). One patient who discontinued treatment owing to jaundice was a member of the non-aged group.

#### *Serum ALB, Hb Concentration, and eGFR during the Clinical Course*

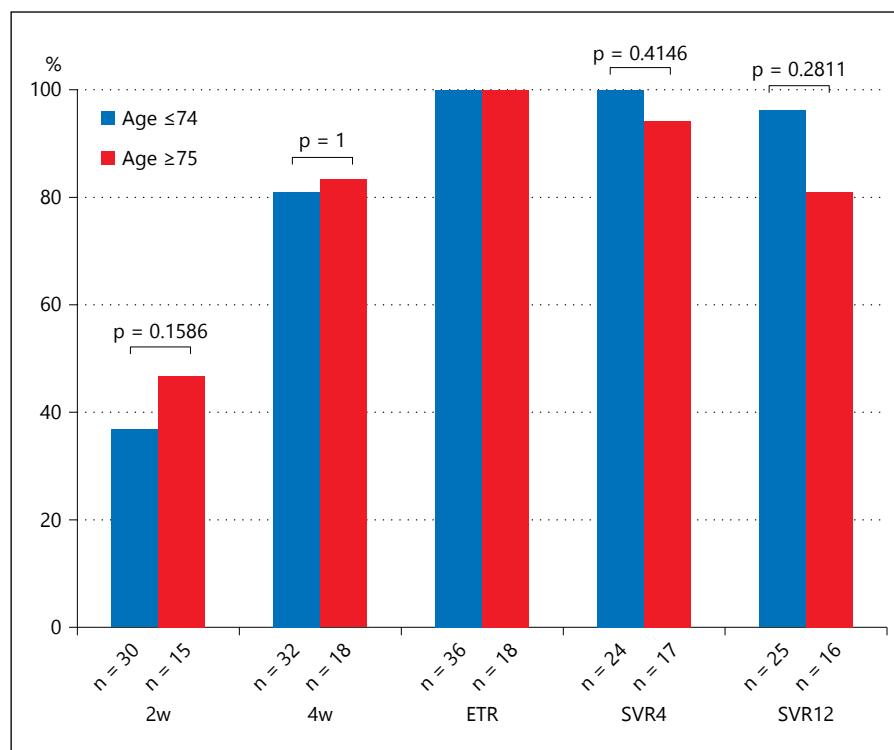
To determine the safety of sofosbuvir and RBV treatment in aged patients, we compared the serum ALB level, Hb concentration, and eGFR during the clinical course between the aged and non-aged group because these laboratory data were significantly lower in the aged than in the non-aged group (fig. 2). At each time point of the clinical course, Hb concentration and eGFR were significantly lower in the aged than in the non-aged group (p values

of each comparison of baseline, at 2 and 4 weeks after the initiation of treatment, at EOT, and at 4 and 12 weeks after the EOT were as follows;  $p = 0.0005$ ,  $p = 0.0016$ ,  $p = 0.0013$ ,  $p = 0.0064$ ,  $p = 0.0050$ ,  $p = 0.0107$  for Hb,  $p = 0.0075$ ,  $p = 0.0072$ ,  $p = 0.0043$ ,  $p = 0.0048$ ,  $p = 0.0043$ ,  $p = 0.0179$  for eGFR, respectively; fig. 2a, b). Although the serum ALB level was significantly lower in the aged group during the treatment, the difference was not significant after the completion of administration ( $p = 0.0165$ ,  $p < 0.0001$ ,  $p = 0.0018$ ,  $p = 0.1655$ ,  $p = 0.1283$ ,  $p = 0.0501$  before treatment, at 2 and 4 weeks after the initiation of treatment, at EOT, and at 4 and 12 weeks after the EOT, respectively; fig. 2c). Despite the low baseline levels of Hb, eGFR, and serum ALB before the treatment in the aged group, all patients aged  $\geq 75$  completed the 12-week treatment.

#### *Decrease of the Serum AFP Level after the Treatment*

We compared the serum AFP level at 12 weeks after the EOT with the baseline level. Among the 41 patients examined, 38 showed decreased levels of serum AFP after the treatment. The decrease in serum AFP level was observed regardless of age (categorized as  $\leq 74$  and  $\geq 75$  years; fig. 3a, b). Figure 3 shows the comparison of serum AFP before

**Fig. 1.** Comparison of the response rate at each timing between the patients aged  $>75$  and  $\leq 74$ . Percentages of the patients who showed negative for serum HCV-RNA are shown. Two and 4 weeks denote the response at weeks 2 and 4 during treatment, respectively. ETR denotes end of treatment response, SVR4 and SVR12 denote SVR at 4 and 12 weeks after the EOT. p values by the Wilcoxon rank-sum test are shown.



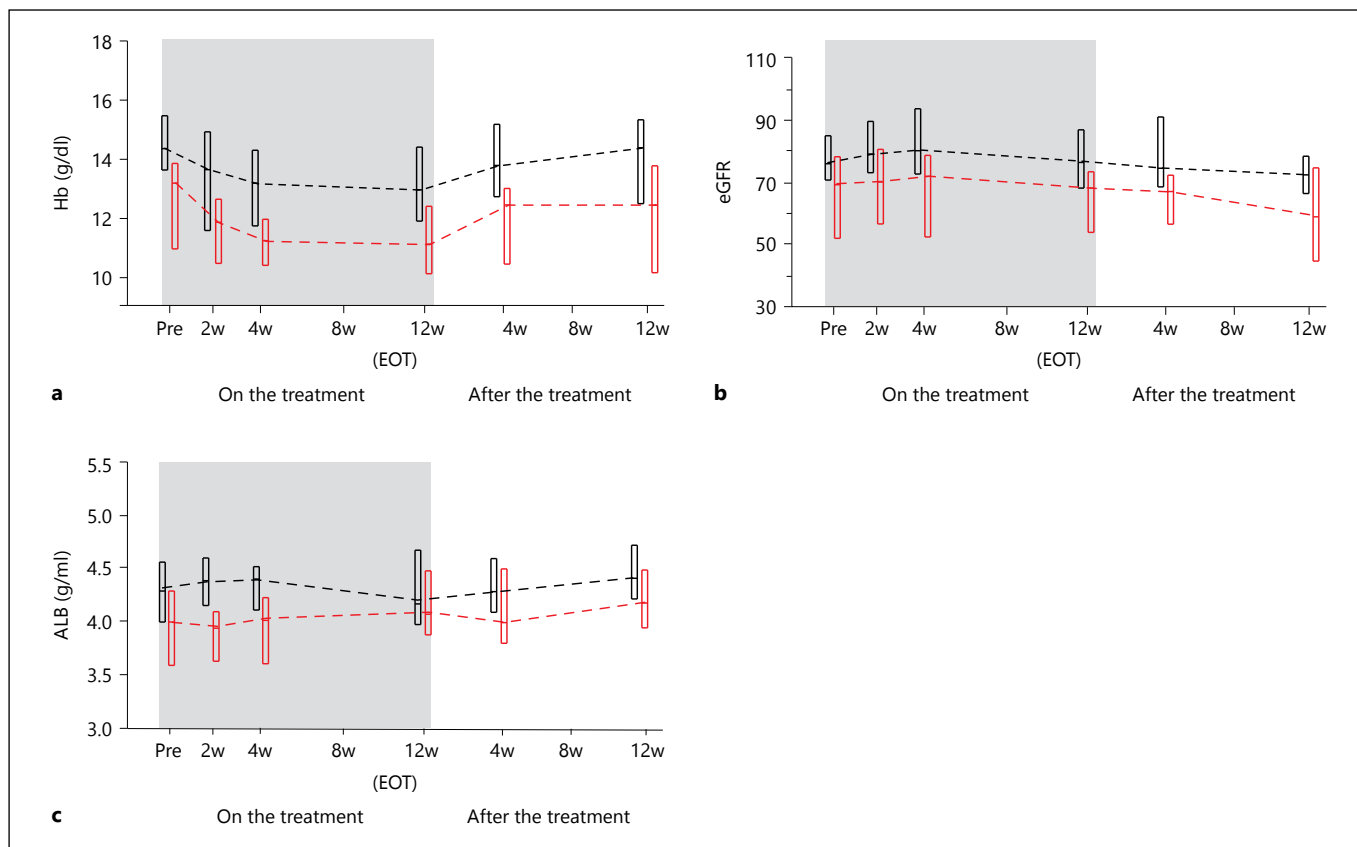
and after treatment in patients who achieved SVR12 (fig. 3a), and those who failed to achieve SVR12 (fig. 3b). The decrease in serum AFP after the treatment was observed regardless of SVR12 status. We also analyzed the association between percentage decrease of AFP ( $\Delta$ AFP) after the treatment (calculated as difference in serum AFP before and after the treatment divided by the baseline serum AFP) and FIB-4 index categorized as  $\leq 3.25$  and  $> 3.25$ ; fig. 3c). The group with an FIB-4 index of  $> 3.25$  showed significantly greater  $\Delta$ AFP (more decrease of serum AFP after the treatment) than the group with an FIB-4 index of  $\leq 3.25$  ( $p = 0.0249$  by the Wilcoxon rank-sum test).

## Discussion

CHC is known to be a leading cause of HCC emergence in Japan [11], and approximately 2% of the population have chronic HCV infection [12]. Although the major strain of HCV in Japan is G1, which is known to be resistant to conventional IFN-based therapy, recent advancements in antiviral therapy using direct-acting antiviral agents have drastically improved the HCV response rate [13]. However, G2 is known as a minor strain in Japan and shows favorable response to IFN-based therapy

[14, 15]. Therefore, the majority of patients with CHC caused by HCV G2 were believed to achieve SVR upon IFN-based treatment. However, because of side effects of IFN, many patients who are intolerant to IFN-based treatment, such as aged patients and those with liver cirrhosis, remain untreated.

In Europe, CHC patients infected with G2 who were treated with recent IFN-free therapy that combined NS5B polymerase inhibitor, sofosbuvir, with RBV for 12 weeks achieved an SVR12 rate of 93% [5]. Similar results were reported for this combination therapy in several regions, such as Japan, Taiwan, Korea where the reported SVR12 rate was 97, 100, and 97%, respectively [6, 8, 9]. Reportedly, a high SVR12 rate was observed even in patients with liver cirrhosis, treatment-experienced, and elderly patients. However, according to previous reports, almost every patient reported in the literature was younger than 75 years; the efficacy and safety of sofosbuvir plus RBV treatment in patients older than 74 years have not been elucidated [5, 6, 8, 9]. Information regarding the safety, tolerability, and efficacy in aged patients is critical for the management of CHC patients in an aging society such as Japan [16]; we compared the efficacy and safety of this combination therapy between patients aged  $\geq 75$  and those aged  $\leq 74$ .



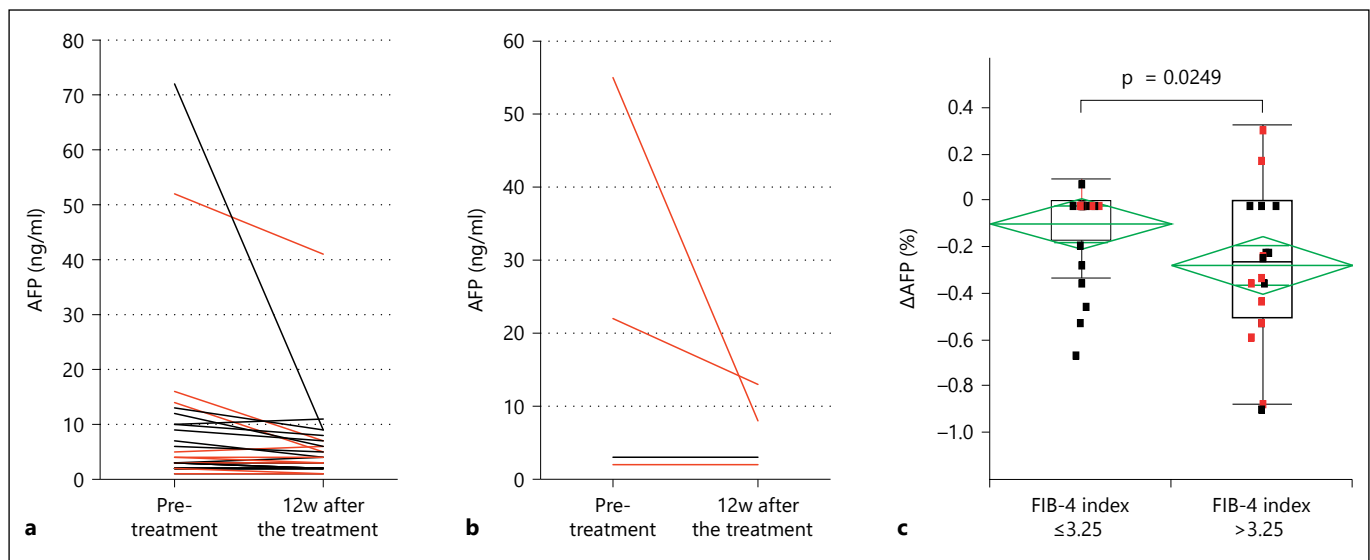
**Fig. 2.** Hb concentration, eGFR, and serum ALB level during the clinical course in patients aged  $\geq 75$  and  $\leq 74$ . Alterations of Hb concentration (**a**), eGFR (**b**), and serum ALB level (**c**) are shown. Red dashed lines show the data of the patients aged  $\geq 75$  and black dashed lines denote that of the patients aged  $\leq 74$ . The boxes denote 75% distributions and the lines in the boxes showed median values. p values (by the Wilcoxon rank-sum test) of each comparison be-

tween patients aged  $\geq 75$  and  $\leq 74$  at baseline, at week 2 (2w) and week 4 (4w) on the treatment, at the EOT, and at 4 and 12 weeks after the EOT were as follows;  $p = 0.0005$ ,  $p = 0.0016$ ,  $p = 0.0013$ ,  $p = 0.0064$ ,  $p = 0.0050$ ,  $p = 0.0107$  for Hb,  $p = 0.0075$ ,  $p = 0.0072$ ,  $p = 0.0043$ ,  $p = 0.0048$ ,  $p = 0.0043$ ,  $p = 0.0179$  for eGFR, and  $p = 0.0165$ ,  $p < 0.0001$ ,  $p = 0.0018$ ,  $p = 0.1655$ ,  $p = 0.1283$ ,  $p = 0.0501$  for ALB, respectively.

As shown in table 1, several patient characteristics significantly differ between  $\geq 75$  and  $\leq 74$  years groups. The aged group includes more women, and patients with a history of HCC. In addition, the aged group shows significantly lower serum ALB level, Hb concentration, and eGFR. We did not perform liver biopsy before the treatment and the presence of liver cirrhosis could not be determined precisely. Therefore, we calculated FIB-4 index as an alternative for assessing the degree of liver fibrosis because an FIB-4 index of  $>3.25$  or  $\leq 3.25$  could adequately reflect the presence or absence of advanced liver fibrosis [17]. As expected, the aged group included more patients with FIB-4 index of  $>3.25$ .

Although both the aged and non-aged groups represented 100% of the ETR rate, the SVR12 rate of the aged group was 81.3%, which was lower than that of the non-

aged groups (SVR12 rate was 96%). Although previous reports suggested a high SVR12 rate irrespective of liver cirrhosis and age [6, 8, 9], the reported cohorts in most previous literature classified the elderly group as the group comprising patients aged  $\geq 65$ , and did not include patients aged  $\geq 75$ . Therefore, it might be possible that advanced liver fibrosis and history of HCC that were associated with the presence of liver cirrhosis might be a cause of a lower SVR12 rate in the aged patients. In addition, it is reasonable to speculate that lower Hb concentration and eGFR contribute to the lower SVR rate in the aged patients because many aged patients received RBV dose reduction for anemia management. However, this association is not statistically significant because of the very small number of the patients who failed to achieve SVR12.



**Fig. 3.** Alteration of serum AFP before and 12 weeks after the EOT. **a** Alteration of serum AFP of the patients who achieved SVR12, and **(b)** that of the patients who failed to achieve SVR12. The red lines denote the data of the patients aged  $\geq 75$  and black lines denote those of the patients aged  $\leq 74$ . **c** Comparison of percentage difference of serum AFP ( $\Delta$ AFP) between the patients with FIB-4 index  $< 3.25$  and those with FIB-4 index  $> 3.25$ . The red dots denote the data of the patients aged  $> 75$  and black dots denote those of the

patients aged  $\leq 74$ . Black box and whisker plots denote 75 and 95% distributions; lines within boxes show median values; the mean percentage  $\Delta$ AFP and 95% CI are shown as green diamonds and lines within the diamonds, respectively. The percentage  $\Delta$ AFP is calculated as difference of the AFP level before and after the treatment divided by baseline AFP level. The minus value denotes decrease of AFP after the treatment. p value by the Wilcoxon rank-sum test is shown.

Consistent with the results from the previous reports [6, 8, 9], all patients were negative for serum HCV at EOT, suggesting a high barrier against the emergence of resistant strain for nucleotide NS5B inhibitor. Of the 4 patients who failed to achieve SVR12, only the patient in the non-aged group discontinued the 12-week treatment because of hyperbilirubinemia. Although this patient was classified as belonging to the non-aged group, the patient was aged 74, had previously received antiviral therapy, had an FIB-4 index  $> 3.25$ , and showed slightly increased T. Bil level and decreased eGFR at baseline (1.3 mg/dl and 59 for T. Bil level and eGFR, respectively). The serum bilirubin level returned to the baseline after the discontinuation of treatment, suggesting the role of sofosbuvir and/or RBV in hyperbilirubinemia in this patient who had advanced liver fibrosis and impaired renal function, which are frequently observed in aged patients. On the other hand, the other 3 patients who failed to achieve SVR12 are the members of the aged group, and 2 of them received a reduced dose of RBV for the management of anemia. In addition, 2 had previously received antiviral therapy and showed an FIB-4 index of  $> 3.25$ . The baseline Hb concentration and eGFR in these 3 patients ranged from 13.3 to 14.8 g/dl and from 68 to 69, respectively, and

the minimum Hb concentration during the treatment was 10.2–13 g/dl. Therefore, although not statistically significant because of the limited number of non-SVR12 patients, dose reduction of RBV, and low Hb concentration and eGFR at baseline should affect the SVR12 rate especially in patients aged  $\geq 75$ .

Among the blood chemical tests examined, the serum ALB level, Hb concentration, and eGFR are significantly lower in the aged group; we compared these levels during and after the treatment. RBV dose reduction was performed in 11 of 37 (29.7%) non-aged and 10 of 19 of aged patients (52.6%) for the management of anemia. Although the Hb concentration and eGFR are significantly lower in the aged group throughout the clinical course, no patient showed Hb concentration of less than 10 g/dl and eGFR of less than 50. In addition, a gradual increase of serum ALB level is observed in aged patients, suggesting that the combination of sofosbuvir plus RBV is tolerable and beneficial in patients aged  $\geq 75$ , although the SVR12 rate is lower in aged than in non-aged patients.

We also examined the decrease of serum AFP before and after the combination treatment. Among the 41 patients for whom serum AFP level before and at 12 weeks after the EOT was evaluated, only 3 showed an increase of AFP and all but

1 patient with the baseline AFP of >5 ng/ml showed a decrease in serum AFP after the treatment, irrespective of age. More importantly, the decrease of AFP was also observed in patients who failed to achieve SVR12 and was more prominent in the patients with an FIB-4 index of >3.25. Because the serum AFP level should be higher in patients with liver cirrhosis, early decrease of AFP could be more prominent in patients with advanced liver fibrosis [18, 19].

In this study, we explored the safety, tolerability, and efficacy of sofosbuvir plus RBV in patients aged  $\geq 75$  with HCV G2 infection. The treatment was safe and well tolerable in aged patients with advanced liver fibrosis, history of HCC emergence, low serum ALB level, low Hb concentration, and low eGFR. However, management of anemia by dose reduction of RBV is necessary for such patients, which could lead to a low SVR12 rate compared to the rate in patients younger than 75 years.

Recently, a new combination therapy using sofosbuvir and the NS5A inhibitor velpatasvir has been reported; the

SVR for CHC G2 in the sofosbuvir plus velpatasvir group is superior to the rate in the sofosbuvir plus RBV group [20]. In addition, this new combination reportedly shows a high SVR12 rate regardless of genotype and even in cases with decompensated cirrhosis [21, 22]; the development of direct-acting antivirals should lead to the elimination of virus in almost all patients with HCV infection in the near future.

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## Disclosure Statement

The authors have no conflicts of interest to disclose.

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