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# Real-world safety and efficacy of sofosbuvir and ledipasvir for elderly patients

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## Abstract

**Background and Aim:** In September 2015, sofosbuvir and ledipasvir were approved for clinical use in Japan for patients infected with genotype 1 hepatitis C virus. We conducted a postmarketing prospective cohort study to elucidate the safety and efficacy of this therapy in a real-world setting.

**Methods:** We treated 509 patients using standard doses of sofosbuvir and ledipasvir for 12 weeks. As sustained virological response (SVR) in 2 patients could not be evaluated, 507 patients were finally analyzed. Patients with daclatasvir plus asunaprevir failure were excluded.

**Results:** Four patients (0.8%) discontinued treatment due to adverse events. SVR rates for the overall cohort, patients <65 years old, ≥65 and <75 years old, and ≥75 years old were 98% (495/507), 98% (161/163), 96% (179/186), and 98% (155/158), respectively. SVR rates among cirrhotic patients, patients with moderate chronic kidney disease (CKD), patients with a history of hepatocellular carcinoma (HCC) treatment, patients with protease inhibitor (PI) triple therapy failure, and patients with resistance-associated substitutions (RASs) to nonstructural protein 5A (NS5A) were 97% (228/235), 98% (117/119), 95% (95/100), 94% (46/49), and 92% (44/48), respectively. In the comparison of factors between patients with and without SVR, high body weight, discontinuation of therapy, and NS5A RASs were significantly associated with non-SVR.

**Conclusions:** In this real-world setting, sofosbuvir and ledipasvir were a safe treatment even in patients ≥75 years old. When patients without pre-existing NS5A RASs and daclatasvir plus asunaprevir failure are selected, extremely high SVR rates can be achieved irrespective of age.

## Introduction

In September 2014, the clinical use of all-oral, interferon (IFN)-free, dual direct-acting antiviral (DAA) combination therapy using the nonstructural protein 5A (NS5A) inhibitor daclatasvir plus the NS3/4A protease inhibitor (PI) asunaprevir for 24 weeks was first approved for IFN-ineligible or -intolerant patients infected with genotype 1 hepatitis C virus (HCV) in Japan. While this therapy was well tolerated in a Japanese Phase III trial, the sustained virological response (SVR) rate was not particularly high (85%), and that of patients with pre-existing NS5A resistance-associated substitutions (RASs) was significantly lower (48%).[1,2] Furthermore, the emergence of a multidrug-resistant virus after failure of this treatment also represented a serious problem. Testing for pre-existing NS5A RASs before this

therapy was therefore recommended in the Japanese guidelines to avoid treatment failure where possible.[2] In fact, the SVR rate for this therapy among patients without NS5A RASs and failure of simeprevir-based triple therapy was extremely high (98%) in our prospective cohort study in a real-world setting.[3]

In September 2015, clinical use of the NS5B polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir was approved for patients infected with genotype 1 hepatitis C virus in Japan. As this combination therapy does not include an NS3 PI, it was also expected to allow the rescue of patients experiencing failure of NS3 PI-based triple therapy. This therapy was also well tolerated and achieved an extremely high SVR rate (100%) in a Japanese Phase III trial.[4] Testing for pre-existing NS5A RASs among patients who had never received DAAs combination therapy was thus not recommended in the Japanese

guidelines.[2] However, patients in the phase III trial were younger than real-world patients, and the number of patients with cirrhosis, failure of NS3 PI-based triple therapy, or chronic renal disease was low. Furthermore, patients with daclatasvir plus asunaprevir failure or a history of treatment for hepatocellular carcinoma (HCC) had been excluded. We therefore conducted a postmarketing prospective cohort study to evaluate the safety and efficacy of this therapy, especially for elderly patients over 75 years of age, and to elucidate whether extremely high SVR rates can also be achieved even in a real-world setting. However, as we raised a concern about the emergence of a virus with stronger multidrug resistance after the failure of this treatment for patients who experienced daclatasvir plus asunaprevir failure, those patients were excluded from the present study.

## Material and methods

**Patients.** This was a multicenter prospective cohort study. Exclusion criteria were any of following: (i) infection with genotypes other than genotype 1; (ii) treatment failure of daclatasvir and asunaprevir; (iii) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m$^2$; (iv) decompensated cirrhosis (Child-Pugh class B or C); or (v) any form of cancer. However, patients who had received radical cancer treatments could be enrolled in this study. Between September 2015 and June 2017, patients at Wakayama Medical University Hospital, Naga Municipal Hospital, Hidaka General Hospital, or Wakayama Rosai Hospital who were eligible were enrolled in the present study.

Liver cirrhosis was diagnosed clinically through liver biopsy or imaging studies using morphological signs of cirrhosis from portal hypertension, such as portosystemic shunt or hypersplenism. All study protocols were approved by the ethics committees of each participating hospital. 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: 000023271).

**Treatment regimens.** A tablet (Harvoni; Gilead, Tokyo, Japan) including sofosbuvir (400 mg) and ledipasvir (90 mg) was orally administered once daily for 12 weeks.

**Assessment of effectiveness.** The amount of HCV RNA was measured using quantitative reverse transcription–polymerase chain reaction (RT-PCR) (COBAS TaqMan PCR assay version 2; Roche Diagnostics, Branchburg, NJ, USA) and was checked on the day of therapy initiation and at every 4 weeks up to 12 weeks after the end of therapy. SVR was defined as a negative HCV RNA at the end of therapy, remaining negative for 12 weeks after the end of therapy.

**Assessment of safety and tolerability.** Patients were assessed for safety and tolerability during treatment by attending physicians who monitored adverse events and laboratory parameters such as blood cell counts and liver and renal function tests every 2 weeks. Adverse events were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) 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 a modified intention-to-treat (ITT) analysis excluding patients for whom SVR could not be evaluated. 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. Values of $P < 0.05$ were considered statistically significant. SPSS for Windows version 24J statistical software (SPSS, Tokyo, Japan) was used for all data analyses.

## Results

**Baseline characteristics of patients.** A total of 509 patients were enrolled in the present study. However, two patients were lost to follow-up, with one patient dying 13 days after starting therapy in a traffic accident and one patient dying 4 weeks after the end of therapy due to acute myocardial infarction. As a result, a final total of 507 patients for whom SVR at 12 weeks could be evaluated were analyzed. Patient characteristics are summarized in Table 1.

**Comparison of pre-treatment factors between patients ≥ 75 and < 75 years old.** The comparison of pretreatment factors between patients ≥75 and <75 years old is shown in Table 2. Except for age, significant differences were

**Table 1** Patients' characteristics

| | $n = 507$ |
|---|---|
| Age (years) | 68 ± 12 |
| ≥75 years | 158 (31%) |
| Gender (male/female) | 259/248 (51%/49%) |
| Cirrhosis | 235 (46%) |
| Other complications requiring medications[†] | 308 (61%) |
| Moderate chronic kidney disease (eGFR < 60) | 119 (23%) |
| History of HCC treatment | 100 (20%) |
| History of IFN-based therapy | 172 (34%) |
| Ribavirin/protease inhibitor | 111/49 |
| NS5A RAS (positive/negative/untested) | 48/83/370 |
| Height (cm) | 159.4 ± 9.1 |
| Weight (kg) | 58.8 ± 12.0 |
| BMI | 23.0 ± 3.6 |
| Baseline HCV-RNA (LogIU/mL) | 6.0 ± 0.8 |
| WBC (/mm$^3$) | 4886 ± 1587 |
| Hb (g/dL) | 13.5 ± 1.7 |
| Platelets (10$^4$/mm$^3$) | 14.8 ± 6.4 |
| AST (IU/L) | 53 ± 35 |
| ALT (IU/L) | 51 ± 41 |
| γ-GT(IU/L) | 53 ± 59 |
| e-GFR | 73 ± 19 |
| AFP (ng/mL) | 14 ± 36 |

[†]Hypertension, diabetes mellitus, autoimmune disease, thyroid disease, heart disease, renal disease, respiratory disease, and psychological disorder were included.

Values are expressed as mean ± standard deviation or numbers (percentage).

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; IFN, interferon; NS, nonstructural; RASs, resistance-associated substitutions; WBC, white blood cells; γ-GT, γ-glutamyl transferase.

seen in gender; height; weight; cirrhosis; chronic kidney disease (CKD); history of HCC treatment; history of IFN-based therapy; presence of NS5A RASs; concentrations of hemoglobin, alanine aminotransferase, and γ-glutamyl transferase; and eGFR.

***Safety and tolerability.*** Adverse events profiles according to age group are summarized in Table 3. A similar safety profile was observed between patients ≥ 75 and <75 years old. The discontinuation rate due to adverse events was 0.8% (4/507). Reasons for discontinuation were drug-induced dermatitis (Grade 3) in two patients, conjunctival hyperemia and lip swelling in one patient, and exacerbation of depression in one patient. The most frequent adverse event was elevation of uric acid level (Grade 1). No severe liver injury or exacerbation of renal dysfunction was seen.

***Treatment response.*** The overall SVR rate was 98%. SVR rates for the overall cohort and by age group are shown in Figure 1. No significant difference was observed among age groups. SVR rates according to background factors are summarized in Figure 2. The SVR rate of patients with a history of HCC treatments tended to be lower than that of patients without prior HCC treatment ($P = 0.067$). SVR rates according to previous treatments and the presence of NS5A RASs are summarized in Figure 3. A significant difference in the SVR rate was seen between the NS5A RAS-positive group and the untested group.

***Treatment failure.*** Non-SVR was observed in 12 patients (2%). Background factors between patients with and without SVR are compared in Table 4. Significant differences were

evident in body weight, discontinuation of therapy, and presence of NS5A RASs.

## Discussion

This was a multicenter postmarketing prospective cohort study of real-world clinical settings in Japan. Many elderly patients were enrolled in the present study: 68% of the patients were >65 years old, 46% had cirrhosis, 61% had comorbidities, 23% had moderate CKD, and 20% had a history of HCC treatment. As our study population was more elderly and cirrhotic compared to the population of Phase III trials, our results can provide useful information regarding IFN-ineligible patients in the Asia-Pacific region.

Some real-world data based on large-scale cohort studies of sofosbuvir plus ledipasvir have been reported from Western countries.[5–9] Although the mean age was younger (around 60 years old) than that of our study (68 years old), the treatment discontinuation rate of sofosbuvir plus ledipasvir for 12 weeks was very low and ranged from 0 to 5.7%. On the other hand, the discontinuation rate according to real-world data from Japan (including our data) was also extremely low (0.4–3.3%).[10–13] Tsuji *et al.*[13] reported that the frequency of adverse events did not differ between patients ≥75 and <75 years old. In the present study, no significant differences were seen in adverse event profiles between ≥75-year-old and <75-year-old patient groups. This therapy would thus be highly safe even in elderly patients ≥75 years old. However, cardiac arrest and bradycardia have been reported in association with this therapy for patients with underlying cardiac disease.[14,15] Hagiwara *et al.* reported that 3% (3/91) of patients experienced serious cardiac adverse events leading to treatment discontinuation, such as bradycardia,

**Table 2** Comparison of pretreatment factors between patients ≥ 75 and <75 years old

| Factors | Patients aged ≥75 years ($n = 158$) | Patients aged <75 years ($n = 349$) | $P$ |
|---|---|---|---|
| Age (years) | 79 ± 4 | 63 ± 10 | <0.001 |
| Gender (male/female) | 67/91 (42%/58%) | 192/157 (55%/45%) | 0.009 |
| Height (cm) | 155.6 ± 8.4 | 161.2 ± 8.9 | <0.001 |
| Weight (kg) | 54.9 ± 10.0 | 60.6 ± 12.4 | <0.001 |
| BMI | 22.6 ± 3.1 | 23.2 ± 3.8 | 0.080 |
| Cirrhosis | 93 (59%) | 142 (41%) | <0.001 |
| Chronic kidney disease (eGFR < 60) | 63 (40%) | 56 (16%) | <0.001 |
| History of HCC treatment | 46 (29%) | 54 (15%) | <0.001 |
| History of IFN based therapy | 43 (27%) | 115 (33%) | 0.032 |
| History of protease inhibitor therapy | 11 (7%) | 38 (11%) | 0.166 |
| NS5A RASs positive | 27 (17%) | 21 (6%) | <0.001 |
| Baseline HCV-RNA (LogIU/mL) | 6.0 ± 0.7 | 6.0 ± 0.8 | 0.905 |
| WBC (/mm$^3$) | 4704 ± 1515 | 4999 ± 1642 | 0.056 |
| Hb (g/dL) | 13.0 ± 1.6 | 13.7 ± 1.7 | <0.001 |
| Platelets (10$^4$/mm$^3$) | 14.2 ± 6.5 | 15.3 ± 6.3 | 0.070 |
| AST (IU/L) | 51 ± 32 | 54 ± 36 | 0.392 |
| ALT (IU/L) | 42 ± 29 | 55 ± 46 | <0.001 |
| γ-GT(IU/L) | 43 ± 42 | 56 ± 64 | 0.005 |
| AFP (ng/mL) | 16 ± 44 | 13 ± 30 | 0.373 |
| e-GFR | 64 ± 16 | 77 ± 19 | <0.001 |

Values are expressed as mean ± standard deviation or numbers (percentage).
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; IFN, interferon; NS, nonstructural; RASs, resistance-associated substitutions; WBC, white blood cells; γ-GT, γ-glutamyl transferase.

**Table 3** Adverse events during treatment

| | Patients aged ≥ 75 years (*n* = 158) | Patients aged < 75 years (*n* = 349) | Total (*n* = 507) |
|---|---|---|---|
| Treatment discontinuation | 1 (0.6%)[†] | 3 (0.9%)[‡] | 4 (0.8%) |
| Mild eruption | 0 | 1 (0.3%) | 1 (0.2%) |
| Depression | 0 | 2 (0.6%) | 2 (0.4%) |
| Infection[§] | 4 (2.5%) | 4 (1.1%) | 8 (1.6%) |
| The other adverse events | 3 (1.9%) | 2 (0.6%) | 5 (1.0%) |
| Elevation of bilirubin level | 0 | 0 | 0 |
| Elevation of transaminase level (Grade1) | 3 (1.9%) | 3 (0.8%) | 6 (1.2%) |
| Elevation of serum ammonia level | 1 (0.6%) | 4 (1.1%) | 5 (1.0%) |
| Elevation of uric acid level | 21 (13.2%) | 42 (12.0%) | 63 (12%) |
| Sudden transient loss of consciousness | 1 (0.6%) | 0 | 1 (0.2%) |

[†]Conjunctival hyperemia and lip swelling.
[‡]Two drug-induced dermatitis (Grade 3) and one exacerbation of depression.
[§]Bacterial and viral infections were included.
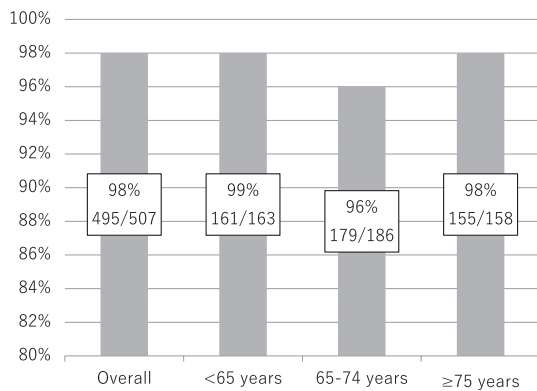


**Figure 1** Sustained virological response rates according to age group. No significant difference was seen among age groups.

paroxysmal atrial fibrillation, and heart failure with QT prolongation.[10] Kanda *et al.*[11] and Tsuji *et al.*[13] also indicated that 0.8% (2/240) and 0.2% (3/1461) of patients experienced cardiac adverse events, respectively. However, Ogawa *et al.*[12] reported no serious cardiac events among their 772 Japanese patients. Likewise, the present study encountered no serious cardiac events. Serious cardiac events during this treatment must be paid special attention but would be very rare in patients without cardiac disease. The most frequent adverse event in the present study was the elevation of uric acid concentration. This finding has not been reported previously. Sofosbuvir is metabolized in the kidneys, and hyperuricemia might impair kidney function. This adverse effect was controlled by the oral administration of allopurinol in the present study. Hasegawa *et al.* indicated that eGFR was unchanged before and after treatment.[10] Okubo *et al.* and Tsuji *et al.* also reported that ledipasvir plus sofosbuvir did not affect eGFR in patients with CKD stage 3.[13,16] No exacerbation of renal function was seen in the present study.

Regarding the efficacy for elderly patients ≥75 years old, Kanda *et al.*[11] indicated that the SVR rate among patients ≥75 years old was equal to that of patients <75 years old (98.1% *vs* 98.4%). Tsuji *et al.*[13] also found that the SVR rates among patients ≥75 and <75 years old were 97.5% (420/431) and 98.8%
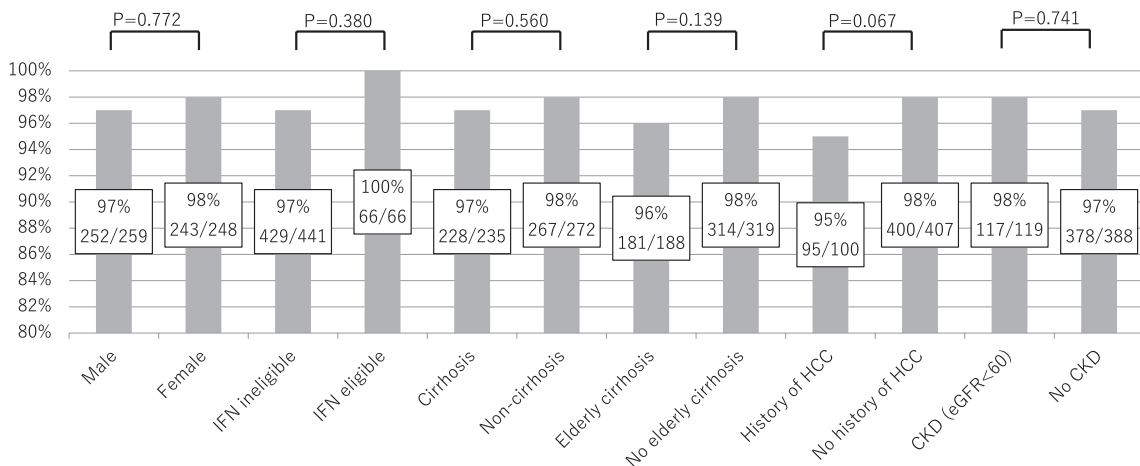


**Figure 2** Sustained virological response rates according to background factors. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; IFN, interferon.
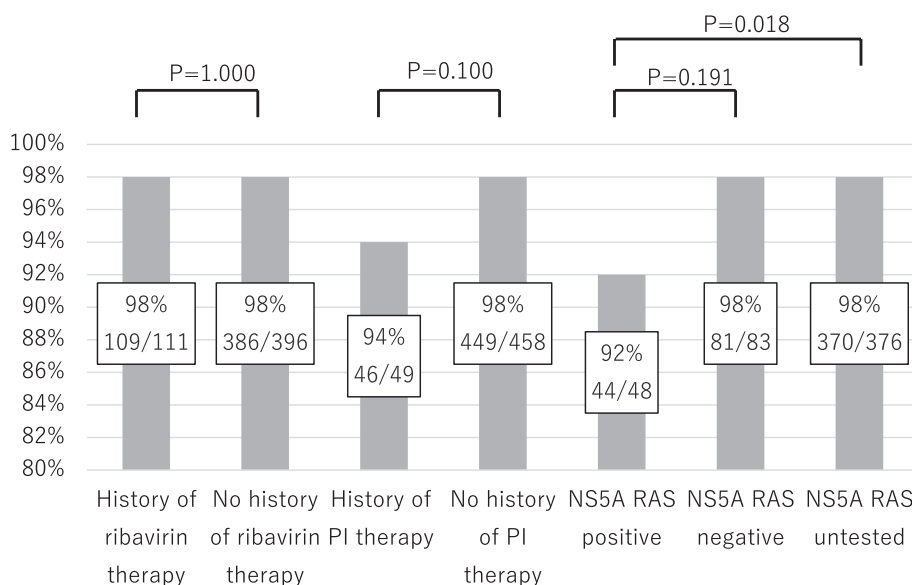
**Figure 3** Sustained virological response rates according to previous treatments and nonstructural protein 5A resistance-associated substitutions. NS5A, nonstructural protein 5A; PI, protease inhibitor; RAS, resistance-associated substitution. A significant difference in SVR rate was seen between the NS5A RAS-positive group and the untested group.

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

| Factors | SVR (n = 495) | Non-SVR (n = 12) | P |
|---|---|---|---|
| Age (years) (range) | 68 (16–92) | 69 (49–79) | 0.767 |
| Gender (male/female) | 252/243 | 7/5 | 0.772 |
| Height (cm) | 159.8 (134.7–181.1) | 164.6 (145.7–172.7) | 0.299 |
| Body weight (kg) | 57.0 (32.0–120.0) | 66.7 (43–77.7) | 0.037 |
| BMI (kg/m$^2$) | 22.8 (12.5–38.9) | 24.4 (19.6–28.1) | 0.072 |
| Cirrhosis | 228 | 7 | 0.560 |
| Discontinuation of therapy | 1 | 3 | <0.001 |
| History of HCC treatment | 95 | 5 | 0.067 |
| CKD | 4 | 4 | 1.000 |
| eGFR | 73.1 (30–240.2) | 72.2 (50.5–105.8) | 0.791 |
| History of IFN-based therapy | 169 | 3 | 0.759 |
| History of protease inhibitor therapy | 46 | 3 | 0.100 |
| NS5A RAS (positive/negative/untested) | 44/81/370 | 4/2/6 | 0.018 |
| White blood cell (/mm$^3$) | 4800 (1760–11 000) | 4760 (3540–6020) | 0.876 |
| Hemoglobin (g/dL) | 13.5 (7.1–17.7) | 14.3 (6.3–20.8) | 0.367 |
| Platelets (×10$^4$/mm$^3$) | 14.7 (2.7–46.6) | 11.7 (10.4–25.2) | 0.115 |
| AST (IU/L) | 44 (13–266) | 55 (24–110) | 0.310 |
| ALT (IU/L) | 38 (7–277) | 58 (15–154) | 0.110 |
| γ-GTP (IU/L) | 34 (7–464) | 52 (13–461) | 0.052 |
| AFP (ng/mL) | 5.2 (1.0–445.0) | 10.6 (1.3–29.7) | 0.135 |
| HCV-RNA (logIU/mL) | 6.1 (2.7–7.6) | 6.3 (3.3–7.0) | 0.427 |

Values are expressed as medians (range) or numbers of patients.
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; IFN, interferon; NS, nonstructural; RASs, resistance-associated substitutions; SVR, sustained virological response; γGTP, γ-glutamyltransferas.

(1018/1030), respectively. Ogawa et al.[12] reported that SVR rates among patients <65, 65–74, and ≥75 years old were 99.2, 98.0, and 99.6%, respectively. In the present study, despite elderly patients ≥ 75 years old having a smaller constitution; a greater rate of ineligibility for IFN; and greater frequencies of cirrhosis, cytopenia, CKD, and history of HCC treatment than patients < 75 years old, the SVR rate was extremely high (98%), comparable to that of younger patients. This therapy would therefore be able to achieve high SVR rates irrespective of age, even in real-world settings.

Factors reportedly associated with unfavorable SVR include male gender,[12] cirrhosis,[6,7,12] lower albumin,[6,8] higher total bilirubin,[6] thrombocytopenia,[7] history of HCC,[17] baseline NS5A RASs,[12] failure of daclatasvir/asunaprevir treatment,[17] and twice-daily proton pump inhibitor (PPI) use.[6,18] Considering these findings, SVR rates seem to be lower, along with advanced fibrosis and reduced liver function. Concerning the impact of pre-existing RASs on SVR, Sarrazin *et al.* and Mizokami *et al.* reported that pre-existing NS5A RASs had no significant impact on treatment outcome with sofosbuvir plus ledipasvir in clinical trials,[19,20] However, Ogawa *et al.*[12] indicated, in their real-world data, that the SVR rate for cirrhosis patients with baseline NS5A RASs (87.5%, 49/56) was significantly lower than those for other groups, and this tendency was observed, except for patients with prior daclatasvir/asunaprevir failure. Our data also showed that pre-existing NS5A RASs resulted in a possibility of reduced SVR rates. However, even if baseline NS5A RASs are positive, an SVR rate of approximately 90% can be expected. Baseline NS5A RASs are thus not a reason to avoid this therapy.

Some reports have described rescue treatment using sofosbuvir plus ledipasvir for patients with DAA failure. In a Japanese Phase III trial, the SVR rate for patients with PEGylated-IFN plus ribavirin triple therapy using various PIs, such as simeprevir, telaprevir, vaniprevir, and faldaprevir, was 100% (14/14).[4] Kanda *et al.*[11] also indicated, in their real-world data, that 100% SVR rates (25/25) were achieved in patients previously treated with triple therapy with various PIs. Tsuji *et al.*[13] indicated that the SVR rates of patients with and without prior telaprevir or simeprevir triple therapy were 98.4% (125/127) and 98.4% (1313/1334), respectively. In the present study, although the SVR rate of patients with PI triple therapy failure was 94% (46/49), no significant difference ($P = 0.100$) was seen. This therapy may well have sufficient potential as a rescue treatment for patients with PI triple therapy failure. On the other hand, Itakura *et al.* reported that treatment-emergent RASs after failure with daclatasvir plus asunaprevir combination therapy are highly complex in more than 50% of patients.[21] Iio *et al.*[17] reported that the SVR rate was significantly lower in patients with prior daclatasvir plus asunaprevir failure compared to those without (69.2% [18/26] *vs* 98.4% [496/504], $P < 0.001$). Akuta *et al.*[22] reported that the SVR rate in 54 patients with prior daclatasvir plus asunaprevir failure was 70%. Sofosbuvir plus ledipasvir would thus be unsuitable for patients experiencing daclatasvir plus asunaprevir failure. In the present study, patients with daclatasvir plus asunaprevir treatment failure were excluded. As a result, extremely high SVR rates could be achieved. On univariate analysis, higher body weight, discontinuation of therapy, and baseline NS5A RASs were significant unfavorable factors related to SVR. In addition, the SVR rate of patients with a history of HCC tended to be lower ($P = 0.067$). The high SVR rate among patients ≥ 75 years old may be attributable in part to their lower body weight. Increasing the drug dose for patients with high body weight may represent a more obvious option, but increased doses for this drug have not yet been approved.

In November 2016, a next-generation DAA regimen combining elbasvir and grazoprevir was approved in Japan.[23] This regimen can be safely used even for severe renal failure.[24] However, this regimen carries a small risk of severe liver dysfunction. In addition, Toyoda *et al.* indicated, based on real-world data,

that patients with a history of failure of IFN-free DAA therapy or with double NS5A RASs remain difficult to treat using this regimen.[25] In November 2017, the next combination therapy with glecaprevir and pibrentasvir was also approved in Japan. This regimen is extremely effective for patients with DAA failure.[26] Furthermore, 8 weeks of therapy with this combination for noncirrhotic patients has also been approved.[27] As shortening the treatment period represents a great advantage, this regimen will become a first-line treatment not only for patients with DAA failure but also for noncirrhotic patients in the near future. However, this regimen uses a combination of an NS5A inhibitor plus an NS3/4A PI and carries a small risk of severe liver dysfunction. Real-world data must be accumulated to achieve reliable use of this regimen. On the other hand, large-scale, real-world evidence for the sofosbuvir and ledipasvir regimen has been reported. As no severe liver dysfunction was apparent in our real-world data, the sofosbuvir and ledipasvir regimen appears highly advantageous for cirrhotic patients without sufficient hepatic functional reserve compared to the combination of an NS5A inhibitor plus an NS3/4A PI. The sofosbuvir and ledipasvir regimen should thus be used for cirrhotic patients without a history of DAA therapy as a first-line treatment and can be reliably used for elderly patients with comorbidities on the basis of real-world evidence.

Some limitations to the present study must be considered. First, some selection biases are inevitably present in cohort studies. Second, the number of patients was too small to reach definitive conclusions and generalize about the safety and efficacy of elderly patients. Third, the reason for treatment failure of this therapy could not be clarified by our analysis because the number of patients who did not achieve SVR was too low, at only 12 patients (2%). To validate our results and clarify the reasons for treatment failure, a larger-scale cohort study and detailed analysis of RASs at baseline is needed.

In conclusion, sofosbuvir and ledipasvir provided extremely safe and effective treatment even for patients ≥ 75 years old in a real-world setting. If patients without pre-existing NS5A RASs and daclatasvir plus asunaprevir failure are selected, extremely high SVR rates can be achieved irrespective of age. This treatment could be considered one of the first-line treatments with obvious real-world evidence for DAA-naïve patients ineligible for IFN, such as elderly patients with compensated cirrhosis and/or various comorbidities.

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