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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Real-world efficacy and safety of ledipasvir and sofosbuvir in patients with hepatitis C virus genotype 1 infection: a nationwide multicenter study by the Japanese Red Cross Liver Study Group

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Abstract

Background We aimed to describe the real-world efficacy and safety of combination therapy with ledipasvir and sofosbuvir (LDV/SOF) for chronic hepatitis C virus (HCV) genotype 1 (GT1) infection.

Methods This retrospective analysis of a prospective, nationwide, multicenter registry included GT1-infected patients treated with LDV/SOF for 12 weeks. We assessed the rate of sustained virological response at 12 weeks post-treatment (SVR12), incidence of adverse events, and serum markers of hepatocellular carcinoma (HCC).

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Results Among the 1461 patients included (mean age, 69 years; 29.5% aged > 75 years; cirrhosis, 23.8%; history of treatment for HCC, 10.9%), the overall SVR12 rate was 98.4% (1438/1461). Factors associated with treatment failure were cirrhosis (odds ratio, 4.19; $p = 0.014$) and resistance-associated substitutions (RASs) in NS5A at baseline (odds ratio, 7.78; $p = 0.0004$). The SVR12 rate in patients with cirrhosis and NS5A RASs was 93.0% compared to 100% in patients without cirrhosis or NS5A RASs. In patients with SVR, the levels of alpha-fetoprotein (AFP), AFP-L3, and Mac-2 binding protein glycosylation isomer (M2BPGi) decreased from baseline to end of treatment (from 13.4 ± 37.6 to 6.0 ± 10.6 ng/mL, $p < 0.0001$; from 2.2 ± 4.9 to 1.5 ± 6.3%, $p < 0.005$; and from 3.6 ± 3.7 to 2.0 ± 3.5 cut-off index, $p < 0.0001$; respectively). Adverse events were rare and not associated with age. No decrease in estimated glomerular filtration rate was observed in patients with baseline chronic kidney disease stage 3.

Conclusions LDV/SOF therapy is highly effective and safe in elderly Japanese patients with HCV GT1, even in the presence of cirrhosis or NS5A RASs. Patients with SVR may have a lower risk of HCC.

Keywords Chronic hepatitis C · Ledipasvir · Sofosbuvir · Alpha-fetoprotein

Introduction

Chronic hepatitis C virus (HCV) infection is associated with progressive liver disease that can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [1, 2]. Recently, direct-acting antivirals (DAAs) have replaced pegylated-interferon (PEG-IFN) plus ribavirin (RBV) as the standard HCV treatment. Eliminating the reliance on PEG-IFN plus RBV as the backbone of therapy spares patients from often severe IFN- or RBV-related adverse events such as hemolytic anemia. DAA therapies have consistently demonstrated high sustained virological response (SVR) rates, good tolerability, and efficacy with shorter treatment durations. Consequently, the number of DAA therapies approved worldwide has been steadily increasing [3–5].

In Japan, patients with chronic HCV infection tend to be older, and they have a higher risk of liver carcinogenesis [6, 7]. In such patients, early HCV eradication is crucial. Since September 2014, numerous Japanese patients with HCV genotype 1 (GT1) have been treated using combination therapy with the NS5A inhibitor daclatasvir (DCV) and the protease inhibitor asunaprevir (ASV) [8–10]. However, the major drawback of this therapy was that baseline resistance-associated substitutions (RASs) involving amino acid position 168 of NS3 or amino acid positions 31 or 93 of NS5A significantly decreased the SVR rates [11]. In DAA-naïve patients, RASs at position 168 of NS3 are rarely observed, while RASs at position 31 or 93 of NS5A occur in around 20% of cases [12]. Therefore, according to the guideline proposed by the Japanese Society of Hepatology, patients with hepatitis C should undergo determination of NS5A RASs at baseline, and only those without such RASs should be indicated for therapy with DCV plus ASV [5]. A major breakthrough in HCV treatment occurred in Japan in 2015 with the approval of the combination therapy with the NS5A inhibitor ledipasvir and NS5B inhibitor sofosbuvir (LDV/SOF) [13]. A phase 3 trial reported an overall SVR rate of 100% in patients treated using LDV/SOF without RBV. Some large cohorts have shown SVR rates of 98%, irrespective of age [14, 15]. Furthermore, in a phase 3 trial performed in Japan, patients with NS5A RASs at baseline who received LDV/SOF with or without RBV achieved an SVR rate of 98% [16]. Based on these data, the guideline proposed by the Japanese Society of Hepatology did not recommend testing for NS5A RASs at baseline in patients with hepatitis C indicated for LDV/SOF [5]. Nevertheless, the validity of this recommendation should be tested on real-world data.

As SVR rates are currently high, it becomes important to assess the risk of HCC development after HCV eradication. Several studies reported that post-treatment serum alpha-fetoprotein (AFP) levels are associated with HCC development in patients who achieved SVR with IFN-based therapy [6, 17, 18]. Recent reports revealed that AFP levels are reduced in patients who achieved SVR by DAA therapy [19, 20], and that reduced AFP is associated with reduced risk of HCC after SVR [21]. Furthermore, reduced serum levels of Mac-2 binding protein glycosylation isomer (M2BPGi) were also found to be associated with reduced risk of HCC after SVR [21].

In this nationwide, large-scale, multicenter, real-world cohort study, we assessed the safety and efficacy of LDV/SOF therapy in patients with HCV GT1, focusing specifically on the effect of baseline RASs and the impact of age. We also investigated the impact of SVR on the predictors of future HCC development, such as serum AFP, AFP-L3, and M2BPGi levels [23, 24].

Methods

Patients

This nationwide multicenter cohort assembled by the Japanese Red Cross Liver Study Group consisted of 1461 consecutive HCV GT1-infected patients who received a

12-week treatment with LDV (90 mg/day) and SOF (400 mg/day) (Havoni; Gilead Sciences, Tokyo, Japan) without RBV between September 2015 and November 2016 at any of 19 participating institutes throughout Japan. Of the 1461 patients included in the study, 378 underwent determination of single nucleotide polymorphism data of the IL-28B gene (rs8099917). At baseline, serum AFP levels were measured in 1412 patients, AFP-L3 levels in 264 patients, and M2BPGi levels in 509 patients. The presence of NS5A RASs was tested in 1216 patients, and the cause of treatment failure was analyzed in patients who completed the treatment and had NS5A-RAS data. At the end of treatment response (EOT), AFP levels, AFP-L3 levels, and M2BPGi levels were re-measured in 1269, 168, and 488 patients, respectively.

Cirrhosis was defined in patients with signs of cirrhosis on pretreatment liver biopsy or transient elastography (Fibroscan cut-off value, 12 kPa) [25], or with FIB-4 index > 3.25 [26] and signs of cirrhosis on ultrasound examination. Patients with decompensated cirrhosis of Child–Pugh grade B or C, those with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at baseline, and those who had a history of therapy with DCV plus ASV were excluded. This retrospective study was approved by the Ethics Committee of each participating hospital associated with the Japanese Red Cross, and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Laboratory tests

HCV RNA levels were measured using the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The detection limit for the assay was 1.2 log IU/mL. SVR was defined as undetectable HCV RNA at 12 weeks post-treatment. HCV genotype was determined by sequence determination in the 5′ non-structural region of the HCV genome, which was followed by phylogenetic analysis. Genetic polymorphism, defined as a single nucleotide polymorphism located near the IL-28B gene (rs8099917), was determined using the TaqMan PCR assay. Briefly, DNA was isolated from the peripheral blood using the standard phenol–chloroform method. Genotyping was performed using a predesigned TaqMan probe (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's protocol.

Detection of drug-resistant substitutions

The amino acid sequences of NS5A-L31 and NS5A-Y93 were determined via population sequencing using either the Invader assay (BML Laboratory, Tokyo, Japan) or direct sequencing (SRL Laboratory, Tokyo, Japan; or LSI Laboratory, Tokyo, Japan), as previously described [26–29]. Patients were considered to have RASs if minor sequences of RASs were detected in more than 10% of the strength of the major sequence (when tested using direct sequencing), or if more than 10% of the fluorescence signal corresponded to RAS variants (when tested using the Invader assay).

Safety

Safety was assessed in terms of the incidence and intensity of adverse events, which were graded according to CTCAE v4.0-JCOG (National Cancer Institute, Bethesda, MD, USA).

Statistical analysis

Continuous variables are expressed as median (range), while qualitative data are expressed as number (frequency). The Chi squared test and Wilcoxon signed-rank test were applied to detect significant associations. Univariate and multivariate analyses were used to examine the association between treatment outcome and potential risk factors, with $p < 0.05$ as the criterion for inclusion in the multivariate model. The results of the risk analysis were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). All statistical tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using JMP® version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

The baseline characteristics of the 1461 patients included in the study are summarized in Table 1. The median age was 69 years, and 431 (29.5%) participants were ≥ 75 years old. Approximately 70% ($n = 1030$) of patients were treatment-naïve and 30% ($n = 431$) had a history of IFN therapy (telaprevir plus PEG-IFN and RBV, $n = 29$; simeprevir plus PEG-IFN and RBV, $n = 10$). Cirrhosis was noted in 23.8% ($n = 347$) of patients, and 10.9% ($n = 159$) had a history of HCC. Single nucleotide polymorphism data of the IL-28B gene (rs8099917) was available in 378 patients, and 46.3% ($n = 175$) had unfavorable single nucleotide polymorphisms (TG/GG). The NS5A RAS data of 1216 patients (83.2%) were available for analysis, and 30.8% ($n = 375$) of patients were found to have NS5A-Y93 RASs, while 8.1% ($n = 99$) were found to have NS5A-L31 RASs.

Table 1 Patient characteristics

Characteristics	Total (n = 1461)
Age, years	69 (22–91)
Age ≥ 75 years	431 (29.5%)
Sex, male/female	564/897
IL-28B SNP rs8099917, TT/non-TT/ND	203/175/1083
History of IFN therapy, no/yes	1030/431
History of telaprevir plus peg-IFN and RBV therapy, no/yes	1432/29
History of simeprevir plus peg-IFN and RBV therapy, no/yes	1359/102
Platelet count, × 10^4 cells/μL	15.1 (2.1–122)
AST, IU/L	40 (13–548)
ALT, IU/L	36 (4–1033)
AFP*, ng/mL	5 (0–688.9)
AFP-L3**, %	0 (0–50.9)
M2BPGi†, COI	2.12 (0.24–20.0)
eGFR, mL/min/1.73 m^2	73.0 (31.6–244.4)
Cirrhosis, no/yes	1114/347
History of HCC, no/yes	1302/159
HCV RNA, log IU/mL	6.2 (1.3–8.0)
Geographic area within Japan, East/West	526/935
NS5A-Y93, wild-type/RASs/ND	841/375/245
NS5A-L31, wild-type/RASs/ND	1117/99/245
East: NS5A-Y93, wild-type/RASs/ND	322/137/67
NS5A-L31, wild-type/RASs/ND	432/27/67
West: NS5A-Y93, wild-type/RASs/ND	519/238/178
NS5A-L31, wild-type/RASs/ND	685/72/178

Categorical data are represented as the number of patients, while continuous data are represented as median (range)

AFP α-fetoprotein, *ALT*, alanine aminotransferase, *AST* aspartate aminotransferase, *COI* cut-off index, *eGFR* estimated glomerular filtration rate, *HCC* hepatocellular carcinoma, *IFN* interferon, *M2BPGi* Mac-2 binding protein glycosylation isomer, *RAS* resistance-associated substitution, *RBV* ribavirin, *ND* not determined

The number of patients with available data were *AFP: n = 1412, **AFP-L3: n = 264, †M2BPGi: n = 509

Regarding the NS5A RAS rate by geographic area, the prevalence of NS5A-Y93 RASs did not differ between East and West Japan (29.9%, 137/459 versus 31.4%, 238/757), but the prevalence of NS5A-L31 RASs was higher in West Japan than in East Japan (9.5%, 72/757 versus 5.9%, 27/459; p = 0.03).

Host and viral factors associated with SVR

Of the 1461 patients included in this study, 1452 patients (99.4%) achieved the EOT. The overall SVR12 rate was 98.4% (1438/1461), while the rate of treatment completion was 99.0% (1438/1452). All 1438 patients who achieved SVR12 achieved SVR24 as well.

Figure 1 provides an overview of SVR12 rates in subgroups of patients with various host and viral factors potentially associated with SVR. No significant association with SVR was noted for sex, age, polymorphisms of the IL-28B gene, geographic area, or history of HCV therapy with IFN or with telaprevir or simeprevir. Significant univariate predictors of treatment failure included cirrhosis ($p < 0.0001$) and history of HCC ($p < 0.005$). Multivariate logistic regression analysis identified cirrhosis (OR 4.26; 95% CI 1.72–10.86; p = 0.002) as an independent predictor of treatment failure. A total of nine patients discontinued treatment: seven of the 1216 patients with NS5A-RAS data, and two of the 245 patients without NS5A-RAS data.

In the sub-cohort of 1209 patients who completed the treatment and had NS5A RAS data, the prevalence of cirrhosis and NS5A-Y93 RASs was significantly higher among patients who did not achieve SVR. Multivariate logistic regression analysis identified cirrhosis (OR 4.19; 95% CI 1.34–14.37; p = 0.014) and NS5A-Y93 RASs (OR 7.78; 95% CI 2.38–34.82; p = 0.0004) as independent predictors of treatment failure (Table 2).

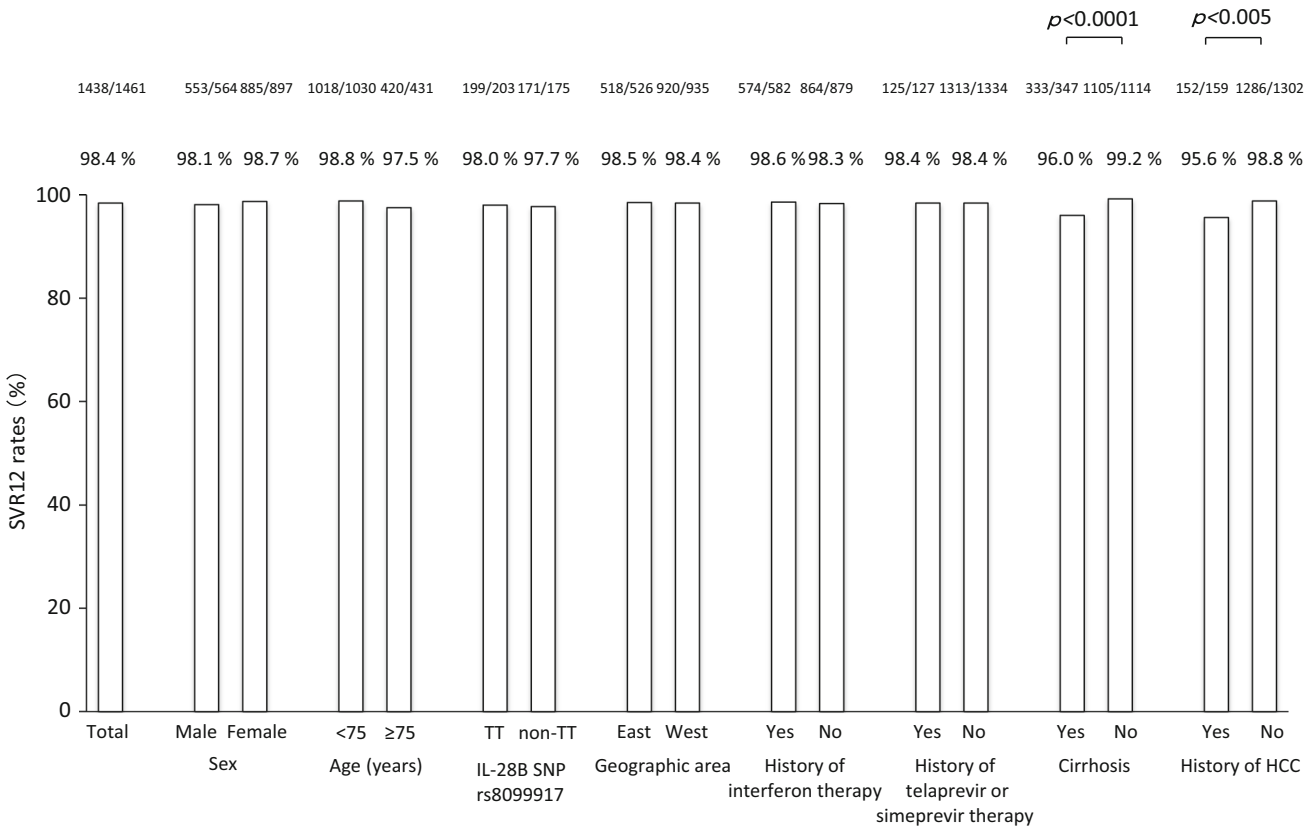

Fig. 1 SVR12 rates per category. *HCC* hepatocellular carcinoma, *IL-28B* interleukin-28B, *SNP* single nucleotide polymorphism, *SVR12* rate of sustained virological response at 12 weeks post-treatment

Impact of NS5A-Y93 RASs and cirrhosis on SVR

The 1216 patients with NS5A RAS data were divided into four groups according to the prevalence of NS5A-Y93 RASs and cirrhosis (Fig. 2). The SVR12 rate of patients without cirrhosis and without NS5A-Y93 RASs was 100%, which was significantly higher than the SVR12 rates of the other three groups (98.5% among patients with NS5A-Y93 RASs but without cirrhosis, $p < 0.005$; 97.6% among patients with cirrhosis but without NS5A-Y93 RASs, $p < 0.0005$; and 93.0% among patients with cirrhosis and NS5A-Y93 RASs, $p < 0.0001$).

Serum predictors of HCC at baseline and after LDV/SOF therapy

Data regarding serum AFP levels at both baseline and EOT were available for 1216 of 1438 patients who achieved SVR12. The mean AFP levels decreased from 13.4 ± 37.6 ng/mL at baseline to 6.0 ± 19.6 ng/mL at EOT in patients who achieved SVR ($p < 0.0001$) (Fig. 3a). Data regarding serum AFP-L3 levels both at baseline and EOT were available in 168 of 1438 patients who achieved SVR12. The mean AFP-L3 levels decreased from 2.2 ± 4.9% at baseline to 1.5 ± 6.36% at EOT in patients who achieved SVR ($p < 0.005$) (Fig. 3b). Serial data regarding serum M2BPGi levels at baseline and EOT were available in 488 patients. Serum M2BPGi levels decreased significantly from baseline to EOT in patients who achieved SVR (baseline, 3.6 ± 3.7 cut-off index; EOT, 2.0 ± 3.5 cut-off index, $p < 0.0001$) (Fig. 4).

Safety

The safety profile of LDV/SOF therapy is shown in Table 3. Adverse events were rare and included headache (0.6%), tiredness (0.5%), and diarrhea (0.3%). The frequency of adverse events did not differ between patients aged < 75 years and those aged ≥ 75 years. Treatment was discontinued in nine patients (0.6%) due to: arrhythmia or palpitation (two patients), not feeling well (two patients), heart failure (one patient), ascites (one patient), cerebral infarction (one patient), and lack of compliance (two patients). Only three patients had grade III adverse events (0.2%; 3/1461): one patient had cerebral infarction, one had heart failure, and one had ascites accumulation. Even among the 259 patients with low eGFR (30–59 mL/min/1.73 m^2) at baseline, no change in eGFR was observed

Table 2 Host and viral factors associated with treatment failure in patients with resistance-associated substitutions in NS5A

Risk factor	SVR12 (n = 1195)	Non-SVR (n = 14)	Univariate analysis p	Multivariate analysis OR (95% CI)	p
Age, < 75/≥ 75 years	850/345	8/6	0.25		
Sex, male/female	452/743	8/6	0.14		
History of interferon therapy, no/yes	685/510	6/8	0.28		
History of telaprevir therapy, no/yes	1168/27	14/0	0.57		
History of simeprevir therapy, no/yes	1106/89	12/2	0.34		
Aspartate aminotransferase, < 50/ ≥ 50 IU/L	795/400	6/8	0.063		
Alanine aminotransferase, < 50/ ≥ 50 IU/L	847/348	9/5	0.59		
Estimated glomerular filtration rate					
30–60/≥ 60 mL/min/1.73 m^2	209/986	4/10	0.28		
Cirrhosis, no/yes	911/284	5/9	0.0004	4.19 (1.34–14.37)	0.014
History of HCC, no/yes	1069/126	10/4	0.030		
Viral load, < 6/≥ 6 log IU/mL	400/795	6/8	0.46		
NS5A-Y93, wild-type/RASs	832/363	3/11	0.0001	7.78 (2.38–34.82)	0.0004
NS5A-L31, wild-type/RASs	1100/95	11/3	0.067		
Geographic area, East/West	451/744	7/7	0.56		

AFP α-fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *COI* cut-off index, *HCC* hepatocellular carcinoma, *95% CI* 95% confidence interval, *OR* odds ratio, *SVR12* rate of sustained virological response at 12 weeks post-treatment, *non-SVR* without sustained virological response, *ND* not determined

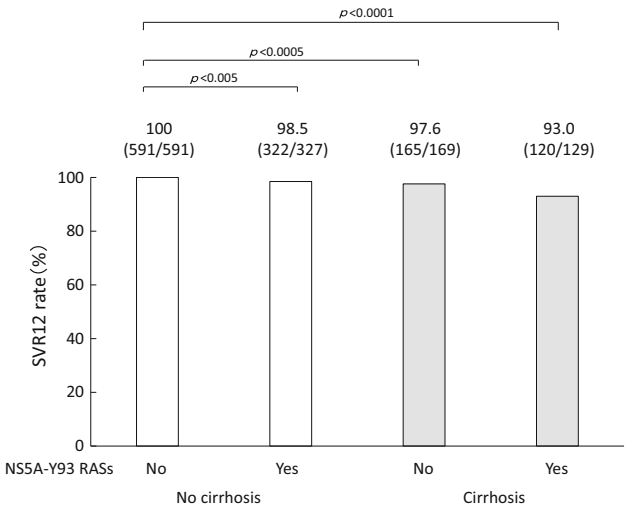

Fig. 2 SVR12 rates according to NS5A-Y93 RAS and cirrhosis status. *RAS* resistance-associated substitution, *SVR12* rate of sustained virological response at 12 weeks post-treatment

(baseline, 52.6 ± 6.0 mL/min/1.73 m^2; EOT, 53.1 ± 9.1 mL/min/1.73 m^2), and none of the patients discontinued the therapy because of progressive eGFR reduction.

Discussion

This was a nationwide multicenter study conducted by the Japanese Red Cross Liver Study Group, which included core hospitals in large cities as well as small-volume hospitals in various provinces across Japan. Therefore, data from this nationwide cohort reflect the current real-world situation in Japan. Although 30% of the patients were ≥ 75 years old, the SVR rate was not attenuated by age, and LDV/SOF therapy was highly effective in the elderly patients enrolled in this Japanese real-world cohort (overall SVR rate, 99%). Moreover, the frequency of adverse events was small and not associated with age. Another important point was that the SVR rates were similarly high across various regions of Japan, showing that this treatment is effective irrespective of geographic area or scale of hospitals. Our results confirm the high SVR rates reported in regional cohorts from the northern Kyushu area [15] and Chiba prefecture [16] in Japan. These real-world efficacy and safety data of LDV/SOF therapy are expected to be representative for Asian populations with HCV GT1 infection.

In this large cohort, the presence of cirrhosis and NS5A-Y93 RASs at baseline was found to be associated with treatment failure. The SVR12 rate of patients without cirrhosis and without NS5A-Y93 RASs at baseline was 100%,

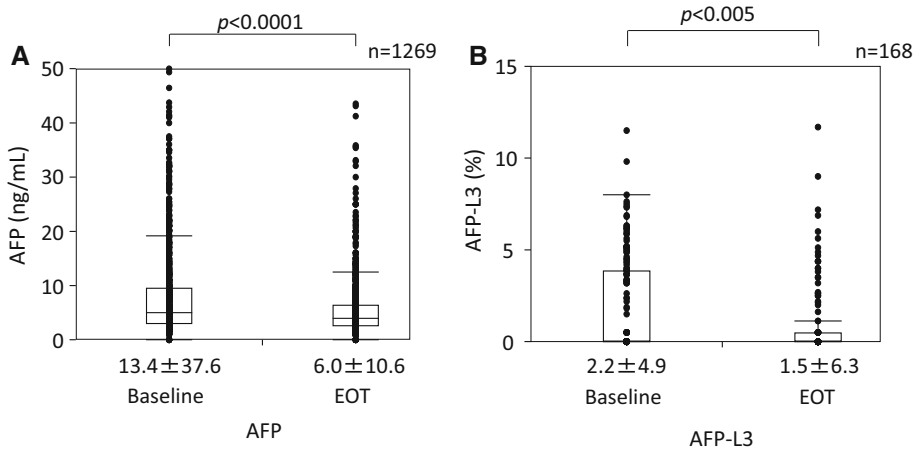

Fig. 3 Serum AFP and AFP-L3 levels at baseline and at the end of treatment (EOT) in patients with sustained virological response. Data are presented as mean ± standard deviation. *AFP* α-fetoprotein. Data regarding serum AFP and AFP-L3 levels at both baseline and EOT were available in 1216 and 168 patients, respectively, of the 1438 patients who achieved SVR12

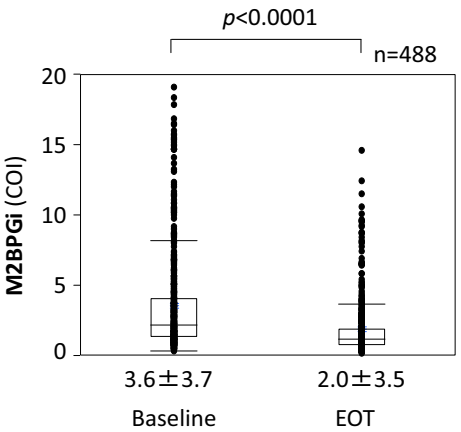

Fig. 4 M2BPGi levels at baseline and at the end of treatment response (EOT) in patients with sustained virological response. Data are presented as mean ± standard deviation. *COI* cut-off index, *M2BPGi* Mac-2 binding protein glycosylation isomer. Data regarding M2BPGi levels at both baseline and EOT were available in 488 of 1438 patients who achieved SVR12

which is similar to the rate reported in the northern Kyushu area [15] and significantly higher than the rates noted among patients without cirrhosis but with NS5A-Y93 RASs (98%), with cirrhosis but without NS5A-Y93 RASs (98%), or with cirrhosis and NS5A-Y93 RASs (95%). However, it should be noted that, although the presence of cirrhosis and NS5A-Y93 RASs at baseline was associated with lower SVR rate, the rate was still as high as 95% even in these difficult-to-treat patients.

In the present study, the target population was patients not previously treated using IFN-free DAA regimens, and therefore our cohort did not include patients who had received prior DCV plus ASV therapy without achieving SVR. These patients may have higher prevalence of RASs in the HCV NS3/4A and NS5A regions [10, 30], and the efficacy of retreatment with LDV/SOF may be attenuated. In fact, Akuta et al. found that the SVR rate of SOF/LDV therapy was only 70% for patients who had previously failed DCV/ASV therapy [31]. A larger scale nationwide study is currently underway to elucidate the prevalence of RASs after DCV plus ASV, as well as the efficacy of re-treatment using LDV/SOF in these patients.

While it is expected that patients with SVR will have lower risk of HCC development, it is obvious that the risk of HCC is not entirely eliminated by SVR. Serum AFP and AFP-L3 have been established as non-invasive predictive markers of the development of HCC in patients with HCV [23, 24]. Several studies reported that post-treatment serum AFP levels are associated with HCC development in patients who achieved SVR with IFN-based therapy [6, 17, 18] or IFN-free DAA therapy [20]. In the present study, AFP and AFP-L3 levels decreased significantly from baseline to EOT in patients who achieved SVR12 at EOT. Our study is the first to evaluate the changes in AFP-L3 levels following DAA therapy. Serum M2BPGi, a non-invasive marker to assess liver fibrosis [22], was reported to be predictive of HCC development after SVR [21, 32]. As the current study was specifically focused on SVR12, we did not analyze long-term prognosis including HCC occurrence. However, M2BPGi levels decreased significantly from baseline to EOT in patients who achieved SVR at EOT. This may suggest that viral eradication by LDV/SOF therapy has the potential to reduce HCC risk.

Adverse events were rare in our cohort, and the frequency of adverse events showed no association with age. Importantly, no change in eGFR was observed, and none of the patients discontinued therapy because of progressive eGFR reduction.

The findings in this real-world cohort suggest that LDV/SOF therapy is highly effective in elderly Japanese patients, with an overall SVR rate of 98.4%. The presence of cirrhosis and NS5A RASs at baseline was associated with a lower SVR rate, but the rate was still as high as 95% in these difficult-to-treat patients. Importantly, no serious adverse events were noted. The serum levels of markers for

Table 3 Comparison of adverse events in younger and older patients

Adverse events	Overall (n = 1461) (%)	75 years (n = 1030) (%)	≥ 75 years (n = 431)	p
Overall	43 (2.9)	30 (2.9)	13 (3.0)	0.92
Headache	9 (0.6)	7 (0.7)	2 (0.5)	
Tiredness	7 (0.5)	6 (0.6)	1 (0.2)	
Diarrhea	4 (0.3)	4 (0.4)	0 (0.0)	
Discomfort in the throat	3 (0.2)	3 (0.3)	0 (0.0)	
Arrhythmia or palpitation	2 (0.1)	0 (0.0)	2 (0.5)	
Stomatitis	2 (0.1)	1 (0.1)	1 (0.2)	
Not feeling well	2 (0.1)	1 (0.1)	1 (0.2)	
Itching	2 (0.1)	1 (0.1)	1 (0.2)	
Elevated aminotransferase levels	1 (0.1)	0 (0.0)	1 (0.2)	
Heart failure	1 (0.1)	0 (0.0)	1 (0.2)	
Ascites	1 (0.1)	0 (0.0)	1 (0.2)	
Cerebral infarction	1 (0.1)	1 (0.1)	0 (0.0)	
Heartburn	1 (0.1)	1 (0.1)	0 (0.0)	
Burning sensation	1 (0.1)	1 (0.1)	0 (0.0)	
Gastrointestinal bleeding	1 (0.1)	1 (0.1)	0 (0.0)	
Arthralgia	1 (0.1)	1 (0.1)	0 (0.0)	
Renal dysfunction	1 (0.1)	1 (0.1)	0 (0.0)	
Rash	1 (0.1)	1 (0.1)	0 (0.0)	
Urinary tract infection	1 (0.1)	0 (0.0)	1 (0.2)	
Constipation	1 (0.1)	0 (0.0)	1 (0.2)	

the prediction of HCC development, such as AFP, AFP-L3, and M2BPGi, improved after SVR.

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