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ORIGINAL ARTICLE

The effectiveness and safety of glecaprevir/pibrentasvir in chronic hepatitis C patients with refractory factors in the real world: a comprehensive analysis of a prospective multicenter study

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Abstract

Background Direct-acting anti-virals (DAAs) have markedly improved the effectiveness of anti-viral therapy for chronic hepatitis C (CHC) patients. In a phase III trial in Japan, treatment with the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir (G/P) resulted in a small number of patients with refractory factors. We aimed to evaluate the effectiveness and safety of G/P, especially among patients with these refractory factors, and the influence of these factors on treatment.

Methods In a prospective, multicenter study involving 33 medical institutions, 1439 patients were treated with G/P, and their efficacy, safety, and most frequent adverse effects (AEs) were analyzed.

Results Overall SVR12 rates were 99.1% (1397/1410) in the per-protocol-analysis, and genotype sustained virologic response SVR12 rates were: genotype 1, 99.4% (707/711); genotype 2, 99.4% (670/674); genotype 3, 80.0% (16/20). DAA-naïve patients ($p=0.008$) with HCV genotype except 3 (genotype 1 vs. 3, $p=2.68\times10^{-5}$; genotype 2 vs. 3, $p=3.28\times10^{-5}$) had significantly higher SVR12 rates. No significant difference was observed between CKD stage 1–3 (99.1% [1209/1220]) and chronic kidney disease (CKD) stage 4–5 (98.9% [188/190]) patients, or between cirrhotic (99.0% [398/402]) and non-cirrhotic (99.1% [999/1008]) patients. Multiple logistic regression analysis revealed that genotype 3 [OR 33.404, 95% CI (7.512–148.550), p value ($p=4.06\times10^{-5}$)] and past experience of IFN-free DAAs [OR 3.977, 95% CI (1.153–13.725), p value ($p=0.029$)] were both significantly independent predictors of non-SVR12. AEs were reported in 28.2% of patients, and 1.6% discontinued treatment owing to drug-related AEs. AEs were significantly higher in CKD stage 4–5 (41.6% [79/190]) than CKD stage 1–3 (26.1% [319/1220]) patients ($p=2.00\times10^{-5}$). AEs were also significantly higher in cirrhotic (38.6% [155/402]) than in non-cirrhotic (24.1% [243/1008]) ($p=2.91\times10^{-18}$) patients.

Conclusions G/P regimen is highly effective and safe to treat CHC patients even with refractory factors such as CKD and advanced liver fibrosis. However, patients with past experience of IFN-free DAA treatment and genotype 3, CKD stage 4 or 5, and advanced liver fibrosis should be more closely observed.

Keywords Glecaprevir · Pibrentasvir · Chronic hepatitis C · Refractory factors · Multicenter study

Introduction

Currently, interferon (IFN)-free, direct-acting anti-viral (DAA) treatment is the standard of care for chronic hepatitis C, and it achieves a high sustained virologic response 12 (SVR12) rate. Glecaprevir/pibrentasvir (G/P) is a

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pangenotypic regimen recently approved for treating chronic hepatitis C virus (HCV) infection. Glecaprevir is a nonstructural (NS) protein 3/4 A protease inhibitor, which is combined with pibrentasvir, NS5A inhibitor. In phase II and III registration trials, this combination administered for 8–12 weeks resulted in the SVR12 rate of > 95%, without safety issues [1–6]. Clinical trials conducted in Japan also showed similar results [7, 8]. However, in clinical trials, restricted inclusion and exclusion criteria for the target patients might influence treatment outcomes. In fact, patients receiving treatment in the real world differ from those enrolled in clinical trials by age, stages of fibrosis, and prevalence of co-morbidities and co-medications, and all these conditions potentially affect the SVR12 rate. In this prospective study, we evaluated the efficacy and safety of glecaprevir/pibrentasvir in a large cohort of Japanese patients with chronic hepatitis C with refractory factors such as compensated cirrhosis, DAA experience, renal impairment, and HCV genotype 3 infection.

Patients and methods

In a prospective, 33-multicenter study in Japan (UMIN registration no. 000032073), patients with HCV genotype 1, 2, or 3 infections treated with glecaprevir/pibrentasvir between November 2017 and June 2018 were recruited. Patients with previous three reports of sub-group analyses were included in this comprehensive analysis [9–11]. Inclusion criteria were: (a) HCV genotype 1, 2, or 3 infection; (b) serum HCV RNA level of > 1.2 log IU/mL; and (c) aged ≥ 18 years. (d) Exclusion criteria were: (a) decompensated liver cirrhosis (Child–Pugh class B or C); (b) active malignant tumors [except curative HCC (ablation or resection) at least 1 dynamic CT/MRI assessment not later than 6 months before starting G/P regimen]. (c) Administration of contraindicated drugs for glecaprevir/pibrentasvir, namely atazanavir sulfate, atorvastatin calcium hydrate, and rifampicin; (d) co-infection of human immunodeficiency virus and hepatitis B virus; (e) pregnant or lactating status; and (f) pre-existence of NS5A P32 deletion, which is reportedly associated with a strong resistance to glecaprevir/pibrentasvir [12, 13].

Treatment protocol and laboratory tests

Patients received three tablets of MAVIRET® once daily (300 mg glecaprevir and 120 mg pibrentasvir; AbbVie, Tokyo, Japan) for 8 or 12 weeks. The treatment duration was determined principally based on the indication criteria approved by the Japanese government. For patients with liver cirrhosis, HCV genotype 3 infection, or treatment failure with prior IFN-free, DAA treatment, the treatment duration was 12 weeks. For the remaining patients (those who were DAA-naïve and had HCV genotype 1 or 2 infection, without cirrhosis), the treatment duration was 8 weeks. Cirrhosis was diagnosed based on fibrotic markers, such as platelet count and FIB-4 index, and imaging tests, such as ultrasonography and computed tomography. Physical, hematological, and biochemical examinations were performed at treatment initiation, every 2 weeks during the treatment period, and each post-treatment visit (4, 8, and 12 weeks post-treatment) during the 12-week follow-up period. As for hemodialysis treatment, patients underwent 3–4-h hemodialysis sessions three times per week. They all took oral glecaprevir and pibrentasvir 5 h before the start of hemodialysis. The drugs were considered taken in all cases without any interruption or withdrawal reports. Adverse events (AEs), including laboratory abnormalities, were graded according to the Common Terminology Criteria for Adverse Events version 4.0, as presented by the National Cancer Institute Cancer Therapy Evaluation Program. Serum HCV RNA level was measured using a real-time polymerase chain reaction (PCR)-based method (COBAS TaqMan HCV Test 2.0; Roche Molecular Systems, Pleasanton, CA, USA). The lower limit of quantification was 1.2 log IU/mL. HCV genotype was assessed using the HCV GENOTYPE Primer Kit (Institute of Immunology Co., Ltd, Tokyo, Japan) and phylogenetic analysis of core gene sequences [14]. Furthermore, the presence of known resistance-associated substitutions (RASs) in NS5A including P32 variants and NS3 was detected using a direct sequencing method [15], except in patients with genotype 3b HCV, in whom sequencing was performed based on the GT-3 specific primer as described [16]. The FIB-4 index, a surrogate marker of liver fibrosis, was calculated using the following formula [17]:

$$\text{AST (IU/L)} \times \text{age (years)} / \text{platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (IU/L)}}$$

Definition and classification of chronic kidney disease and severe renal impairment

Chronic kidney disease (CKD) was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for CKD as follows: stage 1, estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2; stage 2, 90 mL/min/1.73 m^2 > eGFR ≥ 60 mL/min/1.73 m^2; stage 3a, 60 mL/min/1.73 m^2 > eGFR ≥ 45 mL/min/1.73 m^2; stage 3b, 45 mL/min/1.73 m^2 > eGFR ≥ 30 mL/min/1.73 m^2; stage 4, 30 mL/min/1.73 m^2 > eGFR ≥ 15 mL/min/1.73 m^2; and stage 5, eGFR < 15 mL/min/1.73 m^2 [18]. Severe renal impairment was defined as eGFR < 30 mL/min/1.73 m^2 (i.e., CKD stages 4 and 5) on at least two occasions at an interval of 90 days. Patients with hemodialysis were defined as stage 5d. eGFR was calculated using the

formula for Japanese population developed by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × creatinine (mg/dL)$^{-1.094}$ × age (years)$^{-0.287}$ (× 0.739 if female) [19].

Definition of treatment responses

SVR12 was defined as negative for serum HCV RNA at 12 weeks after the end of treatment. Patients with negative HCV RNA at the end of treatment were considered to achieve end-of-treatment response. Patients with end-of-treatment response in whom viral RNA reappeared after treatment completion were considered to have a relapse.

Statistical analyses

Continuous variables are presented as median and range. Categorical variables are presented as number and percentage. Friedman test was used to evaluate the time-course changes in the eGFR level. To compare two groups with respect to treatment responses and AEs, Fisher's exact test was used. Univariate and multiple logistic regression analyses were performed to determine the factors significantly influencing the emergence of pruritus. Results with a p value < 0.05 were regarded as statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 23.0 (IBM Japan, Tokyo, Japan).

Results

Patient characteristics

Totally, 1439 patients with chronic hepatitis C were included in the study. The baseline patient characteristics are shown in Table 1. The patients comprised 746 males and 693 females. The median age was 67 years (range 18–96 years). Based on the results of diagnostic imaging and fibrotic marker analyses, 408 (28.4%) patients were considered to have liver cirrhosis. The number of patients with genotype 1/2/3/mixed was 718/696/20/5, respectively. A total of 247 patients had CKD stage 1, 731 had stage 2, 264 had stage 3, 46 had stage

Table 1 Background characteristics of the patients

Variable	$N = 1439$
Gender (male/female)	746/693
Age (years)	67 (18–96)
WBC (/mm^3)	4900 (1300–14,100)
Hemoglobin (g/dL)	13.4 (7.8–19.2)
Platelets (× 10^4/mm^3)	17.1 (1.4–49.6)
AST (U/L)	34 (4–429)
ALT (U/L)	31 (6–598)
Serum albumin (g/dL)	4.1 (1.6–5.3)
Serum creatinine (mg/dL)	0.8 (0.3–14.5)
eGFR (mL/min/1.73 m^2)	70.8 (2.0–176.1)
CKD stage 1 (eGFR levels ≥ 90 mL/min/1.73 m^2)	247
CKD stage 2 (90 mL/min/1.73 m^2 > eGFR levels ≥ 60 mL/min/1.73 m^2)	731
CKD stage 3a (60 mL/min/1.73 m^2 > eGFR levels ≥ 45 mL/min/1.73 m^2)	194
CKD stage 3b (45 mL/min/1.73 m^2 > eGFR levels ≥ 30 mL/min/1.73 m^2)	70
CKD stage 4 (30 mL/min/1.73 m^2 > eGFR levels ≥ 15 mL/min/1.73 m^2)	46
CKD stage 5 (eGFR levels < 15 mL/min/1.73 m^2)	151
CKD stage 5d (CKD on hemodialysis)	132
Non-cirrhosis/cirrhosis	1031/408
FIB-4 index (< 3.25/≥ 3.25)	928/511
AFP (ng/mL)	4.0 (0.8–2151.7)
HCV RNA (log IU/mL)	6.2 (1.2–7.9)
Genotype (1/2/3/mixed)	718/696/20/5
Past experience of IFN-free DAAs (absence/presence)	1220/219
Past experience of HCC treatment (absence/presence/unknown)	1282/145/12
Treatment duration (8 weeks/12 weeks)	859/580

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *AFP* α-fetoprotein, *HCV* hepatitis C virus, *IFN* interferon, *DAA* direct acting anti-viral, *HCC* hepatocellular carcinoma

4, and 151 had stage 5. 132 (9.2%) patients were undergoing hemodialysis or hemodiafiltration (CKD stage 5d). A total of 219 (15.2%) patients had previously received IFN-free, DAA treatment, 859 (59.7%) received the 8-week regimen, 580 (40.3%) received the 12-week regimen, and 29 were lost to follow-up.

Virologic responses

The overall SVR12 rate was 97.1% (1397/1439) in the intention-to-treat population and 99.1% (1397/1410) in the per-protocol-analysis (Fig. 1). We assessed the effect of refractory factors such as compensated cirrhosis, DAA experience, HCV genotype, and renal impairment. Patients that were DAA-naïve ($p=0.008$) and had HCV genotypes 1 or 2 (genotype 1 vs. 3, $p=2.68\times10^{-5}$; genotype 2 vs. 3, $p=3.28\times10^{-5}$) had significantly higher SVR12 rates. In contrast, the presence or absence of cirrhosis ($p=0.768$) and CKD stages (CKD stages 1–3 vs. 4–5, $p=0.691$; CKD 4–5 vs. 5d, $p=1.000$; CKD stage 1–3 vs. 5d, $p=0.351$) did not show significant differences in the SVR12 rate (Fig. 2). Patients with genotype 1 and DAA experience ($p=0.002$) or 12 W treatment duration ($p=0.044$) had significantly lower SVR12 rates. In contrast, the presence or absence of cirrhosis and history of HCC and treatment duration did not show significant differences (Fig. 3). Moreover, presence or absence of cirrhosis combined with DAA experience showed significantly lower SVR12 rates [cirrhosis(−) and DAA experience(−) vs. cirrhosis(−) and DAA experience(+), $p=0.160$; cirrhosis(−) and DAA experience(−) vs. cirrhosis(+) and DAA experience(+), $p=0.004$] (Fig. 4). In genotype 2, the presence or absence of cirrhosis and DAA experience, previous history of HCC, and treatment duration did not show significant differences in the SVR12 rate (Supplementary Fig. 1). Higher AST and ALT levels were significant factors contributing to SVR12 (Supplementary Table). In genotype 3, the presence or absence of cirrhosis and DAA experience and previous history of HCC did not show significant differences. Patients with HCV genotype 3b infection showed only 33.3% (2/6) SVR12 rate. In contrast, genotype 3a (14/14) showed 100% SVR12 rate (Fig. 5). Characteristics of patients with genotype 3 HCV infection are shown in Table 2. Case 18 was treated for 8 weeks as genotype 2 due to genotyping error.

Factors associated with non-SVR12

Overall, we had 13 non-SVR12 patients. The baseline characteristics are shown in Table 3. The details are those of 6 DAA-experienced patients and 7 naïve patients. Genotype 1 was 4 (1b), genotype 2 was 4 (2a, 2; 2b, 1; 2a/2b, 1), genotype 3 was 4 (3b, 3; 3a/3b, 1), and mixed genotype was 1 (1b/2a). Cases 5 and 9 were thought as co-infection, because 2a at case 5 and 2b at case 9 were only detected at relapse. Four patients had a past history of treatment for HCC. Also, four patients had cirrhosis. Furthermore, multiple logistic regression analysis revealed that HCV genotype 3 [OR 33.404, 95% CI (7.512–148.550), p value ($p=4.06\times10^{-5}$)] and past experience of IFN-free DAAs [OR 3.977, 95% CI (1.153–13.725), p value ($p=0.029$)] were both significant independent predictors of non-SVR12 (Table 4).

Analysis of resistance

We assessed polymorphisms in HCV from 11 of 13 non-SVR12 patients (Table 3). In case 4 and 13, preserved serum was not available. For three genotype 1 HCV-infected patients, baseline NS5A polymorphisms at

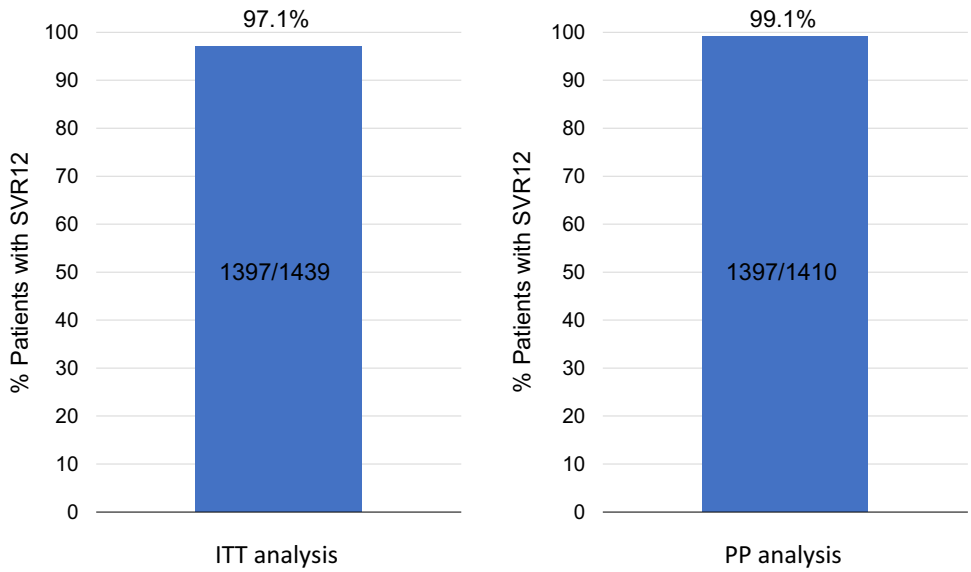

Fig. 1 Rates of virologic response with G/P treatment. SVR12 rates in the ITT or PP population. *ITT* intention to treat, *PP* per protocol, *SVR12* sustained virologic response at week 12

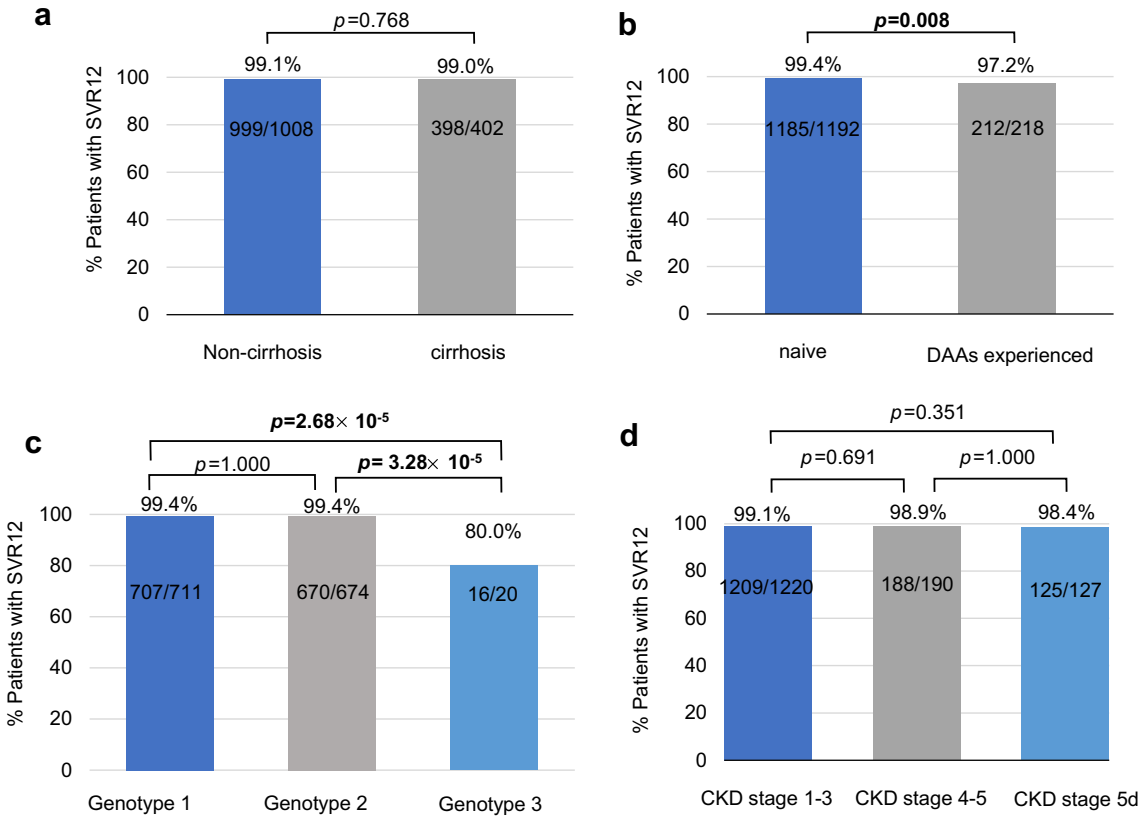

Fig. 2 Rates of SVR12 according to refractory factors in 1410 patients with HCV treated with any duration of G/P (PP analysis). **a** Non-cirrhosis vs cirrhosis. **b** Naïve patient vs DAAs experienced patients. **c** Genotype 1 vs genotype 2 vs genotype 3. **d** CKD stage 1–3 vs stage 4–5 vs stage 5d. *G/P* glecaprevir/pibrentasvir, *HCV* hepatitis C virus, *PP* per protocol, *SVR12* sustained virologic response at week 12

position L31 were present in 33% (1/3), NS5A Y93H in 67% (2/3), and NS5A A92 was not observed. Treatment-emergent substitution P32L in NS5A was detected in one of the three patients who had a relapse. For four genotype 2 (2a, 2; 2b, 1; 2a/2b, 1) HCV-infected patients, baseline NS5A polymorphisms at position L31M were present in 50% (1/2) in genotype 2a HCV-infected patients, and M31L in 100% (1/1) in one genotype 2b patients. In addition, M31L was present in 100% (1/1) in 2a/2b. We previously reported RASs of NS3 and NS5A found in three genotype 2 patients and one mixed genotype 1b/2a patient who received 8-week regimen. In this report, the substitution A156 of NS3 was not found. Treatment-emergent substitutions at position F28L and C92S in NS5A were detected in one genotype 2a HCV-infected patient, and P77S in NS5A in one 2a/2b HCV-infected patient who had a relapse. For mixed genotype 1b + 2a patients, only 2a HCV was detected at relapse, and M31L was present [10]. For three genotype 3b HCV-infected patients, both baseline A30K and L31M NS5A polymorphisms were present. Treatment-emergent substitutions in NS5A Y93H were detected in one of three patients who had a relapse.

Adverse events

Overall, AEs were observed during the treatment period in 28.2% (398/1439) of the patients: pruritus, 153 (10.9%); eruption, 43 (3.0%); fatigue, 42 (3.0%); headache, 29 (2.1%); total bilirubin elevation, 24 (1.7%); and nausea, edema, appetite loss, dizziness, AST, or ALT elevation, and serum creatinine elevation (Table 5). AEs leading to treatment discontinuation were found in 23 patients (1.6%). Of the 23 patients, 21 patients (91.3%) achieved SVR12. On the occurrence of an adverse event of grade 2 or higher, reduction or discontinuation of the drug was considered based on the judgment of the attending physician. In the sub-analysis, the presence or absence of cirrhosis and CKD stages (CKD stages 1–3 vs. 4–5) showed significant differences in the incidence of AEs (Fig. 6). Furthermore, the multiple logistic regression analysis revealed that CKD stage 4 or 5 and the presence of liver

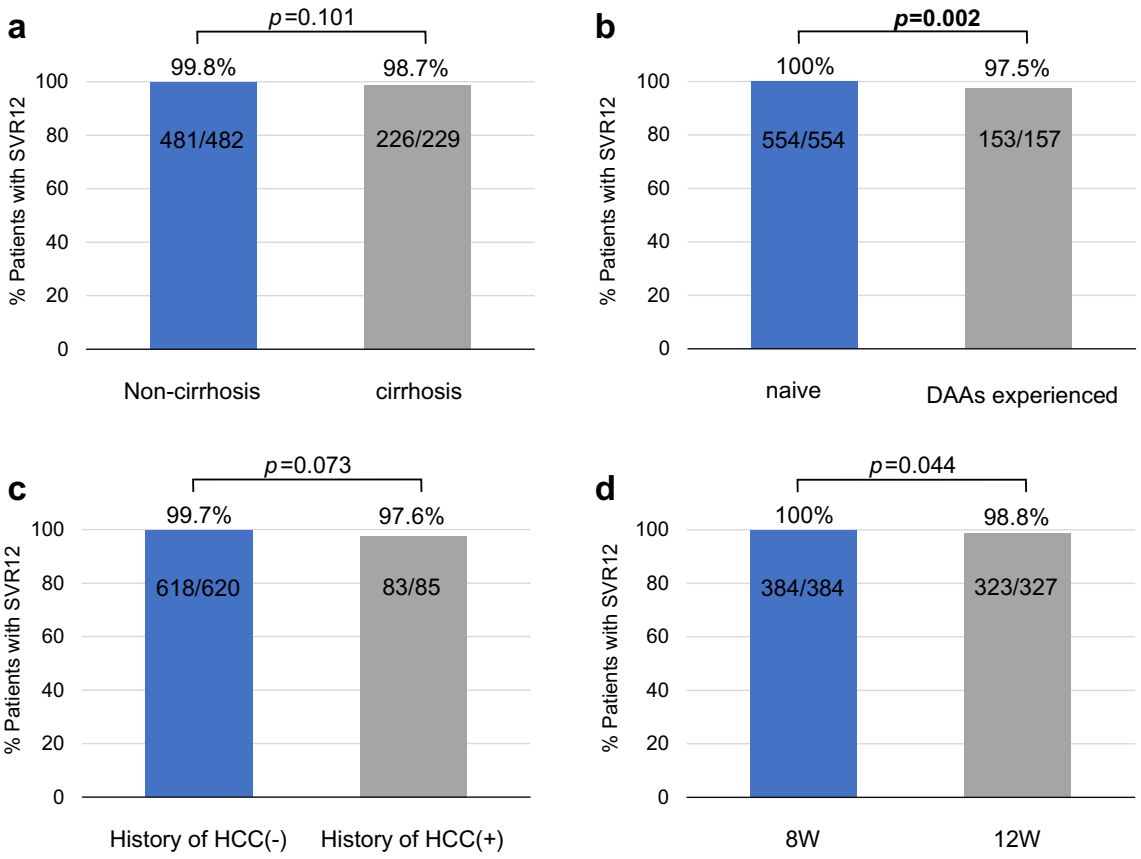

Fig. 3 Rates of SVR12 according to refractory factors in 711 patients with genotype 1 HCV treated with G/P (PP analysis). **a** Non-cirrhosis vs cirrhosis. **b** Naïve patient vs DAAs experienced patients. **c** The presence or absence of history of HCC. **d** G/P treatment duration. *G/P* glecaprevir/pibrentasvir, *HCV* hepatitis C virus, *PP* per protocol, *SVR12* sustained virologic response at week 12

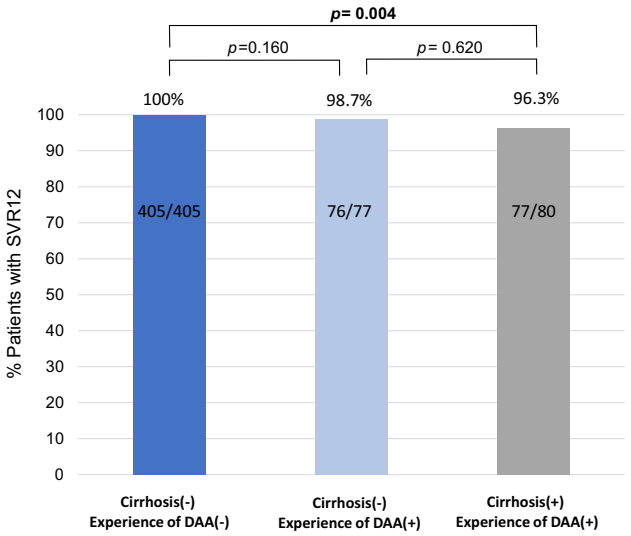

Fig. 4 Rates of SVR12 according to the presence or absence of cirrhosis and DAA experience in patients with genotype 1 HCV treated with G/P (PP analysis). *G/P* glecaprevir/pibrentasvir, *HCV* hepatitis C virus, *PP* per protocol, *SVR12* sustained virologic response at week 12

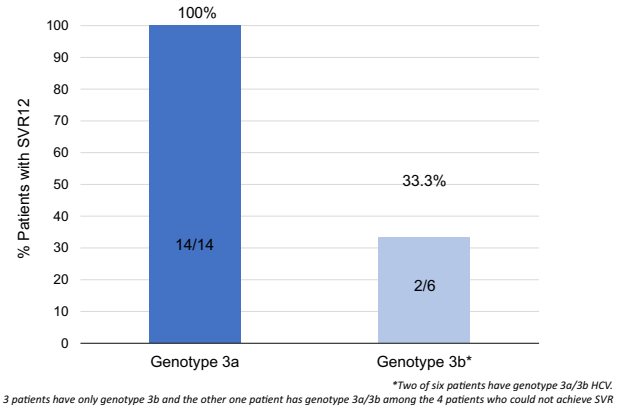

Fig. 5 SVR12 rates by subtype in the patients with genotype 3 HCV treated with G/P (PP analysis). *G/P* glecaprevir/pibrentasvir, *HCV* hepatitis C virus, *PP* per protocol, *SVR12* sustained virologic response at week 12

Table 2 Background characteristics: genotype 3

Case	Age	Gender	Genotype	Experience of DAAs	Cirrhosis	FIB4 index	Treatment duration	Past treatment for HCC	Treatment result
1	34	Male	3a	Naïve	No	0.64	12W	Absence	SVR12
2	33	Male	3a	Naïve	No	0.76	12W	Absence	SVR12
3	46	Female	3a	Naïve	No	1.19	12W	Absence	SVR12
4	32	Male	3a	Naïve	No	1.36	12W	Absence	SVR12
5	59	Female	3a	Naïve	No	2.22	12W	Absence	SVR12
6	69	Male	3a	SOF/RBV	No	2.48	12W	Absence	SVR12
7	49	Female	3a	Naïve	Yes	2.22	12W	Absence	SVR12
8	75	Male	3a	Naïve	Yes	6.07	12W	Presence	SVR12
9	85	Female	3a	SOF/RBV	Yes	5.89	12W	Presence	SVR12
10	43	Female	3a	Naïve	No	0.77	12W	Absence	SVR12
11	77	Female	3a	SOF/RBV	Yes	4.76	5W (discontined by edema)	Presence	SVR12
12	34	Male	3a	Naive	No	0.49	12W	Absence	SVR12
13	66	Female	3a	Naive	No	4.29	12W	Presence	SVR12
14	53	Male	3a	Naive	Yes	2.45	12W	Absence	SVR12
15	66	Male	3a/3b	SOF/RBV	No	2.30	12W	Presence	Non-SVR12
16	33	Female	3a/3b	Naïve	No	1.1	12W	Absence	SVR12
17	58	Female	3b	Naïve	Yes	2.86	12W	Absence	Non-SVR12
18	58	Male	3b	Naïve	No	Unknown	8W	Absence	Non-SVR12
19	65	Female	3b	DCV/ASV	No	3.86	12W	Absence	Non-SVR12
20	46	Female	3b	Naïve	No	1.23	12W	Presence	SVR12

SVR12 sustained virological response at 12 weeks after the end of treatment, *DAA* direct acting anti-viral, *SOF* sofosbuvir, *RBV* ribavirin, *DCV* daclatasvir, *ASV* asnaprevir

cirrhosis were both significant independent predictors of AEs (Table 6).

Discussion

In a large-scale real-world study, we demonstrated the efficacy and safety of 8- or 12-week G/P regimen in a cohort of Japanese patients with HCV. Earlier reports on G/P therapy primarily comprised clinical trials. Reports on real-world cohorts were limited to those from Europe [20] and a few Japanese reports [21, 22].

In this study, we analyzed 1439 patients on a G/P regimen, significantly exceeding 1000 cases, and found high anti-viral efficacy and a wide safety margin. In our cohort, the SVR12 rates were excellent (99.1%). Patients with HCV genotype 1 infection were found to have SVR12 rate of 99.1%, irrespective of subtype. Among patients infected with HCV genotype 2, four relapsed, resulting in SVR12 rate of 99.4%.

We focused on refractory factors, such as genotype 3, advanced fibrosis, prior treatment history of IFN-free DAAs regimens, prior history of hepatocellular carcinoma, or severe renal impairment in this comprehensive analysis. First, the SVR12 rates for genotype 3 genotype cohorts were 80.0% (16/20). Patients infected with HCV genotype 3b showed SVR12 rate of only 33.3% (2/6). In contrast, those with genotype 3a (14/14) showed the highest SVR12 rates (100%). Zeuzem et al. showed that GT-3-infected patients with A30K variant in NS5A at baseline had a lower rate of SVR12 in the ENDURANCE-3 trial. However, the majority of patients achieved SVR12 regardless of the presence of A30K [4]. In contrast, Wyles et al. showed that among patients with virologic failure in the SURVEYOR-II Part 3 study, treatment-emergent substitutions detected at the time of failure included Y56H, A156G, or Q168R in NS3 and A30K, L31F, or Y93H in NS5A [5]. Moreover, Smith et al. recently reported a resistance analysis of genotype 3 HCV and found two mutations (A30K and L31M) on nonstructural protein 5A in all genotype 3b and 3g subjects. In particular, L31M RAS was not observed in genotype 3a subjects. These mutations confer resistance to pibrentasvir in a replicon assay [23]. Hence, the observed resistance to G/P regimen in genotype 3 patients could be specific to genotypes 3b in this cohort. In fact, Tamori et al. recently reported that patients infected with HCV genotype 3b showed SVR12 rate of only 50.0% (2/4) in the 12-week regimen [24]. However, these patients are quite rare in the real world, and further analysis is needed. For the other regimen, daclatasvir plus sofosbuvir with or without ribavirin, the SVR12 rate was

Table 3 Background characteristics: non-SVR12

Case	Age	Gender	Genotype	Past experience of IFN-free DAAs	Cirrhosis	FIB4 index	Treatment duration	CKD stage	Past treatment for HCC	NS5A RAS
1	36	Female	1b	SOF/LDV	No	0.75	6 W (discontinuation due to pregnancy)	1	Absence	None
2	79	Male	1b	DCV/ASV → SOF/LDV	Yes	4.55	12 W	3b	Absence	L31M P32L Y93H
3	76	Female	1b	DCV/ASV → DCV/ASV/BCV	Yes	4.31	12 W	2	Presence	Y93H
4	75	Male	1b	SOF/LDV	Yes	12.31	12 W	2	Presence	N/A
5	57	Male	1b/2a	Naïve	No	1.74	8 W	2	Absence	L31M
6	69	Male	2a	Naïve	No	1.40	8 W	1	Presence	F28L L31M C92S
7	75	Female	2a	Naïve	No	2.44	1 W (discontinuation due to edema)	1	Absence	None
8	63	Male	2b	Naïve	No	0.95	8 W	5d	Absence	M31L
9	41	Male	2a/2b	Naïve	No	0.56	8 W	1	Absence	M31L P77S
10	65	Female	3b	DCV/ASV	No	3.86	12 W	2	Absence	A30K L31M Y93H
11	58	Male	3b	Naïve	No	3.24	8 W	5d	Absence	A30K L31M
12	58	Female	3b	Naïve	Yes	2.86	12 W	2	Absence	A30K L31M
13	66	Male	3a/3b	SOF/RBV	No	2.3	12 W	2	Presence	N/A

SRV12 sustained virological response at 12 weeks after the end of treatment, *IFN* interferon, *DAA* direct acting anti-viral, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir, *ASV* asnaprevir, *BCV* beclabuvir, *RBV* ribavirin, *N/A* preserved serum was not available

Table 4 Analyses of factors associated with non-SVR12

Factors	Category	Univariate			Multivariate		
		OR	95% CI	*p* value	OR	95% CI	*p* value
CKD stage	HD state	1.850	0.406–8.441	0.427			
HCV genotype	Genotype 1	–	–	–	–	–	–
	Genotype 2	0.482	0.148–1.573	0.227	1.172	0.301–4.565	0.819
	Genotype 3	38.361	10.701–137.522	2.16×10^{-8}	33.404	7.512–148.550	4.06×10^{-6}
Liver cirrhosis	Presence	1.116	0.342–3.643	0.856			
Past experience of IFN-free DAAs	Presence	4.791	1.595–14.396	0.005	3.977	1.153–13.725	0.029
Past treatment for HCC	Presence	3.924	1.193–12.907	0.024			

Multiple logistic regression analyses

Table 5 Safety: adverse events

Adverse events	Total
Any adverse events	398 (28.2%)
Death	0 (0%)
Serious adverse events	0 (0%)
Adverse events leading to treatment discontinuation	23 (1.6%)
Adverse events in 0.5% of all patients	
Pruritus	153 (10.9%)
Eruption	43 (3.0%)
Fatigue	42 (3.0%)
Headache	29 (2.1%)
Edema	14 (1.0%)
Nausea	13 (0.9%)
Dizziness	9 (0.6%)
Appetite loss	8 (0.6%)
Laboratory abnormalities in 0.5% of all patients	
Total bilirubin elevation	24 (1.7%)
AST or ALT elevation	13 (0.9%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

less than 90%, and there was no information on the number of GT-3b HCV-infected patients in France and USA [25, 26]. Hence, it is estimated that a majority of non-SVR12 patients were infected with GT-3b HCV.

In contrast, there were no genotype 4 (GT4) HCV-infected patients in the cohort. There have been many GT4 HCV-infected patients in Central Africa and the Middle East [27], while only one case has been reported in Japan [24]. However, it is possible that the number of GT4 HCV-infected patients may increase in Asia due to the current state of transportation.

The characteristics of non-SVR12 cases are as follows: most genotype 1 cases had cirrhosis and needed retreatment; genotype 2 had an 8-week regimen of unknown cause and genotype 3, especially genotype 3b, is considered refractory. For genotype 2, it cannot be denied that a short treatment period is the cause of treatment failure. Previous studies indicate that genotype 1 is slightly ameliorated with 92 K, and genotype 2 intractable factors have appeared with 156 RAS of NS3 [28] and T24A, F28S, L31M of NS5A [29].

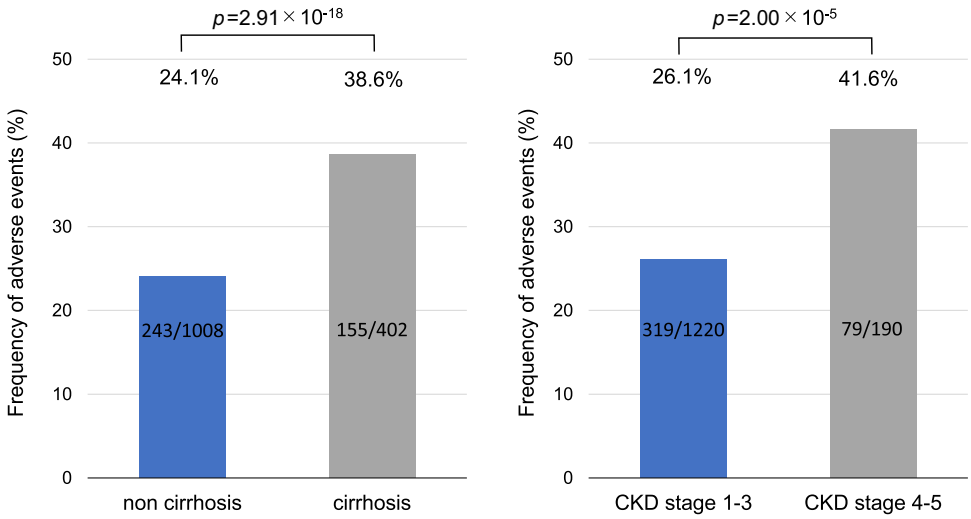

Fig. 6 Frequency of adverse events according to the presence or absence of cirrhosis and CKD stages (CKD stages 1–3 vs. 4–5) in sub-analysis

Table 6 Factors associated with the presence of adverse events

Factors	Category	Univariate			Multivariate		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Age	≥ 65 years old	1.323	1.021–1.713	0.034			
CKD stage	CKD stage 4 or 5	2.135	1.537–2.966	6.09×10^{-6}	2.339	1.665–3.285	9.47×10^{-7}
Liver cirrhosis	Presence	1.649	1.264–2.151	2.25×10^{-4}	1.450	1.079–1.947	0.014
Past experience of IFN-free DAAs	Presence	1.558	1.128–2.152	0.007	1.533	1.091–2.155	0.014
Past treatment for HCC	Presence	1.656	1.136–2.413	0.009			

Multiple logistic regression analyses

Genotype 3 is refractory to treatment if substitutions such as Y93H, A30K, and L31M of NS5A are present [4, 5, 23]. The present results are consistent with these reports. In 13 non-SVR12 patients, we detected L31 or M31 RAS in 9 patients and Y93RAS in 4 patients. However, the effect of RAS on the therapeutic results in our prospective clinical study is considered to be limited, because overall SVR12 rate was 99.1%.

Second, the presence or absence of cirrhosis did not show significant differences in the SVR12 rate in our large cohort. This finding is compatible with previous reports: 99.5% SVR12 rate for GT 2, 4, 5, or 6 HCV-infected patients without cirrhosis for 12 weeks or 99.0% SVR12 rate for GT 1, 2, 4, 5, or 6 HCV-infected patients with compensated cirrhosis [30, 31]. In contrast, the combination of the presence or absence of cirrhosis and DAA experience showed significantly lower SVR12 rates. However, this significant difference was observed only in the genotype 1 cohort. Therefore, the effect of advanced fibrosis on the therapeutic results is considered to be limited.

Third, prior history of hepatocellular carcinoma also did not show significant differences in the SVR rate in our large cohort in a multivariate analysis. Moreover, Cabibbo et al. recently reported that DAAs after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients [32]. Hence, anti-viral therapy with DAAs for HCV-cirrhotic patients with HCC post-curative therapies should be administered. In contrast, the HCC recurrence rate in the DAAs group was lower than that in the No DAAs group, but the difference was not significant in this report. Careful and continuous imaging assessments to diagnose recurrence should be performed in patients with HCV eradication.

Fourth, we previously reported the efficacy and safety of elbasvir/grazoprevir for Japanese patients with CKD including those undergoing hemodialysis (CKD stage 5d) in subgroup-analysis [33]. In this report, all 20 patients undergoing HD achieved SVR12. However, the E/G regimen is only approved for genotype 1 HCV-infected patients. We also reported the efficacy and safety of ombitasvir/paritaprevir/ritonavir in dialysis patients with genotype 1b chronic hepatitis C. Many drugs are contraindicated or carefully administered in combination with ombitasvir/paritaprevir/ritonavir because of drug–drug interactions [34]. Currently, combination therapy with sofosbuvir and ribavirin is available as an effective regimen for genotype 2. We also reported the efficacy of this regimen in the real world [35]. However, these drugs cannot be used in patients with CKD stages 4–5, because both drugs are metabolized through the kidney. On the other hand, Suda et al. recently reported the safety and efficacy of G/P regimen in HD patients with genotype 2 hepatitis C virus infection [36]. The strength of G/P regimen is that it is highly effective in all genotypes, and that interferon-free of ribavirin-free regimens can be administered in patients with genotype 2 or genotype 3 HCV infection. Although the 2018 EASL guidelines do not recommend, 2019 AASLD HCV Guidance and 2019 APASL clinical practice recommendation recommend a combination of glecaprevir/pibrentasvir for 8–16 weeks in patients with all HCV genotypes and stage 4 or 5 CKD [1, 37, 38]. CKD is, therefore, no longer an intractable factor in the treatment strategy of chronic hepatitis C complicated with CKD.

In addition, AEs occurred in 28.2% of all patients, and the observed frequency was similar to previous estimates. Observed AEs (in descending order of frequency) were pruritus, fatigue, eruption, headache, total bilirubin elevation, nausea, edema, appetite loss, dizziness, AST or ALT elevation, and serum creatinine elevation; but none were serious. The presence or absence of cirrhosis and CKD (stages 1–3 vs. 4–5) significantly affected the incidence of AEs, which were significantly higher in these patients. For elderly patients, DAA-related AEs leading to treatment discontinuation or serious AEs were rare for patients aged ≥ 65 and < 65 years in the study cohort. Foster et al. recently reported a similar observation [39]. Thus, G/P regimen can be considered a well-tolerated therapy for elderly patients with chronic HCV infection. A Japanese retrospective study also described that there were many serious adverse events leading to treatment discontinuation at the age of ≥ 75 [24]. Hence, the G/P regimen is thought to be a well-tolerated therapy for elderly patients, but careful observation may be necessary in patients aged ≥ 75 years.

In the context of efficacy, our estimate of 99.1% was in agreement with previously reported estimates of 95% and 100% [1–6]. With regard to CKD, as reported in our cohort, the presence or absence of CKD alone was not a determinant of treatment outcome [9]. However, patients with CKD 4–5 experienced significant AEs. Thus, appropriate monitoring is needed for these patients. Whereas AEs for genotype 1 patients have been rigorously studied, there are a few studies for genotype 2, a knowledge gap of our study aimed to bridge. To the best of our knowledge, this study is the first multivariate analysis on G/P AE and, hence, is highly beneficial. We were also able to extract information regarding the history of DAA use and HCV genotype 3 to identify factors contributing to non-SVR not available from the current literature. According to previous reports, owing to the limited number of cases, the determinants of non-SVR12 could not be ascertained [10].

Furthermore, as described in the previous studies, a considerably higher efficacy was observed compared to previously used DAAs such as DCV/ASV, and very few non-SVR12 cases have been reported [1–6, 12, 20–22]. To date, the P32 deletion of NS5A has become a non-healing case at the case report level [40]. In this study, P32 deletion cases were excluded based on previous reports [12, 13]. According to previous reports, HCV genotypes 1b, 2a, and 2b form the majority in Japan, and the cohort in this study represents the majority.

For patients with G/P treatment failure, there is SOF/VEL/RBV therapy for 24 weeks only available in Japan [41]. IFN-monotherapy may be indicated for patients undergoing HD with genotype 2 HCV infection who cannot use ribavirin, and a REACH study is underway to assess this issue. Treatment for patients with genotype 1 HCV should, therefore, be SOF/VEL/RBV therapy for 24 weeks. Patients with genotype 2 HCV infection should be treated with SOF/RBV for 12 weeks, but 24 weeks may be needed with SOF/VEL/RBV therapy. Treatment-naive genotype 3 should be classified as a sub-genotype at baseline, and genotype 3a can be treated with glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 weeks. However, for treatment-naïve genotype 3b patients with NS5A RASs at A30K or L31M at baseline and retreatment for genotype 3 patients, daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg), and weight-based ribavirin should be administered for 16 weeks as per the AASLD guidelines [42]. A combination of sofosbuvir/velpatasvir/voxilaprevir can also be administered for previous treatment failures with glecaprevir/pibrentasvir in patients with chronic hepatitis C infection [43, 44]. However, currently, there is no genotype 3b patient data, thereby warranting further research on the topic.

In conclusion, the G/P regimen is highly effective and safe to treat CHC patients, including those with refractory conditions such as CKD and advanced liver fibrosis. We demonstrate for the first time that the SVR12 rate in patients with previous DAA treatment or genotype 3 HCV infection was significantly lower than that of patients with no previous treatment. We also found that the frequency of AEs was higher among patients with CKD stage 4–5 and advanced liver fibrosis, suggesting the need for an appropriate monitoring of these patients.

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Ethical approval The study was conducted according to the Helsinki Declaration of 1975, as revised in 2008, and was approved by the Institutional Review Board at Nippon Medical School, Tokyo, Japan and participating study centers.

Informed consent Written informed consent was obtained from all participants.

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