Received: 11 December 2021 | Revised: 2 February 2022 | Accepted: 9 February 2022

DOI: 10.1111/jcpt.13624

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Retrospective multicentre study on the effectiveness of first-line direct-acting antivirals against hepatitis C virus genotype-1

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Funding information
Funding was provided by the Medical Practice Plan grant aimed at improving research at our institution, the Mt. Fuji Foundation for Healthcare Innovation and Cluster Development (Nagaizumi-cho, Sunto-gun, Shizuoka Prefecture, Japan) and the Shizuoka General Hospital (Shizuoka City, Shizuoka Prefecture, Japan). Neither sponsor had any role in the study design, analysis or interpretation of the data, the writing of the manuscript or the decision to submit the manuscript for publication.

Abstract

What is known and objective: In Japan, ledipasvir/sofosbuvir, elbasvir/grazoprevir and glecaprevir/pibrentasvir are recommended as first-line treatments for patients with untreated hepatitis C virus genotype 1. Although they have demonstrated a high efficacy in clinical trials, there are no direct comparative studies. Clarification of their effectiveness and safety in real-world clinical practice is required. Therefore, we conducted a retrospective multicentre study on the effectiveness of these direct-acting antivirals in real-world clinical practice.

Methods: We retrospectively evaluated the clinical data of untreated patients with persistent HCV genotype 1 infection who started first-line treatment with ledipasvir/sofosbuvir, elbasvir/grazoprevir or glecaprevir/pibrentasvir between September 2015 and January 2019 at 11 medical institutions in Japan. The primary efficacy endpoint was a sustained virologic response after 12 weeks of treatment. The secondary endpoints included sustained virologic response after 24 weeks of treatment and end of treatment response. The safety endpoint was treatment completion rate.

Results and discussion: During the study, 420 patients (median age, 70 years; 181 males) received ledipasvir/sofosbuvir, 48 (median age 72, years; 29 males) received elbasvir/grazoprevir and 63 (median age 66, years; 35 males) received glecaprevir/pibrentasvir. For ledipasvir/sofosbuvir, elbasvir/grazoprevir and glecaprevir/pibrentasvir, the sustained virologic response after 12 weeks of treatment was 98.6%, 97.9% and 100%; the sustained virologic response after 24 weeks of treatment was 99.0%, 97.7% and 100%; the end of treatment response was 99.8%, 97.9% and 98.4%; and the treatment completion rate was 98.3%, 91.7% and 100% respectively.

What is new and conclusion: In real-world clinical practice, hepatitis C virus treatment with ledipasvir/sofosbuvir, elbasvir/grazoprevir and glecaprevir/pibrentasvir was effective with safety.

KEYWORDS

DAA, hepatitis C virus, liver, real world, virologic response

1 | WHAT IS KNOWN AND OBJECTIVE

To date, seven hepatitis C virus (HCV) genotypes have been identified. In Japan, approximately 70% of patients with HCV are infected with genotype 1 (GT1), most of whom are infected with subtype 1b.[1,2] The rate of HCV antibody positivity estimated from hepatitis virus screening and blood donation in Japan is 0.6%.[3] Approximately 70% of HCV infections in healthy adults progress from persistent infection to chronic hepatitis. The natural rate of viral clearance following chronic progression is approximately 0.2% per year. Persistent inflammation of the liver induces fibrosis, which progresses to end-stage liver disease and hepatocellular carcinoma.[4-6]

Achieving sustained virologic response after 12 weeks of treatment (SVR12) with antiviral drugs, including interferon, reduces the risk for liver-related morbidity and mortality.[7,8] Peginterferon (pegIFN) + ribavirin (RBV) combination therapy improves the prognosis of patients with HCV. Daclatasvir +asunaprevir combination therapy was introduced as a pegIFN-free antiviral regimen and was found to improve the SVR to approximately 90%.[9] Since then direct-acting antivirals (DAAs) have emerged, representing a marked progress in the treatment of patients with HCV. All currently available oral DAAs are highly effective and have an adverse effect profile, making them easy to use in clinical practice. Ledipasvir/sofosbuvir (LDV/SOF), elbasvir/grazoprevir (EBR/GZR) and glecaprevir/pibrentasvir (GLE/PIB) are recommended as first-line treatments for patients with untreated HCV GT1.[10] While these DAAs are highly effective against HCV GT1 and well-tolerated, no direct comparisons have been performed, and their efficacy and safety in real-world clinical practice require clarification. Therefore, we conducted a retrospective multicentre study comparing the effectiveness and safety of DAAs in patients with HCV in real-world clinical practice.

Lay Summary

We retrospectively evaluated the clinical practice data of 531 untreated patients with persistent HCV genotype 1 infection who started first-line treatment with ledipasvir/sofosbuvir, elbasvir/grazoprevir or glecaprevir/pibrentasvir. In real-world clinical practice, hepatitis C virus treatment with ledipasvir/sofosbuvir, elbasvir/grazoprevir and glecaprevir/pibrentasvir was effective with safety.

2 | METHODS

2.1 | Patients and treatment

This retrospective multicentre study was conducted at 11 hospitals in Shizuoka, Japan (Chutoen General Medical Center, Hamamatsu Medical Center, Hamamatsu University Hospital, Iwata City Hospital, Japanese Red Cross Shizuoka Hospital, JA Shizuoka Kohseiren Enshu Hospital, Kikugawa General Hospital, Seirei Mikatahara General Hospital, Shizuoka City Shimizu Hospital, Shizuoka General Hospital and Yaizu City Hospital). In this study, 90/400 mg of LDV/SOF once daily (12 weeks of oral treatment), 50/100 mg of EBR/GZR once daily (12 weeks of oral treatment) or 300/120 mg of GLE/PIB once daily (8 weeks of oral treatment for hepatitis and 12 weeks of oral treatment for cirrhosis) were the standard regimens for patients with hepatitis or cirrhosis with untreated HCV GT1 infection. This study involved patients whose HCV RNA was measured 12 weeks after the end of treatment. Patients who discontinued treatment or who underwent dose reduction or drug suspension due to adverse effects (AEs) were also included. Patients previously treated with antivirals, including pegIFN, were excluded.

2.2 | Data collection

All data, including clinical information and laboratory data, of patients were obtained directly from the medical records of each facility and were anonymized and at Shizuoka Prefectural General Hospital. Considering variabilities in clinical practice, HCV RNA measurement for SVR determination was performed 12 and 24 weeks after the end of oral treatment, with a ±4-week allowance. HCV RNA was measured between −2 and +4 weeks from the scheduled end of treatment to determine the end of treatment response (ETR). Information on the underlying condition (cirrhosis or hepatitis) was collected from the doctors' chart at the start of treatment.

2.3 | Efficacy and safety endpoints

HCV RNA level was measured using standard test methods. The primary efficacy endpoint was SVR12, which was defined as HCV RNA level below the lower limit of quantification. The secondary endpoints were SVR24 and ETR, to which the same definition was applied. The safety endpoint was the completion rate of the 8- or 12-week regimen. Drug compliance, reasons for early discontinuation, withdrawal or dose reduction of DAAs were determined from patients' medical records.

2.4 | Statistical analysis

The total rate and treatment completion rate for SVR12, SVR24 and ETR were controlled by LDV/SOF. EBR/GZR and GLE/PIB were used as controls in the Fisher's exact test; the results are presented with 95% confidence interval. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander, designed to add the statistical functions frequently used in biostatistics.[11] The differences were considered significant at $p < 0.05$.

2.5 | Study oversight

The study protocol was approved by the Ethics Review Board of the Shizuoka General Hospital (approval no.: SGHIRB #2018049) and by the ethics review boards of the participating institutions. The study protocol was implemented in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Each ethics committee exempted the researchers from obtaining direct patient consent, based on the retrospective and non-interventional nature of the study. Rather than obtaining direct consent from patients, a public document was provided, which included an overview of the study outline and enabled patients to refuse to participate in the study.

3 | RESULTS AND DISCUSSION

3.1 | Patient population

Between September 2015 and January 2019, 592 patients with untreated HCV GT1 received LDV/SOF, EBR/GZR or GLE/PIB. Of these, 61 patients without HCV RNA measurements 12 weeks after the end of treatment were excluded. As a result, 420 patients treated with LDV/SOF, 48 patients treated with EBR/GZR and 63 patients treated with GLE/PIB were included in the analysis; in total, the data of 531 patients were(Figure 1).

Table 1 presents the demographic and clinical features of the study participants. The median age of patients was 69 years. Out of the 531 patients, 245 (46.1%) were male, 286 (53.9%) were female, 73 (13.7%) had cirrhosis, 451 (84.9%) had hepatitis (84.9%) and 7 (1.3%) had an unknown disease. Baseline laboratory tests before treatment showed that 11 (2.6%) patients had grade 3 adverse reactions in the LDV/SOF group. In the EBR/GZR group, 1 (2.1%) patient had a grade 3 reaction and 3 (6.3%) had grade 4 reactions. In the GLE/PIB group, 3 (4.8%) patients had grade 3 reactions and 2 (3.2%) had grade 4 reactions.

3.2 | Efficacy (virologic response, SVR12, SVR24 and ETR)

Virologic responses are presented in Table 2. Overall, 524 (98.7%) of the 531 patients achieved SVR12. Seventy of the 73 (95.9%) patients with cirrhosis, 447 of the 451 (99.1%) without cirrhosis and all 7 (100%) patients with an unknown disease achieved SVR12. In the LDV/SOF, EBR/GZR, and GLE/PIB groups, SVR12 was achieved by 414 (98.6%), 47 (97.9%) and 63 (100%) patients, and there were no significant differences among the groups (vs. EBR/GZR $p = 0.53$, odds ratio = 1.47, 95% confidence interval = 0.0313–12.5, vs. GLE/PIB $p = 1$, odds ratio = 0, 95% confidence interval = 0–5.71).

SVR24 was evaluated in 496 patients; this was because HCV RNA was not measured in 35 patients 24 weeks after the end of oral administration. SVR24 was achieved by 392 (99.0%) of the 396 patients in the LDV/SOF group, 43 (97.7%) of the 44 patients in the EBR/GZR group and all 56 (100%) patients in the GLE/PIB group. Two patients in the LDV/SOF group did not achieve SVR12, but achieved SVR24. In contrast, one patient in the LDV/SOF group achieved SVR12 but did not achieve SVR24. There were no significant differences among the groups (vs. EBR/GZR $p = 0.41$, odds ratio = 2.27, 95% confidence interval = 0.0452–23.7, vs. GLE/PIB $p = 1$, odds ratio = 0, 95% confidence interval = 0–10.8).

In 522 evaluable patients, overall ETR was achieved by 519 (99.4%) patients. In the LDV/SOF, EBR/GZR and GLE/PIB groups, ETR was achieved by 413 (99.8%) of the 414 patients, 46 (97.9%) of the 47 patients and 60 (98.4%) of the 61 patients respectively. There were no significant differences among the groups (vs. EBR/

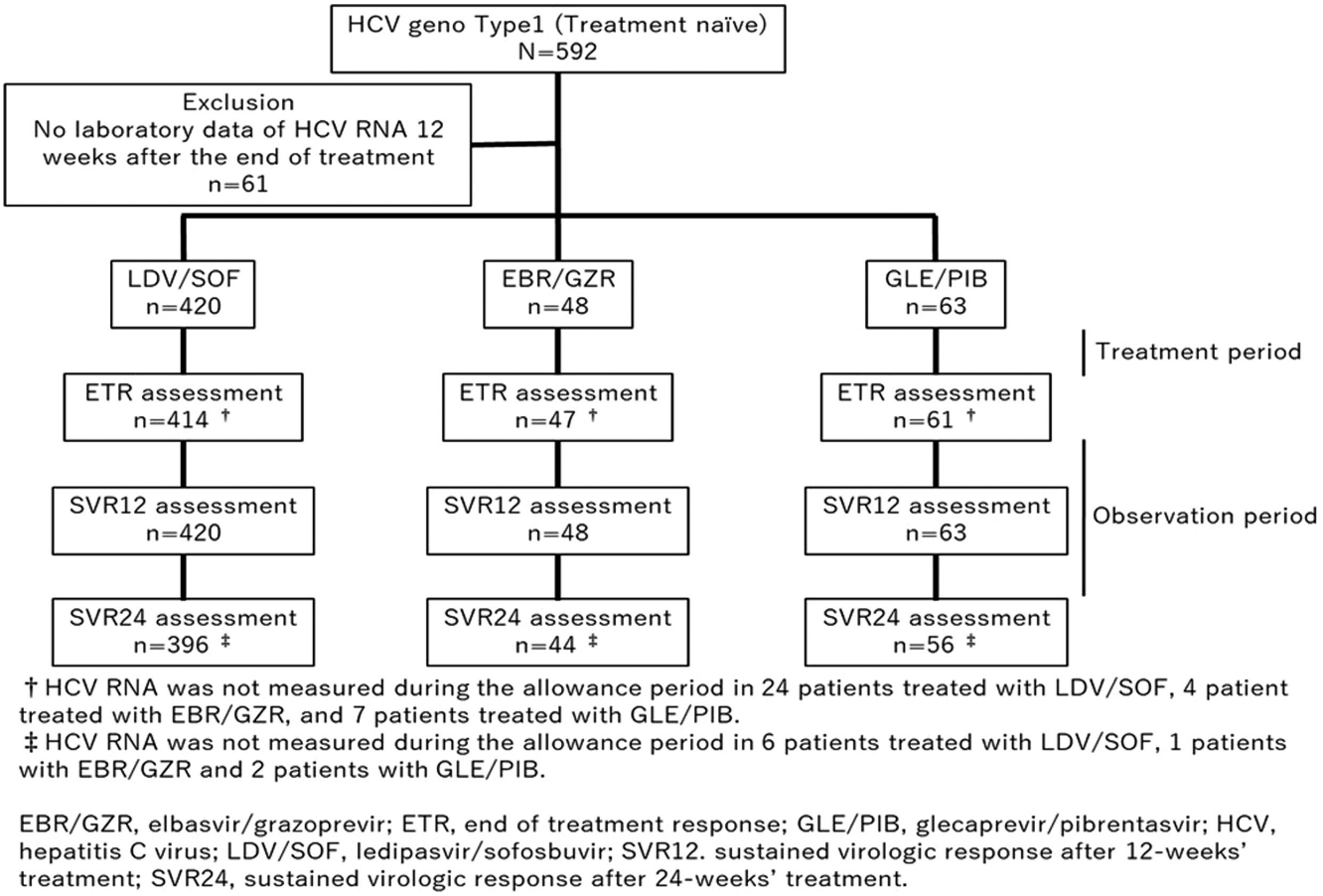

FIGURE 1 Patient disposition

GZR $p = 0.19$, odds ratio = 8.89, 95% confidence interval = .112–702, vs. GLE/PIB $p = 0.24$, odds ratio = 6.83, 95% confidence interval = 0.0863–539).

3.3 | Safety

Table 3 shows the treatment completion rate and the reasons for discontinuation, suspension and dose reduction; laboratory data during the treatment and observation periods; and the occurrence of grade 3 or higher AEs. Overall, 6 (1.1%) of the 531 patients discontinued treatment early because of an AE. These AEs were suspected to be caused by the use of DAAs, but none were confirmed to be due to the use of DAAs. The reasons for discontinuation in the LDV/SOF group were interstitial lung disease in 1 patient, hyperkalaemia in 1 patient, chest discomfort in 1 patient and increased serum creatinine in 1 patient. The reason for discontinuation in the EBR/GZR group was liver dysfunction in three patients. No deaths were recorded during the study period. SVR12 was achieved in all patients who discontinued treatment (data not shown). Treatment suspension or dose reduction was required for five (0.9%) of the 531 patients, one of whom had cirrhosis in the EBR/GZR group. The reasons for temporary discontinuation or dose reduction were hepatic dysfunction in 1 patient, self-assessed discontinuation of medication due to poor physical condition in 1 patient and forgetting to take the drug in 3 patients. Finally, treatment completion without dose reduction or suspension was achieved in 413 (98.3%) of the 420 patients in the LDV/SOF group, in 44 (91.7%) of the 48 patients in the EBR/GZR group and in all 63 (100%) patients in the GLE/PIB group. The rate of treatment completion without dose reduction or suspension in the LDV/SOF group was significantly higher than that in the EBR/GZR ($p = 0.02$, odds ratio = 5.33, 95% confidence interval = 1.10–22.0); the rate of treatment completion without dose reduction or suspension was not significantly different between the LDV/SOF and GLE/PIB group (vs. EBR/GZR $p = 0.60$, odds ratio = 0.95% confidence interval = 0–4.66). There was no additional prescribing data due to misdrinking of DAAs during the treatment period.

4 | DISCUSSION

In this large multicentre study in Japan involving 531 patients with HCV, SVR12 was achieved in 524 (98.7%) patients. Early discontinuation due to an AE occurred in six (1.1%) patients. In the United States and Europe, a phase 3, multicentre, randomized, open-label study was conducted to investigate the efficacy and safety of sofosbuvir/GS-5885 fixed-dose combination ± ribavirin for 12 and 24 weeks in treatment-naive subjects with chronic genotype 1

TABLE 1 Patient characteristics[a]

Characteristic	Treatment group				
	LDV/SOF ($n = 420$)	EBR/GZR ($n = 48$)	GLE/PIB ($n = 63$)	p value	ALL ($N = 531$)
Median age (range), yrs.	70 (18–88)	72 (32–86)	66 (27–85)	vs. EBR/GZR = 0.98 vs. GLE/PIB = 0.06	63 (25–90)
Male	181 (43.1)	29 (60.4)	35 (55.6)	vs. EBR/GZR = 0.03 vs. GLE/PIB = 0.08	245 (46.1)
Without cirrhosis	357 (85.0)	38 (79.2)	56 (88.9)	vs. EBR/GZR = 0.39	451 (84.9)
Cirrhosis	57 (13.6)	9 (18.8)	7 (11.1)	vs. GLE/PIB = 0.81	73 (13.7)
Unknown	6 (1.4)	1 (2.1)	0		7 (1.3)
HCV GT1 subtype					
1a	3 (0.7)	0(0)	0		3 (0.6)
1b	60 (14.3)	12 (25.0)	23 (36.5)		95 (17.9)
Not reported subtype	357 (85.0)	36 (75.0)	40 (1.4)		433 (81.5)
HCV RNA, median (range) $\log_{10}$ IU/ml	6.0 (1.2–7.3)	6.0 (1.3–7.2)	6.0 (3.0–6.9)	vs. EBR/GZR = 0.26 vs. GLE/PIB = 0.95	6.0 (1.2–7.3)
Baseline laboratory findings, median (range)					
Plt (×104/μl)	16.6 (3.4–48)	16.0 (2.2–27.7)	18.0 (5.1–33.9)	vs. EBR/GZR = 0.60 vs. GLE/PIB = 0.43	16.6 (2.2–48)
Albumin (g/dl)	4.0 (1.2–5.1)	4.0 (2.4–4.5)	4.2 (3.0–5.1)	vs. EBR/GZR = 0.10 vs. GLE/PIB = 0.09	4.0 (1.2–5.1)
T-Bil (mg/dl)	0.7 (0.1–5.0)	0.7 (0.3–1.8)	0.7 (0.2–1.5)	vs. EBR/GZR = 0.93 vs. GLE/PIB = 0.62	0.7 (0.1–5.0)
AST (U/L)	40 (14–206)	38 (8–143)	38 (12–186)	vs. EBR/GZR = 0.59 vs. GLE/PIB = 0.55	39 (8.0–206)
ALT (U/L)	37 (8–322)	30 (9–186)	41 (13–257)	vs. EBR/GZR = 0.31 vs. GLE/PIB = 1	37 (8–322)
ALP (U/L)	276 (100–2550)	294 (144–615)	263 (109–2762)	vs. EBR/GZR = 0.78 vs. GLE/PIB = 0.33	276 (100–2762)
γ-GTP(U/L)	30 (10–476)	36 (14–655)	33 (10–314)	vs. EBR/GZR = 0.19 vs. GLE/PIB = 0.29	30 (10–655)
Serum creatinine (mg/dl)	0.70 (0.39–1.29)	0.87 (0.51–6.93)	0.74 (0.35–8.44)	vs. EBR/GZR <0.001 vs. GLE/PIB <0.001	0.72 (0.35–8.44)
eGFR (ml/min/1.73 m^2)	73.0 (35.0–137.5)	63.0 (5.0–117.0)	69.0 (5.8–145.5)	vs. EBR/GZR <0.001 vs. GLE/PIB = 0.008	72.0 (5–145.5)
Patients indicated with grade 3 or higher adverse events in baseline laboratory data, grade 3/grade 4					
Any	11 (2.6)/0	1(2.1)/3(6.3)	3 (4.8)/2 (3.2)		15 (2.8)/5
Thrombopenia	3 (0.7)/0	0/1 (2.1)	0/0		3 (0.6)/1 (0.2)
Hypoalbuminemia	1 (0.2)/0	0/0	0/0		1 (0.2)/0
Increased blood bilirubin	1 (0.2)/0	0/0	0/0		1 (0.2)/0
AST increase	1 (0.2)/0	0/0	0/0		1 (0.2)/0
ALT increase	3 (0.7)/0	0/0	1 (1.6)/0		4 (0.8)/0
ALP increase	1 (0.2)/0	0/0	1 (1.6)/0		2 (0.4)/0
γ-GTP increase	1 (0.2)/0	0/0	1 (1.6)/0		2 (0.4)/0
Increased serum creatinine	0/0	1 (2.1)/2 (4.2)	0/2 (3.2)		1 (0.2)/4 (0.8)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; EBR/GZR, elbasvir/grazoprevir; eGFR, estimated glomerular filtration rate; GLE/PIB, glecaprevir/pibrentasvir; GTP, glutamyl transpeptidase; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; Plt, platelet; T-Bil, total bilirubin; vs, versus.

[a]Data are given as number (percentage) of patients unless otherwise indicated.

TABLE 2 Efficacy (virologic response, SVR12, SVR24, and ERT)[a]

Efficacy end points	Treatment group			*p* value (odds ratio: 95% confidence interval)
	LDV/SOF (*n* = 420)	EBR/GZR (*n* = 48)	GLE/PIB (*n* = 63)	
SVR12				
Total	414 (98.6)	47 (97.9)	63 (100)	vs. EBR/GZR = 0.53 (1.47: 0.0313–12.5) vs. GLE/PIB = 1 (0: 0–5.71)
Without cirrhosis	354 (99.2)	37 (97.4)	56 (100)	
Cirrhosis	54 (94.7)	9 (100)	7 (100)	
Unknown	6 (100)	1 (100)	No data	
SVR24[b]				
Total	392 (99.0)	43 (97.7)	56 (100)	vs. EBR/GZR = 0.41 (2.27: 0.0452–23.7) vs. GLE/PIB = 1 (0: 0–10.8)
Without cirrhosis	337 (99.4)	34 (97.1)	51 (100)	
Cirrhosis	50 (96.2)	9 (100)	5 (100)	
Unknown	5 (100)	No data	No data	
ETR[c]				
Total	413 (99.8)	46 (97.9)	60 (98.4)	vs. EBR/GZR = 0.19 (8.89: 0.112–702) vs. GLE/PIB = 0.24 (6.83: 0.863–539)
Without cirrhosis	353 (99.7)	36 (97.3)	53 (98.1)	
Cirrhosis	55 (100)	9 (100)	7 (100)	
Unknown	5 (100)	1 (100)	No data	

Abbreviations: EBR/GZR, elbasvir/grazoprevir; ETR, end of treatment response; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; SVR12, sustained virologic response after 12 weeks of treatment; SVR24, sustained virologic response after 24 weeks of treatment; vs, versus.

[a]Data are given as number of patients (percentage) unless otherwise indicated.

[b]HCV RNA was not measured during the allowance period in 24 patients treated with LDV/SOF, 4 patients treated with EBR/GZR and 7 patients treated with GLE/PIB.

[c]HCV RNA was not measured during the allowance period in 6 patients treated with LDV/SOF, 1 patient with EBR/GZR and 2 patients with GLE/PIB.

HCV infection (ION-1).[12] In the present study, the LDV/SOF group contained the highest number of patients (420 patients), whereas the total number of enrolled patients was greater than that in ION-1. Therefore, as many patients were enrolled this study, we consider that we were able to collect reliable information. In the present study, SVR12 was achieved in 98.6% of patients in the LDV/SOF group, which was comparable with that reported in ION-1.[13]

In a Japanese phase III clinical trial of EBR/GZR (MK-5172-058), SVR12 was reported in 96.5% of patients with chronic hepatitis and in 97.1% of patients with liver cirrhosis.[14] In the present study, SVR12 was achieved in 97% of patients with chronic hepatitis and in all patients with liver cirrhosis in the EBR/GZR group, consistent with the results of international clinical trials.[15,16]

In a phase III clinical trial of GLE/PIB in Japan (CERTAIN-1), the SVR12 for patients with untreated HCV GT1 without Y93H mutation was 99.1% and the SVR12 for untreated HCV GT1 patients with Y93H mutation was 100%.[17] Although information on gene mutations was not obtained in the present study, we believe that our results demonstrate that GLE/PIB is an effective treatment even in real-world clinical practice.

In this study, the median patient age was 69 years. Although data on complications or the use of concomitant drugs that may affect the pharmacokinetics of DAAs were not collected, it is possible that patients treated in real-world clinical practice have comorbidities and are treated for diseases other than HCV. Under these circumstances, only 1.1% of patients discontinued treatment early due to AEs in our study. This indicates that the drugs have safety even when used in real-world clinical practice. Furthermore, low compliance to treatment may be an issue in clinical practice. However, we believe that this was not significant in our study, because only 4 (0.8%) of the 531 patients decided to discontinue medication during the treatment period.

In this study, 100% SVR12 was achieved only in the GLE/PIB group, and there were no early discontinuations due to AEs. There were no significant differences in the efficacy outcomes among the LDV/SOF, EBR/GZR and GLE/PIB groups. Nonetheless, we should also consider the safety outcomes. We observed a significantly higher rate of treatment completion without dose reduction or suspension in the LDV/SOF group than in the EBR/GZR group, and found no significant difference between the LDV/SOF and GIE/PIB groups. Treatments should also be considered from the perspective of health economics. Maintaining high medication compliance is important in clinical practice. Considering economics and a short dosing period (8 weeks), GLE/PIB may be preferable for the treatment of patients with HCV GT1 who do not have cirrhosis.

The results of this study support the efficacy, safety and compliance of DAAs in real-world clinical practice for untreated patients

TABLE 3 Safety (treatment completion, reason for early discontinuation, reason for suspension/dose reduction, and laboratory data)[a]

Safety end point	Treatment group			
	LDV/SOF (*n* = 420)	EBR/GZR (*n* = 48)	GLE/PIB (*n* = 63)	*p* value (95% confidence interval)
Treatment completion (without dose reduction or suspension)	413 (98.3)	44 (91.7)	63 (100)	vs. EBR/GZR = 0.02 (5.33: 1.10–22.0) vs. GLE/PIB = 0.60 (0: 0.000–4.66)
Treatment completion (with dose reduction or suspension) Total	4 (1.0)	1 (2.1)	0	
Missed dose	3 (0.7)	0/0	0/0	
Poor physical condition (patient decision)	1 (0.2)	0/0	0/0	
Total early discontinuation[b]	3 (0.7)	3 (6.3)	0	
Interstitial lung disease	1 (0.2)	0	0	
Hyperkalemia	1 (0.2)	0	0	
Chest discomfort	1 (0.2)	0	0	
AST and ALT increase	0/0	3/0 (6.3)	0/0	
Increased serum creatinine	1 (0.2)	0	0	
Loss of appetite	0	1 (2.1)	0	
Patients indicated with grade 3 or higher adverse events in laboratory data during the treatment period, grade 3/grade 4				
Thrombopenia	3 (0.7)/0	1 (2.1)/0	0/0	
Hypoalbuminemia	2 (0.5)/0	0/0	1 (1.6)/0	
Increased blood bilirubin	0/0	0/0	0/0	
AST increase	0/0	2 (4.2)/0	0/0	
ALT increase	0/0	2 (4.2)/0	0/0	
ALP increase	0/0	0/0	1 (1.6)/0	
γ-GTP increase	0/0	0/0	0/0	
Increased serum creatinine	0/0	2 (4.2)/2 (4.2)	4 (6.3)/2 (3.2)	
Patients indicated with grade 3 or higher adverse events in laboratory data during the observation period, grade 3/grade 4				
Thrombopenia	4 (1.0)/0	1 (2.1)/0	0/0	
Hypoalbuminemia	0/0	0/0	0/0	
Increased blood bilirubin	0/0	0/0	0/0	
AST increase	1 (0.2)/0	2 (4.2)/0	0/0	
ALT increase	1 (0.2)/0	2 (4.2)/0	0/0	
ALP increase	1 (0.2)/0	0/0	0/0	
γ-GTP increase	0/0	0/0	0/0	
Increased serum creatinine	1 (0.2)/0	2 (4.2)/2 (4.2)	4 (6.3)/2 (3.2)	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; EBR/GZR, elbasvir/grazoprevir; eGFR, estimated glomerular filtration rate; GLE/PIB, glecaprevir/pibrentasvir; GTP, glutamyl transpeptidase; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; vs, versus.

[a]Data are given as number (percentage) of patients unless otherwise indicated.

[b]Patients with multiple reasons for discontinuation were counted as 1.

with persistent HCV GT1 infection, which affects the highest number of individuals in Japan. We believe that the collected data are of high reliability because 11 medical institutions in Shizuoka Prefecture, Japan, participated in the study and initiated the study at the same time. This real-world clinical practice study was retrospective and not randomized. Physicians were free to choose the DAA regimen based on each patient's condition at the start of treatment. Currently, GLE/PIB is the most frequently used DAA, but LDV/SOF can be started earlier than the other two drugs. This explains why the LDV/SOF group contained the highest number of patients in this study. In this study, bias may have arisen due to the differences in the real-world usage of DAA regimens due to the higher number of patients being treated with LDV/SOF than with other regimens. As we evaluated drug compliance from medical records, it was not possible to assess the patients' actual drug compliance with DAAs. Sixty-one patients were excluded from the study due to a lack of laboratory

data on HCV RNA 12 weeks after the end of treatment; therefore, no information was available for these patients. Data on the existence of resistance-related mutations were also not collected in this study. Interestingly, it remains unclear whether gene mutations play a role in patients with no virologic response.

5 | WHAT IS NEW AND CONCLUSION

In summary, the results of this large multicentre study showed that all three treatment regimens were effective and safe as first-line treatments for patients with HCV GT1 with or without cirrhosis. GLE/PIB may confer the highest advantage in terms of health economics and compliance if limited to patients without liver cirrhosis.

CONFLICTS OF INTEREST

All authors report no conflicts of interest.

PATIENT CONSENT STATEMENT

The ethics committee exempted the researchers from obtaining patient consent directly owing to the retrospective and non-interventional characteristics of the study (SGHIRB##2018049). Rather than obtaining direct consent from patients, a public document was provided, which included an overview of the study and enabled patients to refuse to participate in the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

This manuscript does not make use of any previously published material.

DATA AVAILABILITY STATEMENT

Demographic and clinical information collection, laboratory tests and technical tests were conducted according to the site standards. Data were after anonymized copies of the source data (clinical records provided by the participating sites) were integrated at Shizuoka General Hospital.

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How to cite this article: Kaya M, Nakamura K, Sugiyama K, et al. Retrospective multicentre study on the effectiveness of first-line direct-acting antivirals against hepatitis C virus genotype-1. *J Clin Pharm Ther*. 2022;47:940–947. doi:10.1111/jcpt.13624