Efficacy of Glecaprevir/Pibrentasvir for Real-World HCV Infected Patients in the Northern Part of Tokyo, Japan

日本大学医学部　消化器肝臓内科学分野

山名　陽一郎

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指導教員　神田　達郎

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Efficacy of Glecaprevir/Pibrentasvir for Real-World HCV Infected Patients in the Northern Part of Tokyo, Japan

Yoichiro Yamana, Tatsuo Kanda *, Naoki Matsumoto, Masayuki Honda, Mariko Kumagawa, Reina Sasaki, Shini Kanezawa, Taku Mizutani, Hiroaki Yamagami, Ryota Masuzaki, Tomotaka Ishii, Kazushige Nirei and Mitsuhiko Moriyama

Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan; yamana.yoichiro@nihon-u.ac.jp (Y.Y.); matsumoto.naoki@nihon-u.ac.jp (N.M.); honda.masayuki@nihon-u.ac.jp (M.H.); kumagawa.mariko@nihon-u.ac.jp (M.K.); sasaki.reina@nihon-u.ac.jp (R.S.); kanezawa.shini@nihon-u.ac.jp (S.K.); mizutani.taku@nihon-u.ac.jp (T.M.); yamagami.hiroaki@nihon-u.ac.jp (H.Y.); masuzaki.ryota@nihon-u.ac.jp (R.M.); ishii.tomotaka@nihon-u.ac.jp (T.I.); nirei.kazushige@nihon-u.ac.jp (K.N.); moriyama.mitsuhiko@nihon-u.ac.jp (M.M.)

* Correspondence: kanda.tatsuo@nihon-u.ac.jp; Tel.: +81-3-3972-8111

Abstract: Hepatis virus C (HCV) infection causes liver cirrhosis and hepatocellular carcinoma (HCC) worldwide. The objective of our study was to examine the effects of the HCV nonstructural protein (NS) 3/4A inhibitor glecaprevir/NS5A inhibitor pibrentasvir on real-world HCV patients in the northern part of Tokyo, Japan. Although 106 patients were consecutively included, a total of 102 HCV-infected patients with chronic hepatitis or compensated cirrhosis, who received 8- or 12-week combination treatment with glecaprevir/pibrentasvir and were followed up to week 12 after the end of treatment were analyzed retrospectively. Only three patients discontinued treatment due to adverse events; however, they achieved a sustained virologic response at 12 weeks (SVR12). Finally, SVR rates were 99.0% (101/102). Only one patient without liver cirrhosis was a treatment relapser who received hepatic resection for HCC approximately two years after commencement of the 8-week combination treatment with glecaprevir/pibrentasvir. After the exclusion of patients with HCV genotype 1b and P32 deletion in the HCV NS5A region, a 12-week combination of glecaprevir/pibrentasvir led to SVR12 in all nine direct-acting antiviral-experienced patients. Glecaprevir/pibrentasvir had a high efficacy and an acceptable safety profile for real-world HCV patients in a single hospital in Japan.

Keywords: chronic kidney disease; DAA failure; hemodialysis; HCV; NS5A P32 deletion mutant

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1. Introduction

Chronic hepatitis C virus (HCV) infection causes liver cirrhosis and hepatocellular carcinoma (HCC), which are life-threatening diseases worldwide [1,2]. The 12-week combination treatment of direct-acting antivirals (DAAs) has higher eradication rates of HCV (ranging from 95–100%) with fewer adverse events [3,4]. However, there were still some non-responders, who needed other therapeutic regimens [5,6].

Glecaprevir and pibrentasvir are inhibitors of HCV nonstructural (NS) protein 3/4A protease and NS5A, respectively [7]. These combinations of glecaprevir/pibrentasvir have pangenotypic anti-HCV activity with a high barrier to resistance, primarily biliary excretion and negligible renal excretion [8–10]. Therefore, the combination of glecaprevir/pibrentasvir could be used for the treatment of HCV-infected patients on dialysis and those with severe renal impairment or for the retreatment of HCV-infected patients with previous DAA treatment failure.

We report here the real-world experience with glecaprevir/pibrentasvir from the northern part of Tokyo, Japan, generated from a retrospective study of the effectiveness and safety of an 8- or 12-week course of treatment with glecaprevir/pibrentasvir for

HCV-infected patients with chronic hepatitis or compensated cirrhosis in daily clinical practice. We emphasize the efficacy of this regimen in the Japanese population while also highlighting the safety profile.

2. Patients and Methods

2.1. Study Design and Patients

This retrospective study enrolled patients with chronic HCV infection who started to receive interferon-free combination treatment with glecaprevir/pibrentasvir from 1 November 2017 to 31 August 2019. A total of 106 patients were initially included. Eligible patients were 20 years of age and older and had chronic hepatitis or compensated cirrhosis (Child-Pugh A cirrhosis). An 8- or 12-week combination treatment of glecaprevir/pibrentasvir was given in DAA-naïve patients, and a 12-week combination treatment of glecaprevir/pibrentasvir was given in DAA-experienced patients (Figure 1).

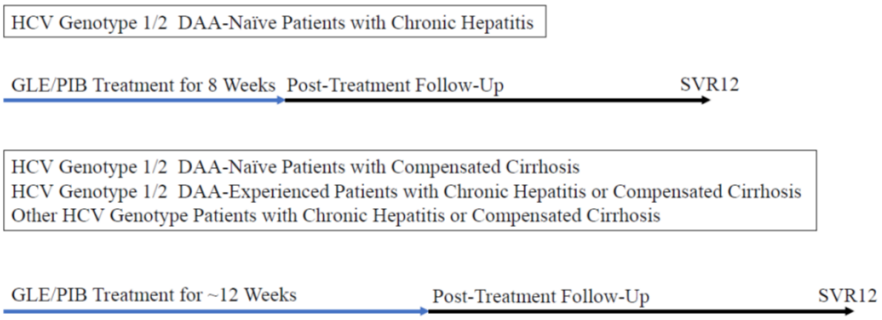

Figure 1. Treatment regimens in the groups of various patients. DAA, direct-acting antiviral; GLE/PIB, glecaprevir/pibrentasvir; SVR12, sustained virologic response at 12 weeks after the end of treatment.

The exclusion criteria were as follows: (1) Child-Pugh B or C cirrhosis; (2) serious other medical conditions such as severe anemia, pulmonary diseases, or heart diseases; (3) the presence of active hepatocellular carcinoma (HCC); (4) human immunodeficiency infection; and (5) patients with virologic failure who had both HCV genotype 1b infection and P32 deletion in the HCV NS5A region at baseline [11]. Patients on dialysis and those with severe chronic kidney disease (CKD) or those with a history of curative HCC treatment were included. Some of these patients had been included in other studies [6,12].

The protocol of this single center study followed the Declaration of Helsinki. The ethics committee of Nihon University School of Medicine Itabashi Hospital approved this retrospective study (protocol number RK-181009-04, and RK-180911-12). Participation in the study was posted at the website of our institution, and informed consent was obtained from all patients.

2.2. Serum Biochemical Tests and Hematological Tests

Serum biochemical tests including liver function tests and the estimated glomerular filtration rate (eGFR), and hematological tests were performed according to standard methods [6].

2.3. Measurement of HCV RNA Levels and Determination of HCV Genotypes

Serum HCV RNA levels were measured by COBAS TaqMan assay (Roch Diagnostics, Tokyo, Japan) with detection limits of ~1.2 LIU/mL. At least, HCV RNA levels were determined at pre-treatment, at the end of treatment and after 12 weeks at the end of treatment. SVR12 was used as the SVR to evaluate the virological response. Virus clearance was defined as undetectable HCV RNA. HCV genotypes were determined by the antibody serotyping method [13] or PCR-based assay with genotype-specific PCR primers [14]. In a non-SVR patient, HCV NS5A resistance-associated substitutions (RASs) at 31L and 93Y

were determined by a commercially available direct-sequencing assays (SRL Laboratory, Tokyo, Japan) [15].

2.4. Assessment of Advanced Liver Fibrosis and Diagnosis of Cirrhosis and HCC

Ultrasonography and hepatic transient elastography on a FibroScan 502 with an M probe (Echosens, Paris, France) were performed. In general, liver stiffness equal to or more than 12.0 kPa or the sign of cirrhosis was considered liver cirrhosis. The sign of cirrhosis was the existence of varices in the esophagus and/or stomach on upper gastrointestinal endoscopy or the existence of compatible findings of liver cirrhosis in computed tomography (CT) scanning or magnetic resonance imaging (MRI). In this study, Child-Pugh A cirrhosis was defined as compensated cirrhosis. In general, HCV-infected patients were followed up through an HCC surveillance program based on ultrasonography evaluations with or without tumor markers/CT/MRI at least every six months [6].

2.5. Statistical Analysis

Data are expressed as the mean ± standard deviation (SD). Statistical analysis was performed by the Student's *t*-test or chi-squared test. A p-value < 0.05 was considered a statistically significant difference.

3. Results

3.1. Patients' Characteristics

A total of 106 consecutive HCV-infected patients who commenced an 8- or 12-week combination treatment of glecaprevir (300 mg daily)/pibrentasvir (120 mg daily) (fixed-dose compound: Maviret, AbbVie, Tokyo Japan) were initially included (Figures 1 and 2).

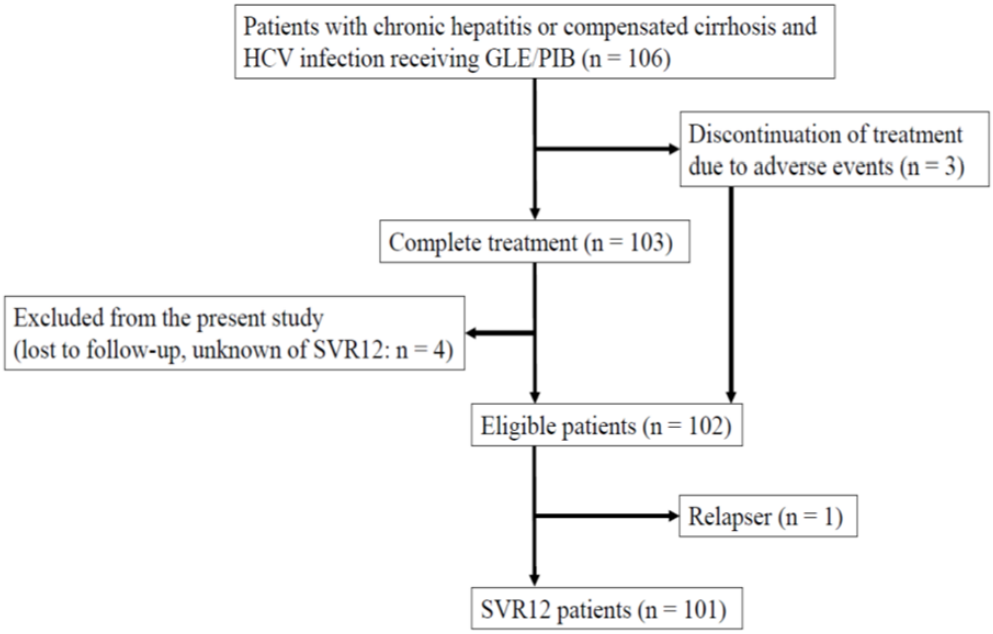

Figure 2. Study profile of this retrospective study.

Of them, 103 patients completed the treatment (Figure 2). As 4 patients were lost to follow-up, 99 patients were included in the study. A total of 3 out of the 106 (2.8%) patients who discontinued treatment by adverse events were also included in the present study, as the SVR was judged in these three patients. In total, 102 patients aged older than 20 years in whom sustained virologic response (SVR) at 12 weeks after the end of treatment (SVR12) was judged were defined as eligible (Figure 2). Overall, 102 patients were included in this retrospective analysis (Table 1).

Table 1. Baseline characteristics of 102 patients in the study.

Characteristics	All (n = 102)
Age (years)	62.7 ± 12.1
Gender (male/female)	41/61
Interferon (naïve/experienced)	88/14
DAAs (naïve/experienced)	93/9
HCV genotypes (1/2/3)	54/45/3
Pretreatment HCV RNA (LIU/mL)	6.0 ± 1.2
Body weight (kg)	58.0 ± 12.9
Body length (m)	1.60 ± 0.10
History of HCC (+/−)	5/97
Chronic hepatitis/cirrhosis	74/28
Liver stiffness (kPa)	9.9 ± 7.9
AST (IU/L)	50.7 ± 30.4
ALT (IU/L)	51.4 ± 39.1
Hemoglobin (g/dL)	13.5 ± 1.6
Platelets ($\times 10^4/\mu L$)	17.6 ± 6.3
eGFR (mL/min/1.73 m^2)	67.6 ± 26.8

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.

The characteristics of the 102 patients at baseline are shown in Table 1. In total, 81 were treatment-naïve patients and did not receive any interferon-including or DAA-including regimens. The HCV subgenotypes of 102 patients were as follows: 1a:1b:1 unknown subgenotype: 2a:2b:2 unknown subgenotype: 3a:2:51:1:24:19:2:3. Six patients went on artificial dialysis for chronic kidney failure.

3.2. The Efficacy and Safety of the 8- or 12-Week Combination Treatment of Glecaprevir/Pibrentasvir

A total 99 patients completed the treatment, and 3 patients discontinued the treatment due to severe adverse events. Among these three patients, an 85-year-old female patient with HCV genotype 1b and chronic hepatitis, stopped the treatment due to her cerebral hemorrhage at 4 weeks after the commencement of the treatment and achieved SVR12; a 74-year-old female patient with HCV genotype 1b and cirrhosis, stopped the treatment due to her hyperbilirubinemia (total bilirubin, 3.8 mg/dL; direct bilirubin, 2.5 mg/dL) at 6 weeks after the commencement of the treatment and achieved SVR12; and a 63-year-old male patient with HCV genotype 1b and cirrhosis, stopped the treatment due to his hyperbilirubinemia (total bilirubin, 3.9 mg/dL; direct bilirubin, 2.8 mg/dL) at 8 weeks after the commencement of the treatment and achieved SVR12. All these patients had diabetes mellitus, and two patients possessing hyperbilirubinemia had cirrhosis. Finally, except for only 1 patient, 101 patients achieved SVR.

Among the three HCV genotype 3a-infected patients, one and two patients were treated with 8- and 12-week combination treatment of glecaprevir/pibrentasvir, respectively, and all three patients achieved SVR12. Among the 24 patients with compensated cirrhosis after excluding two patients who discontinued the treatment due to adverse events, 6 and 18 patients were treated with 8- and 12-week combination treatment of glecaprevir/pibrentasvir, respectively, and all 24 patients achieved SVR12. Among the 73 patients with chronic hepatitis after excluding one patient who discontinued the treatment due to adverse events, 64 and 9 patients were treated with 8- and 12-week combination treatment of glecaprevir/pibrentasvir, respectively, and 72 patients (98.6%) achieved SVR12.

The characteristics of one relapse patient is shown in Table 2. In this patient, HCV RNA was relapsed after 12 weeks of the end of treatment. At this time, his HCV RNA level was 5.2 LIU/mL. He had stopped coming to our outpatient clinic due to his circumstance for two years. He received hepatic resection for HCC ~2 years after the commencement of 8-week combination treatment of glecaprevir/pibrentasvir. HCV RNA level was 5.5 LIU/mL before his surgery. Histological evaluation of non-HCC liver revealed no existence of liver cirrhosis. Due to his severe heart disease, he was retreated with the

12-week combination of the HCV NS3/4A inhibitor grazoprevir/NS5A inhibitor elbasvir after the surgery of HCC. Before this retreatment, his HCV RNA level was 5.6 LIU/mL. Although he achieved SVR24 by this regimen, HCC was relapsed.

Table 2. Baseline characteristics of a relapser after 8 weeks of glecaprevir/pibrentasvir.

Characteristics	A Relapser at Week 12 after Treatment
Age (years)	65
Gender	Male
Interferon	Naive
Interferon-free DAAs	Naive
HCV genotypes	1b
Pretreatment HCV RNA (LIU/mL)	5.4
Body weight (kg)	51
Body length (m)	1.58
History of HCC	No
Chronic hepatitis or cirrhosis	Chronic hepatitis
Liver stiffness (kPa)	7.9
AST (IU/L)	91
ALT (IU/L)	80
Hemoglobin (g/dL)	14.1
Platelets ($\times 10^4/\mu L$)	23.8
eGFR (mL/min/1.73 m^2)	64.4
Adherence > 80%	Yes
* NS5A-L31	Wild
* NS5A-Y93	Wild

DAA, direct-acting antivirals; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate. * Resistance-associated substitutions (NS5A-L31 and Y93) after treatment-relapse were determined by direct-sequence methods.

3.3. Twelve-Week Combination of Glecaprevir/Pibrentasvir for DAA-Failure Patients

There were nine DAA-experienced patients: three HCV genotype 1b-relapsers with chronic hepatitis received HCV NS3/4A inhibitor asunaprevir/NS5A inhibitor daclatasvir; two HCV genotype 1b-patients (one is compensated cirrhosis and the other is chronic hepatitis) discontinued NS5B inhibitor sofosbuvir/NS5Ainhibitor ledipasvir due to adverse events of arrhythmia [16]; one HCV genotype 1b-relapser with chronic hepatitis received grazoprevir/elbasvir; one HCV-genotype 2b-relapser with compensated cirrhosis received sofosbuvir/ribavirin; one HCV genotype 1b-relapser with chronic hepatitis received a second DAA combination of asunaprevir/daclatasvir/NS5B inhibitor beclabuvir following the relapse after the first DAA combination of asunaprevir/daclatasvir; and one HCV genotype 1b-relapser with chronic hepatitis who received the third DAA combination of asunaprevir/daclatasvir/NS5B beclabuvir following the relapse after the second DAA combination of sofosbuvir/ledipasvir and the relapse after the first DAA combination of daclatasvir/asunaprevir. All nine patients received a 12-week combination of glecaprevir/pibrentasvir with no adverse events and achieved SVR12.

3.4. Combination Treatment of Glecaprevir/Pibrentasvir for Patients Undergoing Artificial Dialysis

One cirrhotic patient and five patients with chronic hepatitis were treated with 12 or 8-week combinations of glecaprevir/pibrentasvir, respectively, and all six patients achieved SVR12 with no severe adverse events (Figure 3).

As these six patients took at least eight drugs, polypharmacy seemed common among this group of patients. Careful attention should be paid to the drug-drug interaction under the combination treatment of glecaprevir/pibrentasvir. One patient complained of her pruritus, but it was improved by the oral administration of nalfurafine hydrochloride. Of interest, 4 (66.7%) of the 6 patients took nalfurafine hydrochloride during the combination treatment of glecaprevir/pibrentasvir (Table 3).

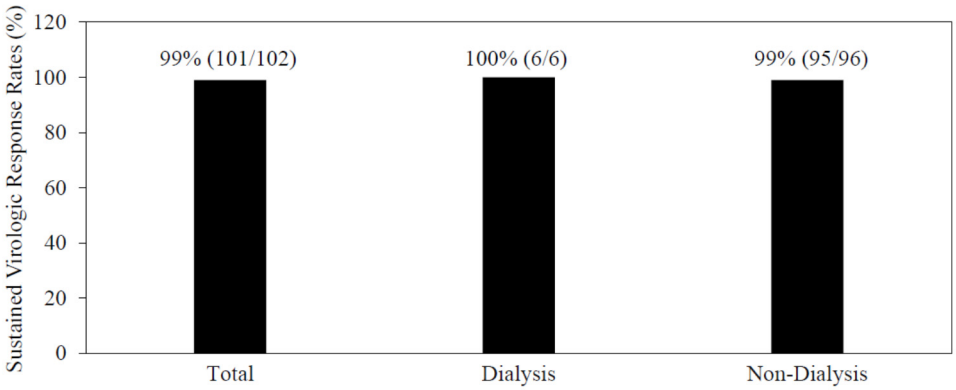

Figure 3. Higher sustained virologic response rates of combination treatment of glecaprevir/pibrentasvir for patients with or without dialysis in the present study.

Table 3. Characteristics of six patients undergoing artificial dialysis with glecaprevir/pibrentasvir treatment.

Characteristics	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Age (years)	82	84	55	57	56	64
Gender	Male	Female	Male	Male	Male	Male
Interferon	Experienced	Naive	Naive	Naive	Naive	Naive
Interferon-free DAAs	Naive	Naive	Naive	Naive	Naive	Naive
HCV GTs	1b	1b	2b	2a	2	2b
Pretreatment HCV RNA (LIU/mL)	6.8	6.3	4.8	3.9	3.3	5.3
Body weight (kg)	58.4	36.5	88.4	67.5	71.9	64.5
Body length (m)	1.60	1.48	1.73	169	1.79	1.64
History of HCC	No	No	No	No	No	No
CH or LC	LC	CH	CH	CH	CH	CH
Liver stiffness (kPa)	13.6	8.3	11.5	11.8	6.1	4.4
AST (IU/L)	50	22	72	27	15	16
ALT (IU/L)	63	10	80	24	17	13
Hemoglobin (g/dL)	14.2	8.8	9.2	10.4	13.7	10.4
Platelets (x 104/μL)	18.2	14.3	16.1	17.3	18.6	15.5
eGFR (mL/min/1.73 m^2)	7.5	7.9	3.8	5	5	6.4
Type of dialysis	HD	HD	PD	HD	HD	HD
Duration of dialysis (years)	0.5	3.5	2	4.5	5	7
DM	No	Yes	Yes	Yes	Yes	Yes
Number of drugs under treatment	8	13	17	12	10	15
Nalfurafine hydrochloride	Yes	Yes	Yes	Yes	No	No

DAA, direct-acting antivirals; HCV, hepatitis C virus; GT, genotype; HCC, hepatocellular carcinoma; CH, chronic hepatitis; LC, liver cirrhosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; DM, diabetes mellitus.

One and five patients were undergoing peritoneal dialysis and hemodialysis, respectively. Thus, 8 or 12-week combination of glecaprevir/pibrentasvir could safely treat patients undergoing artificial dialysis, irrespective of a type of artificial dialysis, and achieve higher SVR rates (Figure 3).

4. Discussion

In this study, real-world data from the northern part of Tokyo indicates that an 8- or 12-week combination treatment of glecaprevir/pibrentasvir could lead to 99.0% (101/102) SVR rates in HCV-infected patients with various background characteristics. Three patients discontinued the treatment because of adverse events: one had a cerebral hemorrhage, and two had hyperbilirubinemia. We assessed the cerebral hemorrhage as being unlikely related to DAAs. Two patients with compensated cirrhosis had grade 2 elevations (i.e., >1.5–3.0× upper limit of normal) in total bilirubin levels; all elevations involved direct

bilirubin and were not accompanied by elevation in alanine aminotransaminase (ALT) levels. Thus, the 8- or 12-week combination treatment of glecaprevir/pibrentasvir could achieve higher SVR rates. However, clinicians should pay attention to adverse events during treatment.

Serious adverse events associated with glecaprevir/pibrentasvir treatment were low rates (2.9% (3/102)), similar to those observed in the NS5B nucleotide polymerase inhibitor-including regimen of sofosbuvir/ribavirin (1.2% (1/86); $p = 0.400$) in our hospital [6]. The combination of glecaprevir/pibrentasvir is a contraindicated regimen in the presence of advanced decompensated cirrhosis [17–19]. Therefore, careful attention should also be paid to the elevation of bilirubin levels in patients with cirrhosis.

We observed HCV RNA relapse at week 12 after the 8-week combination treatment of glecaprevir/pibrentasvir in one treatment-naïve patient with HCV genotype 1b and chronic hepatitis (Table 2). According to the Japanese national insurance system, 8-week or 12-week combination treatment of glecaprevir/pibrentasvir was given for DAA-naïve or DAA-experienced patients, respectively. In the United States, the 8-week combination of glecaprevir/pibrentasvir or the 12-week combination of sofosbuvir/NS5A inhibitor velpatasvir is recommended for treatment-naïve persons without liver cirrhosis, regardless of the HCV genotype [18]. A shorter duration of treatment may be desirable to reduce the cost of treatment and the occurrence rate of adverse events for DAA-treatment-naïve patients with HCV infection [20]. Careful post-treatment follow-up of patients with or without cirrhosis should also be performed for the monitoring of HCC occurrence [21].

Previous study demonstrated that 2 out of 2 (100%) patients who had P32 deletion in HCV NS5A at baseline, experienced virologic failure [22]. P32 deletion in the HCV genotype 1 NS5A confers > 1000-fold resistance to piblentasvir [23]. In Japan, the 24-week combination retreatment of sofosbuvir/velpatasvir plus ribavirin are recommended for HCV-infected patients with virologic failure who had both HCV genotype 1b infection and P32 deletion in the HCV NS5A region at baseline [11]. In our hospital, no HCV genotype 1-infected patients with virologic failure and this mutation, were found. Before the retreatment of DAA-failure patients, we excluded patients with virologic failure who had both HCV genotype 1b infection and P32 deletion in the HCV NS5A region at baseline [11]. After that, we successfully retreated nine patients with DAA failure. HCV genotype 1b with P32 deletion in the HCV NS5A region is more resistant to HCV NS5A inhibitors in vitro and in vivo [24–26]. We reconfirmed the previous report that glecaprevir/piblentasvir was effective for HCV-infected patients who failed to achieve an SVR after prior DAA therapies except in those with HCV genotype 1b carrying NS5A-P32 deletion mutation [25]. Therefore, a 12-week combination of glecaprevir/pibrentasvir could successfully retreat patients who had neither HCV genotype 1b infection nor P32 deletion in the HCV NS5A region at baseline [11].

Other studies showed that the combination treatment of glecaprevir/pibrentasvir is less effective in subjects with HCV genotype 3 [7,27], although the 3 patients with HCV genotype 3 responded well in the present study. However, the small number of subjects limits this observation and additional studies are needed in HCV genotype 3 patient population.

We also demonstrated higher efficacy and safety for the combination treatment of glecaprevir/pibrentasvir in six patients with artificial dialysis. In general, patients with artificial dialysis have polypharmacy, and attention should be paid to the interaction between these drugs and DAAs in the combination treatment of NS3/4A inhibitors/NS5A inhibitors (Table 3). Pruritus may be associated with hemodialysis. Of interest, 4 of these 6 patients took nalfurafine hydrochloride for their pruritus. Pruritus was the most frequent adverse event (30.5%) among patients who had severe renal impairment and received the combination treatment of glecaprevir/pibrentasvir [28]. HCV infection is common in hemodialysis units [29]. Our data supported several HCV guidelines that the combination treatment of glecaprevir/pibrentasvir is highly effective for patients on dialysis [16–18].

We observed one treatment relapse after 8 weeks of combination treatment with glecaprevir/pibrentasvir. HCC occurred ~2 years after the commencement of 8-week combination treatment with glecaprevir/pibrentasvir. It was reported that the existence of HCC could be associated with DAA treatment failure [30].

In Japan, the national health insurance system has approved the combination treatment of glecaprevir/pibrentasvir for HCV-infected patients with chronic hepatitis or Child-Pugh A cirrhosis. So, we excluded HCV-infected patients with Child-Pugh B or C cirrhosis from this study. The Japanese national health insurance system has approved the 12-week combination treatment of sofosbuvir/velpatasvir for HCV-infected patients with Child-Pugh B or C cirrhosis [31].

Prophylactic HCV vaccines are under development, although they will be needed for successful global elimination of HCV infection [32,33]. Therefore, we should have several options to eradicate this virus. In the present study, approximately one third of the patient population had compensated cirrhosis, 91.2% were HCV DAA-treatment naïve, six were on dialysis, and the genotypes were 1 (52.9%), 2 (44.1%) and 3 (0.3%). Treatment outcomes were excellent with only one subject failing to achieve SVR.

Overall, the data provided is strong in showing that the non-clinical trial use of glecaprevir/pibrentasvir therapy is highly effective. The real-world clinical practice use of 8-week glecaprevir/pibrentasvir in treatment-naïve patients with compensated cirrhosis demonstrated that only one patient (0.5%) experienced virologic failure and treatment was well tolerated [34]. Our results are also consistent with those of the phase 3 trial from other countries [7,10,27]. There are several limitations, which include the retrospective nature of the work, the lack of a comparator group, and the exclusion of subjects with HIV and/or Child-Pugh B cirrhosis. Nevertheless, this study is reassuring and provides another real world study supporting the safety and efficacy of this combination HCV antiviral therapy [34].

5. Conclusions

In conclusion, the combination treatment of glecaprevir/pibrentasvir had a high efficacy and an acceptable safety profile for real-world HCV patients in the northern part of Tokyo, Japan. Treatment adherence was high regardless of the condition of the patients.

Author Contributions: Conceptualization, Y.Y. and T.K.; methodology, Y.Y. and T.K.; software, T.K.; validation, Y.Y. and T.K.; formal analysis, Y.Y. and T.K.; investigation, Y.Y., T.K., N.M., M.H., M.K., R.S., S.K., T.M., H.Y., R.M., T.I., K.N., M.M.; resources, Y.Y. and T.K.; data curation, Y.Y. and T.K.; writing—original draft preparation, T.K.; writing—review and editing, Y.Y. and T.K.; visualization, Y.Y. and T.K.; supervision, M.M.; project administration, T.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Nihon University School of Medicine Itabashi Hospital (protocol number RK-181009-04 approved by 16 April 2021; and RK-180911-12 approved by 16 April 2021).

Informed Consent Statement: Participation in the study was posted on the website of our institution, and informed consent was obtained from all patients.

Data Availability Statement: All data underlying this article are available in this article.

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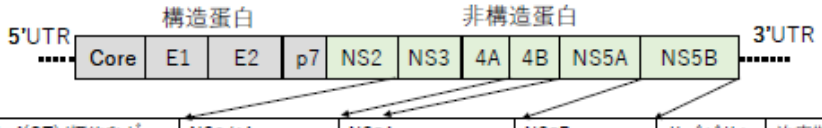
C 型慢性肝疾患患者に対するグレカプレビル/ピブレンタスビル併用療法の実臨床成績

【背景・目的】

C 型肝炎ウイルス(HCV)感染は、急性肝炎、慢性肝炎、肝硬変、肝細胞癌(HCC)や悪性リンパ腫の原因となることが知られている。抗ウイルス療法により HCV の持続陰性化 (Sustained virologic response[SVR])が得られるとこれら病態への進展・発症が防止可能である。

現在 C 型慢性肝疾患患者の治療は HCV に対する経口直接作用型抗ウイルス剤(Direct-acting antiviral [DAA])の内服が主流である(表 1)。DAA は単剤で使用すると容易に薬剤耐性変異(Resistance-associated substitutions [RASs])を生じるため、通常リバビリンと併用するか、2 種類以上の DAA を組み合わせて使用する。

表 1　本邦における C 型肝炎ウイルスに対する経口直接作用型抗ウイルス剤の治療標的などについて (2022 年 4 月現在)



ジェノタイプ(GT)/標的など	NS3/4A	NS5A	NS5B	リバビリン	治療期間
GT1/GT2		レジパスビル	ソホスブビル	なし	12週間
GT2			ソホスブビル	あり	12週間
All GTs	グレカプレビル	ピブレンタスビル		なし	8/12週間
GT1, GT2以外			ソホスブビル	あり	24週間
All GTs		ベルパタスビル	ソホスブビル	なし/あり	12/24週間

本邦を含む治験によると、C 型慢性肝疾患患者に対する HCV 非構造タンパク質 NS3/4A 阻害剤グレカプレビル/HCV NS5A 阻害剤ピブレンタスビル併用療法は、8-12 週間と短い治療期間で、比較的少ない有害事象で、100%に近い高い SVR 率が示されている。しかし、実臨床における実態は不明である。

慢性腎臓病(CKD)患者や透析患者における HCV 感染率は一般人口より高いことが知られている。 CKD 患者や透析患者でも HCV の積極的な排除がその予後を改善する(日本肝臓学会肝炎診療ガイドライン作成委員会. C 型肝炎治療ガイドライン [第 8 版])。Estimated glomerular filtration rate (eGFR) 50 および 30 mL/分/1.73 m^2 未満の CKD 患者・透析患者に対するリバビリンおよび HCV NS5B 阻害剤ソホスブビルの使用はそれぞれ禁忌である。一方、グレカプレビル/ピブレンタスビルは肝代謝を受ける薬剤であ

り、透析患者における使用制限がなく、C 型非代償性肝硬変や HCC 併発症例を除く HCV 感染 CKD 患者や透析患者に使用可能である(表 2)。

表 2　本邦における C 型肝炎ウイルスに対する Estimated glomerular filtration rate (eGFR)別経口直接作用型抗ウイルス剤(DAA) (2022 年 4 月現在)

DAAレジメ	eGFR (mL/分/1.73 m²)
グレカプレビル/ピブレンタスビル	制限なし
ソホスブビル/リバビリン	50以上
ソホスブビル/ベルパタスビル/リバビリン	50以上
ソホスブビル/ベルパタスビル	30以上
ソホスブビル/レジパスビル	30以上

本研究では、日本大学医学部附属板橋病院消化器・肝臓内科における C 型慢性肝疾患患者に対するグレカプレビル/ピブレンタスビル併用療法の治療効果および有害事象を含む実臨床成績を明らかにすることを目的とした。

【対象・方法】

2017 年 11 月 1 日から 2019 年 8 月 31 日まで日本大学医学部附属板橋病院消化器・肝臓内科にてグレカプレビル/ピブレンタスビル併用療法を開始した 106 名の C 型慢性肝疾患患者(C 型慢性肝炎または C 型代償性肝硬変[Child Pugh A、6 点以下]患者)を対象とした後向き研究である。

インターフェロンフリー経口内服グレカプレビル(300 mg/日)/ピブレンタスビル(120 mg/日) 併用療法は 8 週間または 12 週間施行した。本邦では、原則として経口直接作用型抗ウイルス剤(Direct-acting antivirals [DAAs])未使用の HCV Genotype (GT)1/2 の慢性肝炎に対しては 8 週間治療を施行し、HCV GT1/2 代償性肝硬変患者、HCV GT1/2 DAA 既使用者および HCV GT1/2 以外の感染者に対しては 12 週間治療を施行する。DAA 既治療無効 HCV GT1b 患者に関しては、治療前の HCV NS5A P32 欠損を調べ治療対象から除外した。8 週間または 12 週間の選択は基本的にこのような適応基準に従い、実臨床下で主治医が決定した。

治療効果は治療終了後 12 週目における HCV RNA 持続陰性化(SVR at week 12 [SVR12])にて判定した。有害事象に関しても可能な限り、詳細に診療録を調査、検討した。

統計解析は Student's t test または chi-square test で行い、$p<0.05$ で有意差有と判定した。本研究は日本大学医学部板橋病院臨床研究倫理審査委員会（プロトコール番号 RK-181009-04 および RK-180911-12）の承認を得た。

【結果】

1) グレカプレビル/ピブレンタスビル併用療法を施行し、SVR12 が判定可能であった合計 102 名の患者を解析対象として、治療の有効性を検討した。SVR12 判定困難例 4 名は除いた。
2) 本治療による SVR 率は 101/102 (99%)と高率であった。
3) 肝硬変のない 1 名が、グレカプレビル/ピブレンタスビル 8 週間併用療法後に再燃し、約 2 年後に HCC の肝切除術を受けた。
4) DAA 治療歴のある HCV 遺伝子型 1b 患者で NS5A 領域 P32 欠損変異を除外した後、グレカプレビル/ピブレンタスビル 12 週間併用療法を行ったところ、DAA 既治療例の SVR 率は 9/9(100%)であった。
5) 透析施行中患者での SVR 率は 6/6 (100%)と非常に高率であった。4/6 (66.7%)で有害事象として皮膚掻痒感が見られた。
6) 有害事象のために治療を中止したのは 3 名のみであったが、この 3 名は全員とも最終的に SVR12 を達成した。

【考察】

本研究では、グレカプレビル/ピブレンタスビル併用療法を 106 例に施行し、SVR 率は 101/102(99%）と高率であった。1 名のみが、8 週間併用療法後に再燃し、約 2 年後に HCC の肝切除術を受けた。この症例の薬剤アドヒアランスは良好であった。

本邦のグレカプレビル/ピブレンタスビル療法を施行した 1439 名を解析した実臨床における研究(Nozaki A, et al. Hepatol Int. 2020 Mar;14(2):225-238.)では、多変量解析で非 SVR とと関連する因子として、HCV GT3 感染(OR, 33.404; 95%CI, 7.512-148.550; $p=4.06\times10^{-5}$)と過去のインターフェロンフリー DAA 加療歴(OR, 3.997; 95%CI, 1.153-13.725; p=0.029)を報告している。本研究の再燃例は治療前の γ-GTP 値が 236 IU/L と高値で飲酒歴(連日 Beer 700 mL/日)を認めた慢性肝炎例であった。再燃例が少なく、非 SVR との関連因子に関しては今後の検討課題の一つである。

本邦における第 3 相治験では DAA 未治療 C 型慢性肝炎患者および C 型肝硬変を対象としたグレカプレビル/ピブレンタスビル 8 週間併用療法では、SVR 率はそれぞれ 128/129(99.8%; 1 例は経過観察不能例)および 38/38(100%)と報告されている(Chayama K, et al. J Gastroenterol. 2018 Apr;53(4):557-565.)。本実臨床研究

では、グレカプレビル/ピブレンタスビル併用療法でもSVRの得られない症例の存在を示した。また再燃した患者はHCV NS3/4A阻害剤グラゾプレビル/HCV NS5A阻害剤エルバスビル併用12週間併用療法による再治療でSVR24が得られているため、グレカプレビル/ピブレンタスビル12週間併用療法が有効であった可能性が高い。治療期間については今後検討を要する。

本研究で観察された再燃1名のリンパ球・好中球比(Neutrophil to Lymphocyte Ratio [NLR])を検討すると、グレカプレビル/ピブレンタスビル併用療法施行前: 0.922および1.318、End of Treatment (EOT)時: 1.013、再燃時: 0.995、HCC初発時: 2.069、HCC術後: 1.220および1.072、グラゾプレビル/エルバスビル再治療前: 1.675、再治療EOT時: 1.656、SVR12時1.510およびHCC再発時:1.946であり、グレカプレビル/ピブレンタスビル併用療法施行前では低値であり、HCC初発および再発時でやや高値であり、HCC術後で低下していたことは臨床免疫学的に興味深く思えた。NLRは近年PD-1阻害剤の治療効果との関連が示唆されており、非小細胞肺癌ではNLR低値グループの予後が良好であったとの報告もみられる(Zer A, et al. Clin Lung Cancer. 2018 Sep;19(5):426-434.e1.)。NLRがPD-1発現を反映している可能性もあるが、今後、更なるウイルス学的および臨床免疫学的解析が必要と考えられた。DAAによるSVRによる長期的な免疫能の回復は、肝発癌等の防止に役立つと考えられるが、SVR前後には急激な免疫能の変化が観察されるため、感染症悪化やHCC発症には十分注意する必要がある(Sasaki R, et al. J Med Virol. 2019 Mar;91(3):411-418. Ikegami C, et al. In Vivo. 2022 in press)。

HCV GT1b患者でDAA既治療無効例、特にHCV NS3/4A阻害剤アスナプレビル/HCV NS5A阻害剤ダクラタスビル併用療法無効例ではHCV NS5A L31およびY93二重変異に加えてP32欠損がNS5A阻害剤抵抗性に寄与することが報告されている(Izumi N, et al. Hepatol Int. 2018 Jul;12(4):356-367.)。特にHCV NS5A P32欠損がHCV GT1b患者でピブレンタスビル無効に関与することが報告されている(Kumada H, et al. J Gastroenterol. 2018 Apr;53(4):566-575.)。なおこの変異はDAA未使用例には存在しないとされる。本研究では、DAA治療歴をもつHCV遺伝子型1b患者でNS5A領域P32が欠損している患者を除外した後、12週間治療を施行したところ、DAA治療歴をもつ患者全員がSVR12を達成した。

過去の報告では100名の透析患者におけるグレカプレビル/ピブレンタスビル併用療法の検討ではSVR率は99/100(99%)と報告されている(Atsukawa M, et al. Aliment Pharmacol Ther. 2019 May;49(9):1230-1241.)。また同報告では、有害事象として最も多く見られた事象は皮膚掻痒感であり、CKD Stage 5では36/109(33%)と報告されている。今回の我々の検討では、過去の報告と同様、同治療による透析施行中患者のSVR率は6/6(100%)と非常に高いものであった。一方、我々の検討では4/6(66.7%)が比較的強い皮膚掻痒感を訴えNalfurafine hydrochroride の

使用を必要としており、過去の報告より皮膚掻痒感の頻度は高いものであった。Nalfurafine hydrochroride は透析中の皮膚掻痒感に対して既に使用されていることもあり、グレカプレビル/ピブレンタスビル併用療法による皮膚掻痒感を過小評価する一因となっている可能性がある。

有害事象のために治療を中止したのは 3 名のみであったが、この 3 名は全員とも最終的に SVR12 を達成した。また 3 名とも糖尿病および肝硬変を併発していた。本邦からの報告では、B 型慢性肝炎(n=286)、C 型慢性肝炎(n=544)および SVR 後の C 型慢性肝炎(n=122)における糖尿病の頻度はそれぞれ 6.3%、13.6%および 9.0%であり、B 型慢性肝炎と比較し C 型慢性肝炎では有意に糖尿病の頻度が高いことが報告されている($p<0.05$)(Imazeki F, et al. Liver Int. 2008 Mar;28(3):355-62.)。3 名はそれぞれ 63 歳男性、74 歳女性および 85 歳女性であり、黄疸、黄疸および脳出血のため治療中止となっていた。本邦のグレカプレビル/ピブレンタスビル併用療法を施行した 1439 名を解析した実臨床における研究(Nozaki A, et al. Hepatol Int. 2020 Mar;14(2):225-238.)では、多変量解析で有害事象と関連する因子として、慢性腎臓病(CKD、stage 4 または 5)(OR, 2.339; 95%CI, 1.665-3.285; $p=9.47x10^{-7}$)、肝硬変(OR, 1.450; 95%CI, 1.079-1.947; p=0.014)、過去のインターフェロンフリー DAA 加療歴(OR, 1.533; 95%CI, 1.091-2.155; p=0.014)を報告している。我々の 3 名ではいずれも肝硬変を併発していた。HCV による肝硬変患者では HCV 陰性コントロールと比較して 2 型糖尿病の有病率が 3.37 倍高いというメタ解析結果もある(Chen Y, et al. Dig Dis Sci. 2020 Jul;65(7):1940-1950.)が、有害事象と糖尿病については今後さらに検討する必要がある。

本研究の再燃例は治療終了後しばらく個人的な理由で来院をされていなかった。再来時には肝細胞癌が出来ていた。SVR 症例を含めた治療後の経過観察は非常に重要である。HCV 感染者の拾い上げやバイオマーカーの開発などは今後検討すべき重要課題と考えられた。

【結論】

C 型慢性肝疾患患者に対するグレカプレビル/ピブレンタスビル併用療法の実臨床成績を検討したところ SVR12 率は 99%と非常に高いものであった。透析例や HCV NS5A P32 欠損例を除外後の DAA 治療歴のある患者での SVR12 率は 100%であった。本研究結果は Phase 3 臨床試験の結果同様にグレカプレビル/ピブレンタスビル併用療法の非常に高い有効性を支持した。しかし、脳出血、黄疸など重篤な有害事象や透析例における強い皮膚掻痒感出現等の有害事象もみられるため、慎重な投与、経過観察が必要であることが再認識された。