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【 CASE REPORT 】

Japanese Man with HCV Genotype 4 Infection and Cirrhosis Who Was Successfully Treated by the Combination of Glecaprevir and Pibrentasvir

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Abstract:
A 74-year-old man with a history of transfusion at 35 years old in Egypt was referred to our hospital. He was infected with hepatitis C virus (HCV) genotype 4 (GT4), which is a rare HCV GT in Japan, and was also diagnosed with hepatic compensated cirrhosis. We safely treated the patient for 12 weeks with the combination of glecaprevir and pibrentasvir, and a sustained virologic response (SVR) was achieved. This is the first report of HCV GT4 infection in a treatment-naïve Japanese patient with cirrhosis in whom SVR was achieved with the combination treatment of glecaprevir and pibrentasvir.

Key words: cirrhosis, DAA, HCV genotype 4, Japan, transfusion

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Introduction

Hepatitis C virus (HCV) infection induces acute and chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma (HCC) and other extrahepatic manifestations. HCV infection is still a leading cause of HCC in Japan (1). Although effective direct-acting antivirals (DAAs) against HCV have been introduced, making it now easier to achieve a sustained virologic response (SVR) in daily clinical practice, several issues need to be addressed, such as the risk of hepatocarcinogenesis after the achievement of SVR and the long-term prognosis (2, 3).

At present, eight HCV genotypes (GTs) are known to exist (4-6). In Japan, HCV GT1b, GT2a and GT2b have a prevalence of 70%, 20% and 10%, respectively (7). HCV GT4, which is a major genotype in Egypt, is a rare HCV GT in Japan (8). A previous study demonstrated that 0.4% (4/899) of patients infected with HCV have HCV GT4 in Aichi Prefecture, Japan, and these 4 patients with HCV GT4 were hemophilic men who had received blood products from foreign countries (8).

In Japan, the HCV nonstructural protein (NS) 5B inhibitor sofosbuvir-based DAA combination, the combination of the HCV NS3/4A inhibitor glecaprevir and HCV NS5A inhibitor pibrentasvir, and the combination of the HCV NS3/4A inhibitor grazoprevir and HCV NS5A inhibitor elbasvir are available for the treatment of HCV-infected individuals (9-15). The Japanese National Health Insurance system has recommended the combination of sofosbuvir and ribavirin for 24 weeks or the combination of glecaprevir and pibrentasvir for 12 weeks as the treatment for patients infected with HCV GTs other than GT1 or GT2. However, there are no clinical trials analyzing the effects of the combination of glecaprevir and pibrentasvir on patients with HCV GT4 in Japan, so this combination's efficacy in Japa-

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Table 1. Laboratory Data before Starting the Combination Treatment of Glecaprevir and Pibrentasvir in the Present Case.

Item	Values	Item	Values	Item	Values
Peripheral Blood		**Biochemistry**			
WBC	3,900 /μL	AST	160 IU/L	NH_3	29 μg/dL
RBC	497×10⁴ /μL	ALT	225 IU/L	CRP	0.10 mg/dL
Hemoglobin	15.7 g/dL	LDH	275 IU/L	AFP	86.7 ng/mL
Platelets	12.1×10⁴ /μL	ALP	238 IU/L	PIVKA-II	16 mAU/mL
Coagulation system		γ-GTP	81 IU/L	**Serology**	
PT	84 %	T. Bil	0.53 mg/dL	HBsAg	Negative
INR	1.09	TP	7.0 g/dL	Anti-HBs	Negative
		Albumin	3.6 g/dL	Anti-HBc	Negative
		BUN	20.2 mg/dL	Anti-HCV	Positive
		Creatinine	0.70 mg/dL	HCV RNA	5.4 LIU/mL
		Glucose	214 mg/dL	HCV GT	4a
		HbA1c	7.3 %	Anti-HIV	Negative

WBC: white blood cells, RBC: red blood cells, PT: prothrombin time, INR: international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, T. Bil: total bilirubin, TP: total protein, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, NH_3: ammonia, CRP: C-reactive protein, AFP: alpha fetoprotein, PIVKA-II: protein induced by vitamin K antagonist-II, HBsAg: hepatitis B surface antigen, Anti-HBs: anti-hepatitis B surface antibody, Anti-HBc: anti-hepatitis B core antibody, Anti-HCV: anti-hepatitis C virus antibody, GT: genotype, Anti-HIV: anti-human immunodeficiency virus antibody

nese patients with HCV GT4 is unclear (14). However, of note, it was reported that SVR rates were more than 90-95% in HCV GT4-infected Egyptian patients treated with combinations of DAAs (16).

We herein report the interferon-free, 12-week combination treatment with glecaprevir and pibrentasvir that successfully led to an SVR in a treatment-naïve Japanese patient with HCV GT4 infection and hepatic cirrhosis.

Case Report

A 74-year-old man was referred to our hospital because of his positivity for HCV RNA and undetermined HCV genotype to receive treatment to eradicate the virus. In the outpatient clinic, he had shown no symptoms. He had a history of transfusion for typhoid fever at 35 years old in Egypt. He had been diagnosed with positivity for anti-HCV antibody 10 years ago at a clinic near his house in Japan, but he did not receive any antiviral treatment, including interferon or DAAs. He had been receiving irbesartan (100 mg daily) and amlodipine besilate (10 mg daily) for his hypertension and metformin hydrochloride (500 mg daily) for type 2 diabetes mellitus but had no history of surgery. He also had no history of tattooing, drug abuse, or drug allergy. He was a social drinker, and his family had no history of liver disease.

A physical examination showed no signs of ascites, lower leg edema, or disturbance of consciousness. The cirrhotic liver was slightly palpable at his right hypochondrium. Laboratory data before treatment are shown in Table 1. Reduced platelet counts and elevated transaminase levels were observed. His Child-Pugh classification was Grade A (score 5). Although the alpha-fetoprotein level was elevated, no space occupying lesions were detected in the cirrhotic liver by ultrasound or contrast-enhanced computed tomography (Fig. 1). Hepatic ultrasound elastography showed values of 34.3 kPa and 26.1 kPa on a FibroScan 502 with an M probe (Echosens, Paris, France) and shear wave measurement (ARRIETTA 850; Hitachi Medical Systems, Tokyo Japan), respectively, and these values were compatible with hepatic cirrhosis. Upper gastrointestinal endoscopy demonstrated a solitary varix of the esophagus and no varices of the stomach (Fig. 2). We diagnosed him with compensated cirrhosis due to HCV infection without a liver biopsy.

HCV RNA was extracted from his sera before treatment, and nested reverse transcription polymerase chain reaction (RT-PCR) and direct sequencing were performed. Using the HCV-5'-untranslated region-core region (655 nt.) and HCV NS5B region (502 nt.), HCV GT4a infection was confirmed by a phylogenetic tree analysis with the neighbor-joining method (Fig. 3). The primers in the present study were used as previously described (17).

As recommended by the Japanese National Health Insurance system, he received the 12-week oral combination treatment of glecaprevir (300 mg daily) and pibrentasvir (120 mg daily), without any evident adverse events. HCV RNA was not detected at the end of treatment or at 24 weeks after the end of treatment, indicating that he had achieved an SVR at week 24 (Fig. 4). Furthermore, the serum albumin level had also improved to 4.3 g/dL.

Discussion

We herein report a treatment-naïve Japanese man with

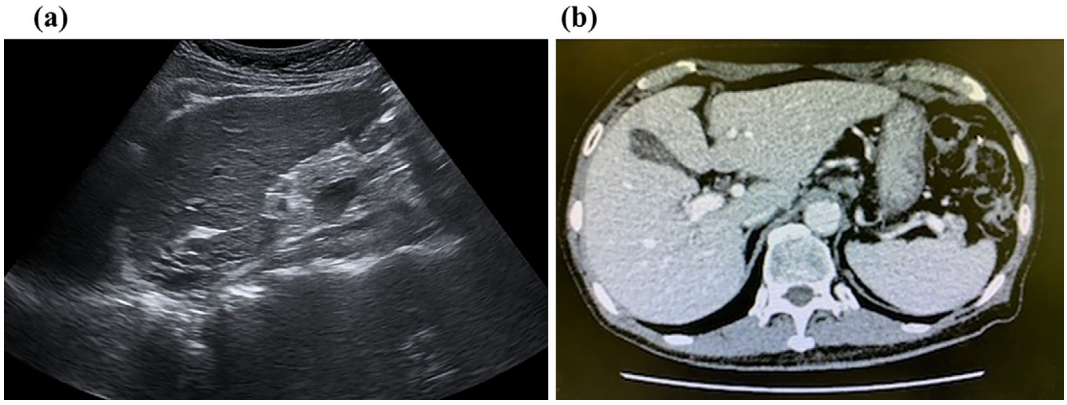

Figure 1. **Findings of abdominal ultrasound (US) (a) and computed tomography (CT) (b). (a) US showed a cirrhotic liver with coarse parenchymal pattern, irregular surface, and dull edge but no space-occupying lesions. (b) Contrast-enhanced CT in the portal-dominant phase showed an irregular surface of the liver and splenomegaly with mild dilatation of the paraumbilical vein but no ascites.**

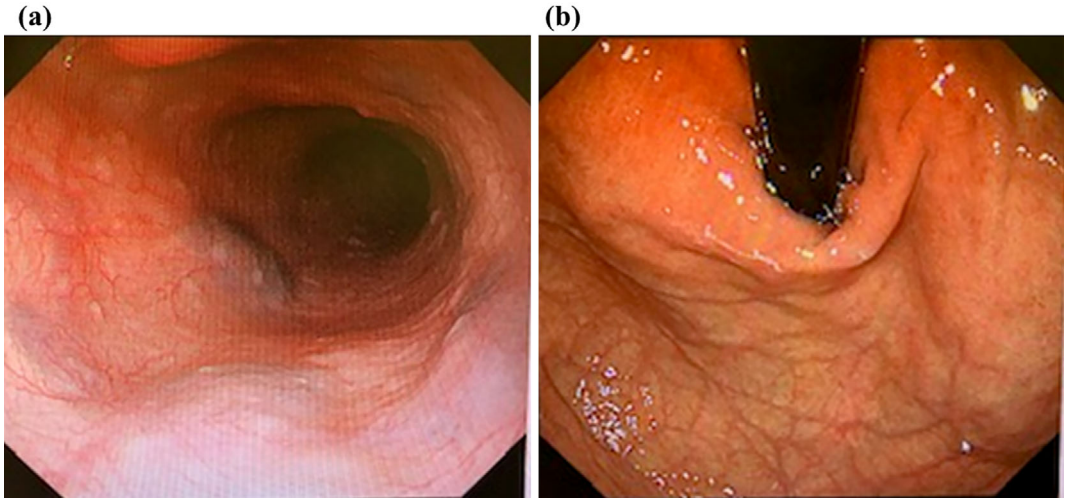

Figure 2. **Findings of upper gastrointestinal endoscopy. (a) Solitary varix of the esophagus. (b) No varices of the stomach.**

HCV GT4a infection and hepatic cirrhosis who successfully achieved an SVR with the 12-week combination treatment of glecaprevir and pibrentasvir. The present report is likely to be the first report of the 12-week combination treatment of glecaprevir and pibrentasvir being effective for a Japanese patient with HCV GT4a infection and hepatic cirrhosis.

It was recently reported that eight HCV GTs exist (4-6). In Egypt, the prevalence of anti-HCV positive rates is relatively high (14.7% in a 2008 nationwide survey) (18), and anti-schistosomal parenteral therapy and blood transfusion are risk factors for HCV infection (7). In Egypt, HCV GT4a, GT4b, GT1, and GT3 have a prevalence of 63%, 30%, 6%, and 1%, respectively (7). The present patient had a history of transfusion in Egypt before 1989, when HCV was discovered by molecular biological methods (19, 20). As HCV GT4a infection is rare in Japan (8) and hemophilia does not run in his family, the route of infection for HCV GT4a in this patient was deemed likely to be the transfusion he had undergone in Egypt.

The combination of glecaprevir and pibrentasvir is a pangenotypic DAA therapy for HCV infection. In Japanese clinical trials, 12-week combination treatment of glecaprevir and pibrentasvir for patients with HCV GT1b and GT2 with compensated cirrhosis showed an SVR at week 12 of 100% (38/38) and 100% (18/18), respectively (12, 13). Forns et al. reported an SVR at week 12 of 100% (16/16) in the phase 3 study of the 12-week combination treatment of glecaprevir and pibrentasvir for HCV GT4 patients with compensated cirrhosis (EXPEDITION-1) (21).

In general, the SVR rates in HCV GT4-infected patients treated with the combination of glecaprevir and pibrentasvir are reported to range from 95.5-100% (Table 2) (22-32). In Japan, clinical trials of this combination treatment for HCV GT4 have not been performed. The 8-week combination treatment of glecaprevir and pibrentasvir for HCV GT4 treatment-naïve patients with compensated cirrhosis led to 100% SVR rates (24, 25), although the 12-week combination treatment of glecaprevir and pibrentasvir for HCV GT4

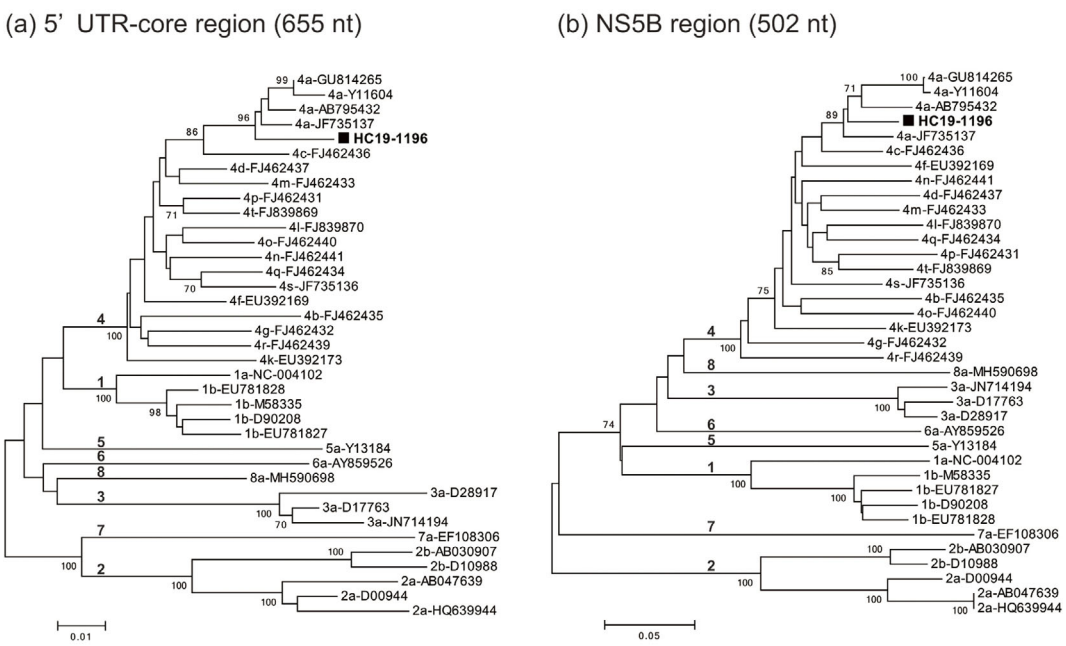

Figure 3. **The phylogenetic trees constructed by the neighbor-joining method based on the hepatitis C virus (HCV)-5'-untranslated region (5'-UTR)-core region sequence (655 nt.) (a) and HCV-non-structural protein (NS)5B region sequence (502 nt.) (b) of the HCV isolated from the present case (HC19-1196) as well as HCV strains of genotypes (GTs) 1-8. In addition to the isolated strain (HC19-1196/black square), 36 representative HCV strains are shown, including the HCV GT, subgenotype, and accession number. Bootstrap values (≧70%) are indicated for the nodes as a percentage of the data obtained from 1,000 resamplings. The scale bar is in units of nucleotide substitutions per site. The nucleotide sequences of the 5'-UTR-core region and NS5B of HC19-1196 are deposited as LC594551 and LC594552, respectively, in the DDBJ/GenBank databases.**

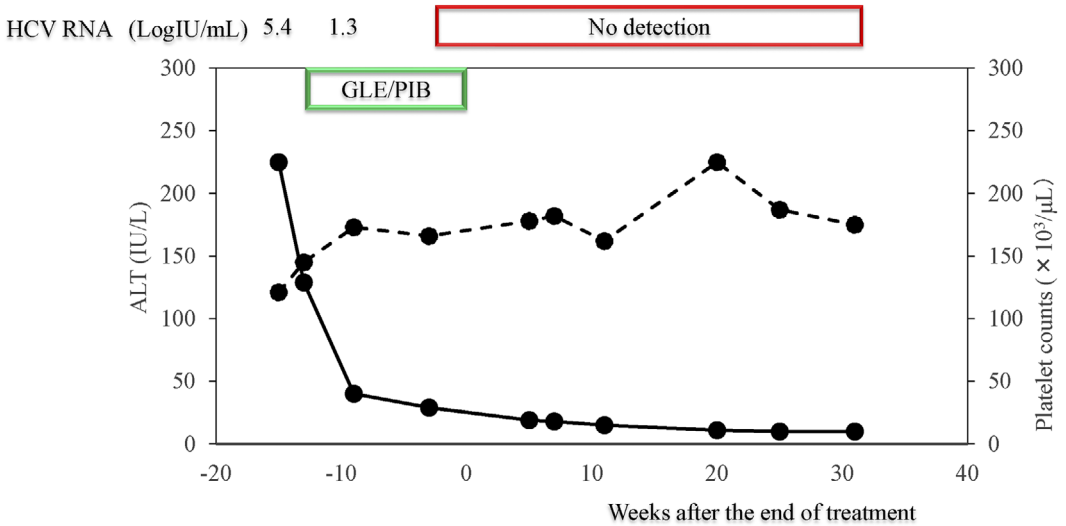

Figure 4. **Clinical course of the present case. The combination of 300 mg daily of glecaprevir (GLE) and 120 mg daily of pibrentasvir (PIB) was given for 12 weeks. Solid line: ALT levels, Dotted line: Platelet counts.**

in treatment-naïve patients with non-cirrhosis or cirrhosis led to 97.8% SVR rates (29) (Table 2). The ideal duration of this combination treatment should be further examined in the future.

Shiha et al. reported that the SVR rates after 12 and 24 weeks of 400 mg daily sofosbuvir plus 60 mg daily daclatasvir (HCV NS5A inhibitor), with or without 800-1,000 mg daily ribavirin, were 96% and 93%, respectively, in Egyptian patients with HCV GT4 (33). In combination treatment with 400 mg daily sofosbuvir and 90 mg daily le-

Table 2. Sustained Virological Response Rates in HCV Genotype 4-infected Patients Treated with the Combination of Glecaprevir and Pibrentasvir.

Reference	Country	Type of diseases	Treatment duration (weeks)	SVR12 rates (SVR/Total patients)
22	Italy	Non-LC, LC	8-16	100% (32/32)
23	Israel	Non-LC, CC	8	95.5% (63/66)
24	USA	CC	8	100% (2/2)
25	USA	CC	8	100% (13/13)
26	UK	Non-LC, CC	8-16	99.4% (161/162)
27	USA	Non-LC, LC (12-17 years)	8	100% (3/3)
28	Germany	Non-LC, LC	8-12	96.3% (26/27)
29	Australia	Non-LC, LC	12	97.8% (174/178)
30	UK	Non-LC, CC	8-16	97.8% (178/182)
31	Italy	Non-LC, LC	8	100% (71/71)
32	USA	Non-LC, CC	8-12	100% (175/175)
Our report	Japan	CC	12	100% (1/1)

HCV: hepatitis C virus, SVR: sustained virological response, LC: liver cirrhosis, CC: compensated cirrhosis

dipasvir (HCV NS5A inhibitor), the SVR rates were 98% and 94-98%, respectively, in treatment-naïve and treatment-experienced patients with HCV GT4 (16). Abd-Elsalam et al. reported that the SVR rate of the 24-week combination treatment of sofosbuvir and ribavirin was only 71.2% in 2,400 Egyptian patients with HCV GT4 infection and cirrhosis (34), and Ahmed et al. reported that the SVR rate of the 12-week combination treatment of sofosbuvir and velpatasvir (HCV NS5A inhibitor) was 99.6% in 120 HCV GT4-infected patients (35).

The SVR rates of DAAs are known to be affected by several factors, such as the existence of HCV GTs, cirrhosis and/or HCC, and IL28B genotype (36-38). HCV NS5A resistance-associated substitutions (RASs), such as P32 deletion and R30E/Q54H/A92K, have effects on the treatment efficacy in patients with HCV GT1b treated with the combination of glecaprevir and pibrentasvir (39). Further studies will be needed to confirm the influence of these factors.

The present case was a treatment-naïve patient; however, an increased prevalence of RASs in treatment-experienced patients with HCV GT4 has been observed (40). Close attention should be paid to these situations in the treatment of HCV GT4-infected patients.

In Japan, 24-week combination treatment of sofosbuvir and ribavirin or 8-week combination treatment of glecaprevir and pibrentasvir is available for patients with HCV GT4 infection without cirrhosis. Patients with HCV GT4 infection and compensated cirrhosis can be treated with the 24-week combination of sofosbuvir and ribavirin or the 12-week combination of glecaprevir and pibrentasvir. We also can use the 12-week combination of sofosbuvir and velpatasvir for patients with decompensated cirrhosis. It is better for patients with HCV GT4 infection and non-cirrhosis to be treated with the 8-week combination of glecaprevir and pibrentasvir than the 12-week combination. At present, the American Association for the Study of Liver diseases (AASLD) recommends the 8-week combination treatment of glecaprevir and pibrentasvir for treatment-naïve patients with HCV GT4 infection and compensated cirrhosis (41).

In conclusion, we encountered a Japanese case of HCV GT4 infection and cirrhosis that was successfully treated with the 12-week combination of glecaprevir and pibrentasvir. To our knowledge, this is the first documentation of the 12-week combination of glecaprevir and pibrentasvir for an HCV GT4-infected Japanese patient.

Author's disclosure of potential Conflicts of Interest (COI).
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