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CASE REPORT

Successful prolonged treatment of glecaprevir/pibrentasvir for chronic hepatitis C patient with treatment failure after 8-week therapy: a case report

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Abstract
Direct-acting antiviral agent (DAA)-based therapies have been the 1st choice of antiviral agents for chronic hepatitis C throughout the world. The treatment period of DAA-based therapy has been greatly shortened by the improvement of their efficiency. Thus, glecaprevir (GLE)/pibrentasvir (PIB) therapy has enabled the therapeutic period to be reduced from 12 to 8 weeks in cases of genotype 1 or 2 chronic hepatitis C without liver cirrhosis. Currently, there is no established rescue therapy for patients who experience treatment failure on GLE/PIB therapy; however, some patients have been rescued by other regimens, including sofosbuvir (SOF)/velpatasvir (VEL) plus ribavirin (RBV) therapy and GLE/PIB, SOF, and RBV therapy. We experienced the case of a DAA-naïve non-cirrhotic patient with genotype 2a who showed virologic relapse at post-treatment week 13 following 8-week GLE/PIB therapy. After we confirmed that he did not have resistance-associated substitutions against GLE or PIB, we tried to rescue the patient using prolonged (12-week) GLE/PIB therapy. Fortunately, a sustained virologic response was achieved without any adverse events. Although this was a single-case report and is assumed to be rare, the same regimen might be effective for treatment failure with 8-week GLE/PIB therapy.

Keywords Chronic hepatitis C · Direct-acting antiviral agents · Rescue therapy · Treatment failure · Treatment period

Introduction

Direct-acting antiviral agent (DAA)-based anti-HCV therapies have been in widespread use and are the 1st choice of antiviral agents for chronic hepatitis C throughout the world. In Japan, sofosbuvir (SOF)/ledipasvir (LDV), elbasvir (EBR)/grazoprevir (GZR), and glecaprevir (GLE)/pibrentasvir (PIB) therapies are the 1st choice of antiviral agents for chronic hepatitis C in the most recent Japan Society of Hepatology (JSH) guideline (ver. 6.2). In these three combination therapies, the treatment period is principally 12 weeks, with the exception of GLE/PIB therapy in a certain population of patients. GLE/PIB therapy enabled the therapeutic period to be reduced from 12 to 8 weeks in cases of genotype 1 or 2 chronic hepatitis C without liver cirrhosis. A sustained virologic response at 12 week post-treatment (SVR12) could be achieved in ≥ 98% of DAA-naïve patients with genotype 1 or 2 who received GLE/PIB therapy, regardless of the presence of liver cirrhosis in the intention to treat (ITT) population [1, 2]. Three patients with genotype 1 and 2 who could not achieve an SVR12 were lost to follow-up after achieving an SVR4 or was discontinued due to an adverse event after 18 days of therapy [1, 2]. Given that no virologic failures were observed in these subjects, the efficacy of GLE/PIB therapy is quite high. However, we experienced one DAA-naïve non-cirrhotic patient with genotype 2 who showed a

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virologic relapse at post-treatment week 13 after 8-week GLE/PIB therapy.

Currently, two treatment regimens are covered by insurance for patients with DAA failure in Japan: GLE/PIB therapy and SOF/velpatasvir (VEL) plus ribavirin (RBV) therapy that has become available more recently. Both regimens have high efficacy and are promising [3, 4]. However, SOF/VEL plus RBV therapy has some notable drawbacks: RBV-containing regimens are likely to cause adverse events such as anemia, the treatment period is relatively long (24 weeks), and so on.

We herein describe a case in which a patient with virologic relapse following 8-week GLE/PIB therapy was successfully rescued by 12-week GLE/PIB therapy. Although this is the single-case report, our case teaches us a great lesson about the selection of the "rescue" regimen in cases of DAA failure. The patient provided his informed consent for publication of this case report.

Case report

A 78-year-old man was referred to our hospital for DAA-based therapy for hepatitis C virus (HCV). The patient had received artificial valve replacement for mitral valve insufficiency in another hospital 1 year previously and anti-HCV antibody positivity was first pointed out at this point. Thereafter, he was followed up for chronic atrial fibrillation by primary care physician and his serum HCV RNA titer was found to be 6.8 log IU/mL by a TaqMan HCV Test v2.0 real-time polymerase chain reaction (PCR) (F. Hoffmann, La Roche Ltd., Basel, Switzerland). Although he received partial gastric resection due to gastric cancer at age 64 years as the previous medical history, the source of HCV transmission was unknown. His laboratory data showed that the serum alanine aminotransferase (ALT) level and Mac-2-binding protein glycosylation isomer (M2BPGi) level were within the normal limits at the initial visit to our hospital. Thus, the extent of liver fibrosis was not considered to have reached the advanced stage. His HCV genotype, which was determined in commercial laboratories (BML, Inc., Tokyo, Japan), was 2a. At the time, SOF/RBV therapy was the only treatment available for patients with genotype 2 HCV in Japan. As he was elderly and had chronic cardiac disease, we waited for GLE/PIB therapy to become available. After GLE/PIB therapy received insurance coverage in Japan, the therapy was introduced to the patient. A rapid virologic response (RVR) was not achieved; however, the serum HCV RNA level finally became undetected after 6 weeks of therapy. Although the serum HCV RNA level remained undetectable at post-treatment week 7, it became positive at post-treatment week 13. We judged that a virologic relapse had occurred. Then, the patient was evaluated for resistance-associated substitutions (RASs), specifically G15, Y56, A156, and D168 in HCV/2a-NS3 for GLE [5], and F28, P29, K30, and M31 in HCV/2a-NS5A for PIB [6]. The genome sequences were analyzed using serum samples after 8-week GLE/PIB therapy and before 12-week GLE/PIB therapy. PCR amplification, followed by direct sequencing, was performed to determine the RASs. Table 1 shows the primers used for cDNA synthesis and amplification. No RASs against GLE or PIB were detected. We decided to use the same regimen, that is GLE/PIB therapy, but the treatment period was prolonged from 8 to 12 weeks. Once again, an RVR was not achieved; however, the serum HCV RNA level was undetectable at the 8th week of therapy. Thereafter, the serum HCV RNA level remained undetectable and an SVR12 was finally achieved. There were no adverse events during therapy. Drug adherence was 100% and treatment was well-tolerated. The laboratory findings, treatments, and outcomes are shown in Table 2. The time course of the two series of GLE/PIB therapy in this case is shown in Fig. 1.

Table 1 Primers used for the amplification of the NS3 and NS5A regions of the genotype 2a HCV genome

Primer name	Sequence (5′ to 3′)[a]	Nucleotide position[b]	Notes
HCV/2a-NS3 region			
HC686	GTGGARCCYATYATCTTCAGTC	3263–3284	1st sense
HC687	GYACAGCHGGYGGYGTGCTG	3991–4010	RT and 1st antisense
HC688	TYATCTTCAGTCCGATGGAG	3273–3292	2nd sense
HC689	HGGYGGYGTGCTGTTGTCAC	3984–4003	2nd antisense
HCV/2a-NS5A region			
HC694	YGCTTCCAGAGGAAACCACG	6118–6137	1st sense
HC695	AGCCCRACGCWRAACGAGAC	6785–6804	RT and 1st antisense
HC696	ACYCAYTACGTGACGGAGTC	6146–6165	2nd sense
HC697	CWRAACGAGACCTCRTCCCG	6776–6795	2nd antisense

[a] R = A/G, H = A/C/T, W = A/T and Y = T/C

[b] Nucleotide positions are numbered in accordance with the HC-J6 strain (D00944) as the HCV/2a reference

Table 2 Laboratory findings at baseline, treatments, and patient outcomes

Parameters	Case
Age (years)	78
Sex	Male
BMI (kg/m^2)	18.4
HCV genotype	2a
IFN-based therapy: outcome	Naïve; NA
DAA-based therapy: outcome	8-week GLE/PIB: relapse at PTW13
At the start of therapy	
HCV RNA (log IU/mL)	6.9
AST (IU/L)	34
ALT (IU/L)	24
WBC (cells/μL)	6000
Hemoglobin (g/dL)	12.9
Platelets (cells/μL)	165,000
AFP (ng/mL)	2
FIB4 index	3.28
APRI	0.624
M2BPGi (COI)	0.74
RAS at baseline[a]	None
Severity of liver disease	Chronic hepatitis
Treatment and outcome	
GLE/PIB dosage (mg)	300/120
Achievement of rapid virologic response	No
Adherence to GLE/PIB	100%
Weeks of therapy	12
Response	SVR12
Concomitant drugs	Warfarin, lansoprazole, methylcobalamin, and patched containing Loxoprofen sodium hydrate
Adverse events	None

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *AFP* alpha-fetoprotein, *APRI* aspartate aminotransferase to platelet ratio index, *M2BPGi* Mac-2-binding protein glycosylation isomer, *BMI* body mass index, *DAA* direct-acting antiviral agent, *GLE* glecaprevir, *HCV* hepatitis C virus, *IFN* interferon, *NA* not applicable, *PIB* pibrentasvir, *PTW* post-treatment week, *RAS* resistance-associated substitution, *SVR* sustained virologic response, *WBC* white blood cells

[a]RASs against GLE or PIB after 8-week GLE/PIB therapy and before 12-week GLE/PIB therapy

Discussion

The important findings from our case are as follows. (1) Although 8-week GLE/PIB therapy was insufficient for viral eradication, the prolongation of the same regimen (12-week therapy) could rescue the patient from treatment failure. (2) Before the 2nd GLE/PIB therapy, we confirmed that there were no RASs against GLE and PIB. (3) Although the rescue therapy has not been established for cases of treatment failure with GLE/PIB therapy, we presented one possible therapeutic option.

In view of virologic efficiency, an RVR was not achieved and viremia was < 1.2 log IU/mL at the 4th week of both the 1st and 2nd GLE/PIB therapy. The disappearance of viremia was confirmed at 7th and 8th weeks of 1st and 2nd GLE/PIB therapies, respectively. Thus, the initial effect on viremia was assumed to be similar, but the maintenance of antiviral activity due to the prolongation of the treatment period could induce an SVR12 in the 2nd GLE/PIB therapy. Besides, a virologic relapse without the development of RASs against GLE or PIB, but not a non-response or virologic breakthrough in the 1st GLE/PIB therapy may have also contributed to the achievement of SVR12 with the 2nd GLE/PIB therapy.

Regarding rescue therapy in cases of DAA failure, GLE/PIB therapy and SOF/VEL plus RBV therapy are currently available in Japan. In the CERTAIN-1 sub-study 2, an SVR12 was achieved by 94% (31/33) of DAA-experienced genotype 1 and 2 patients who received GLE/PIB therapy on an ITT basis [3]. Two patients with virologic failure had

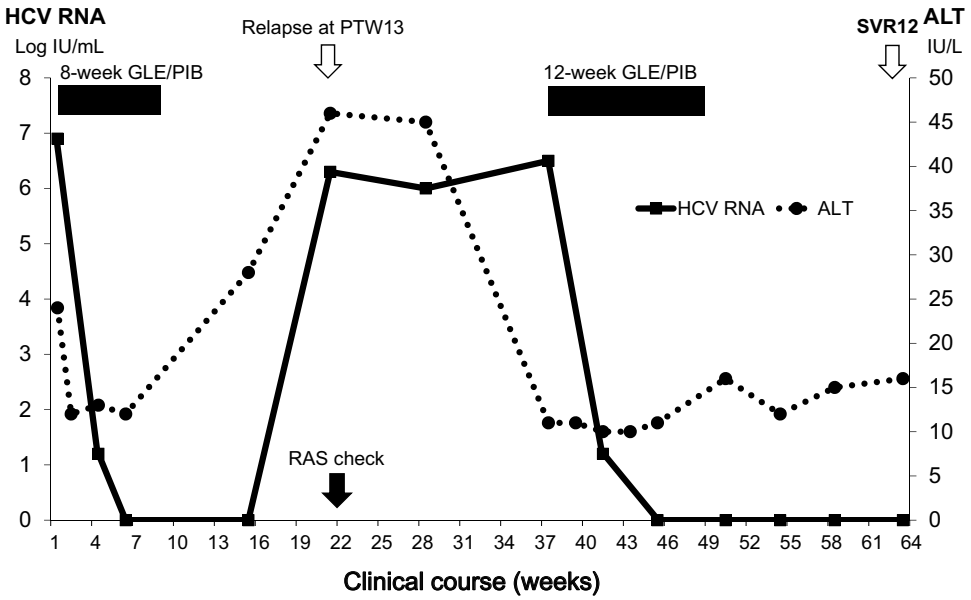

Fig. 1 Clinical course of the patient. After the start of 8-week GLE/PIB therapy, the patient's serum HCV RNA level rapidly declined and subsequently remained undetectable until the end of 8-week glecaprevir (GLE)/pibrentasvir (PIB) therapy. An SVR4 was achieved, but virologic relapse occurred at post-treatment week (PTW) 13. The serum HCV RNA level returned to almost the pretreatment level. We then checked for resistance-associated substitutions (RASs) for GLE and PIB. After confirming that the patient had no RASs against GLE or PIB, we started 12-week GLE/PIB therapy. The serum HCV RNA level rapidly declined again and subsequently remained undetectable at PTW12. Thus, the patient finally achieved an SVR12. The serum alanine aminotransferase (ALT) level remained normal before 8-week GLE/PIB therapy. At virologic relapse, the serum ALT level also increased and we diagnosed mild ALT flare-up. However, the ALT flare-up was temporal and the level returned to the normal range at the start of 12-week GLE/PIB therapy. Later, the serum ALT level remained within the normal limits. The start of 8-week GLE/PIB therapy was designated as 0 week on the horizontal axis

previously received asunaprevir as an NS3-4A serine protease inhibitor and daclatasvir as an NS5A inhibitor and had a P32 deletion in NS5A at baseline; the treatment outcomes were on-treatment virologic failure and virologic relapse, respectively. P32 deletion is known to confer the considerably high resistance to NS5A inhibitors, including PIB, in comparison with the original viruses [7]. P32 deletion is likely to be resistant to SOF/LDV therapy. For example, an SVR12 in patients with P32 deletion at baseline was not achieved in patients treated with SOF/LDV therapy [8], but was achieved in SOF/LDV plus RBV [9, 10], which is not covered by insurance in Japan. In the CERTAIN-1 sub-study 2, however, only one DAA-experienced patient with genotype 2 was recruited and an SVR12 was achieved by 12-week GLE/PIB therapy [3]. On the other hand, all 20 DAA-experienced patients with genotype 1 and 2 who were treated with 12-week GLE/PIB therapy achieved an SVR12 in real-world settings [11]. In this study, P32 deletion was not detected in either case at baseline. Another real-world cohort study showed that 93.3% (28/30) of patients with DAA failure achieved an SVR12 with GLE/PIB therapy [12]. The study subjects had genotype 1b, 2a, 2b, or 3a [12]. Only two patients with genotype 1b failed to achieve an SVR12 [12]. The RASs detected before GLE/PIB therapy were D168E, L31I, P58S, and Y93H in one patient and L31F and P32 deletion in the other [12]. More recently, a real-world cohort study showed that all 41 DAA-experienced patients with genotype 1, 2, and undetermined, who were treated with 12-week GLE/PIB therapy achieved an SVR12 in Japan [13]. In that study, an SVR12 by GLE/PIB therapy was not achieved in 0.96% (3/314) of the overall cases. Among the 3 patients, 1 patient with genotype 1b had no RASs at baseline, while the RASs of the other 2 patients with genotype 2 were not available [13]. Based on these studies regarding GLE/PIB therapy for DAA failure [3, 11–13], 12-week GLE/PIB therapy was assumed to be very effective even for treating genotype 1 and 2 patients with DAA failure, except in cases with P32 deletion.

On the other hand, an overall SVR12 was achieved in 97% (58/60) and 82% (47/57) DAA-experienced patients who received 12-week and 24-week SOF/VEL plus RBV therapy, respectively [4]. The study subjects included patients with genotypes 1 and 2 [4]. Twenty-two patients had genotype 2; thus, the population was greater than that in the CERTAIN-1 sub-study 2. An SVR12 was achieved in patients with genotype 2 with L31M as NS5A-RAS in 78% (7/9) and 90% (9/10) in patients who underwent 12- and 24-week SOF/VEL plus RBV therapy, respectively [4]. This study included one patient with treatment failure with GLE/PIB therapy; however, the treatment period of GLE/PIB therapy

as the prior therapy was not available [4]. Notably, this study showed that 12- or 24-week SOF/VEL plus RBV therapy enabled us to achieve an SVR12 in 80% (4/5) of patients with P32 deletion at baseline [4].

In the MAGELLAN-3 study [14], 12- or 16-week combination therapy with GLE/PIB, SOF, and RBV therapy was used for patients with treatment failure under GLE/PIB therapy. The genotypes of patients included 1a, 1b, 2a, 3a, and 3b [14]. Overall, an SVR12 was achieved in 96% (22/23) of patients and virologic relapse occurred in one patient with genotype 1a [14]. A patient with genotype 1b could achieve an SVR12 despite having L28M and P32 deletion as NS5A-RASs at baseline [14]. Regarding genotype 2a, two patients achieved an SVR12 and neither patient had RASs against NS5A or NS3 after GLE/PIB therapy [14], which was consistent with our case. Unfortunately, combination therapy with GLE/PIB, SOF, and RBV therapy is not available and is not expected to become available in Japan.

Given the previous studies and our case report, we suggest the following strategy to rescue patients with treatment failure after GLE/PIB therapy in Japan. (1) Patients with P32 deletion could be treated by 24-week SOF/VEL plus RBV, which is covered by insurance in Japan, because an SVR12 is unlikely to be achieved by GLE/PIB therapy in this setting. (2) Patients who have experienced 12-week GLE/PIB therapy could be treated by 24-week SOF/VEL plus RBV, because the prolongation of GLE/PIB therapy beyond 12 weeks is not available, and the same regimen and treatment period may not be effective. (3) Patients who have experienced 8-week GLE/PIB therapy could be essentially treated with 24-week SOF/VEL plus RBV. 12-week GLE/PIB therapy might be considered if the case of DAA failure was virologic relapse and had no RASs against GLE or PIB after 8-week GLE/PIB therapy like our case. In addition, 12-week GLE/PIB therapy might be considered in patients with severe renal impairment or severe anemia, because GLE/PIB therapy could be safely used for these patients [3], while SOF-containing regimen is contraindicated in patients with severe renal impairment, and RBV-containing regimens are likely to cause anemia. Furthermore, 12-week GLE/PIB therapy has advantages over 24-week SOF/VEL plus RBV therapy as follows: the treatment period of the former regimen is 12 weeks, which is half of the period for the latter regimen, and the former regimen subsequently alleviates the patient's burden and medical costs. Thus, we suggest that to explore the possibility of 12-week GLE/PIB therapy as the rescue therapy for patients with treatment failure after 8-week therapy by accumulating the cases is much-needed.

Strictly speaking, the serum viral load at post-treatment week 12 after 8-week GLE/PIB therapy was not determined in our case. Thus, the achievement of SVR12 was not confirmed after 8-week GLE/PIB therapy. However, given that serum viral load was relatively high (6.3 log IU/mL) at post-treatment week 13 after 8-week GLE/PIB therapy, viremia was likely to exist at post-treatment week 12 after 8-week GLE/PIB therapy. In addition, the serum before 8-week GLE/PIB therapy was not preserved, and thus, reinfection with HCV could not be excluded as the comparison of HCV sequence between baseline and 13 weeks after end of 8-week GLE/PIB treatment could not be performed.

The reason why the treatment failure occurred in this patient by 8-week GLE/PIB therapy was unclear. However, the exposure of both GLE and PIB to the body was increased after eating [15]. Partial gastric resection might affect the absorption of these drugs, and thus, the antiviral effect might be impaired. In fact, the exposure of simeprevir, one of DAA to the body was low in the patient who had experienced gastric bypass surgery compared to what was described to the literature, although that of SOF was not affected [16].

Our case report is associated with a limitation in that it was based on a single case, because HCV sequences including RASs were not evaluated before 8-week GLE/PIB therapy, and because SVR12 was not determined after 8-week GLE/PIB therapy.

In summary, a hepatitis C patient with genotype 2a was rescued from virologic relapse following 8-week GLE/PIB therapy by 12-week GLE/PIB therapy. Although our case is assumed to be rare, treatment with the same regimen might be considered for rescuing patients from treatment failure after 8-week GLE/PIB therapy. Further studies are much-needed to verify the findings of our case report.

Compliance with ethical standards

Conflict of interest Sato K received lecture fees from MSD K.K. and AbbVie Inc., and research funding from AbbVie. Kakizaki S received lecture fees from MSD K.K., AbbVie Inc. and Gilead Sciences, Inc., and research funding from BMS K.K. and Gilead Sciences, Inc.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the Case report.

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