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【 CASE REPORT 】

Glecaprevir and Pibrentasvir for Japanese Patients with Human Immunodeficiency Virus and Genotype 3 Hepatitis C Virus Coinfection: A Report of Three Cases

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Abstract:
The efficacy and safety of glecaprevir and pibrentasvir in Japanese patients with human immunodeficiency virus (HIV) and/or genotype 3 hepatitis C virus (HCV) infection is yet to be clarified. This is because no or only a few patients have been included in Japanese phase 3 trials. We herein report for the first time the successful treatment of glecaprevir and pibrentasvir in three Japanese patients with HIV and genotype 3 HCV coinfection as well as hemophilia. Glecaprevir and pibrentasvir treatment is safe and effective for Japanese patients with genotype 3 HCV and HIV coinfection.

Key words: genotype 3, glecaprevir, HCV, hemophilia, HIV, pibrentasvir

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Introduction

Hepatitis C virus (HCV) is a major cause of liver cirrhosis, hepatocellular carcinoma, and liver-related deaths globally; thus, safe and effective anti-HCV therapy is crucial. Until recently, interferon (IFN)-based therapy was standard for patients with HCV infection. However, the treatment outcomes and tolerability were insufficient, especially in patients with renal dysfunction, human immune deficiency virus (HIV) coinfection, and liver transplants (1). However, recently developed direct-acting antivirals (DAAs) have revolutionized anti-HCV treatment. Numerous clinical trials and real-world data have proven that DAA combination therapy without IFN is highly effective and safe for patients with HCV infection (2-6). These revolutionary treatments have also changed anti-HCV treatment for the aforementioned populations of patients with HCV infection (1, 3). However, until recently, DAA therapy had several limitations that needed to be resolved, such as a shorter treatment duration (under 12 weeks), pangenetic anti-HCV activity, and reduced drug-drug interactions.

A novel anti-HCV combination therapy consisting of the HCV NS5A inhibitor glecaprevir and the HCV protease inhibitor pibrentasvir administered for 8 to 12 weeks does not require the use of IFN/ribavirin and has relatively few drug-drug interactions. This combination therapy has been shown to have a high therapeutic effect and be safe for HCV-infected patients in various clinical trials, including Japanese phase 3 trials (2, 7, 8). A Japanese phase 3 trial included difficult-to-treat populations (even with DAA therapy), such as patients with renal dysfunction, patients in whom DAA therapy had previously failed, and patients with genotype 3 HCV infection. The treatment efficiency was quite high and achieved a sustained virologic response (SVR) rate of over 95% except for in patients with genotype 3 HCV infection

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(SVR rate of 83.3%; n=10/12). In a global phase 3 study, the administration of glecaprevir and pibrentasvir to patients with genotype 3 HCV infection resulted in an SVR rate of over 95% (9). This discrepancy might be due to the small number of genotype 3 HCV-infected patients in the Japanese phase 3 trial; thus, a further analysis in those Japanese patient populations is required. Importantly, the aforementioned Japanese phase 3 trial included no patients with HIV-coinfection. Thus, more studies on the administration of glecaprevir and pibrentasvir to those patients are required.

In the present case report, we describe for the first time the outcome and safety of glecaprevir and pibrentasvir combination therapy in three Japanese patients with genotype 3 HCV and HIV coinfection.

Case Reports

Case 1

This patient was a 48-year-old man with genotype 3a HCV and HIV coinfection. When he was two years old, he had been diagnosed with hemophilia A and been administrated clotting factor. When he was 35 years old, he had been diagnosed with HCV infection and chronic hepatitis C. In addition, when he was 18 years old, he had been diagnosed with HIV-1 infection. Antiretroviral therapy (ART) consisting of zidovudine + lamivudine + indinavir was initiated when he was 28 years old. He was never treated with anti-HCV therapeutics.

In December 2017, he started a 12-week treatment course of glecaprevir and pibrentasvir combination therapy (Figure A). At the time of treatment initiation, the patient's platelet count was 16.9×10^4/μL, the liver stiffness score obtained by Fibroscan® (transient elastography) was 10.1 kPa, the alanine aminotransferase (ALT) levels were 67 IU/L, the HCV RNA titer was 6.6 $\log_{10}$ IU/mL, HIV RNA was negative, and the CD4+ cell count was 1,101 cells/μL (Table). At the time of treatment initiation with glecaprevir and pibrentasvir, the patient was being treated with tenofovir alafenamide fumarate/emtricitabine + dolutegravir for HIV infection, and no change or reduction in the dose of those drugs was necessary. As shown in Figure A, the HCV RNA titer quickly decreased and was non-detectable at 4 weeks after treatment initiation; this trend persisted until 12 weeks after treatment completion (SVR12). Similar to the HCV RNA titer, the serum ALT levels decreased and were in a normal range at 4 weeks after treatment initiation. He completed the 12-week course of glecaprevir and pibrentasvir treatment, during which the HIV RNA and CD4+ cell counts were stable, and no notable adverse events were observed.

Case 2

This patient was a 53-year-old man with genotype 3a HCV and HIV coinfection. Since the age of 13, he had been administrated clotting factor because of hemophilia A. At 24 and 34 years old, he had been diagnosed with HIV and HCV infections, respectively. At 33 years old, ART (azidothymidine) had been initiated. At 39 years old, he had been treated with peg-IFNα-2a therapy for 72 weeks; however, he experienced a virologic relapse after the treatment ended.

In December 2017, a 12-week treatment course of glecaprevir and pibrentasvir combination therapy was initiated (Figure B). At the time of treatment initiation, the patient's platelet count was 7.5×10^4/μL, the FIB-4 index was 7.43, the ALT levels were 166 IU/L, the HCV RNA titer was 6.4 $\log_{10}$ IU/mL, HIV RNA was negative, and the CD4+ cell count was 330 cells/μL (Table). We were unable to analyze the liver stiffness by Fibroscan® (transient elastography) due to the occurrence of Chilaiditi syndrome caused by liver cirrhosis. The liver stiffness score obtained by acoustic radiation force impulse (ARFI) was 2.46 m/s.

At the time of treatment initiation with glecaprevir and pibrentasvir, the patient was being treated with abacavir sulfate/dolutegravir sodium/lamivudine + rilpivirine as ART, and no change or reduction in the dose of those drugs was necessary. As shown in Figure B, the HCV RNA titer decreased quickly and was non-detectable at 4 weeks after treatment initiation; this trend persisted 12 weeks after treatment completion (SVR12). He completed the 12-week course of glecaprevir and pibrentasvir treatment, during which the HIV RNA and CD4+ cell counts were stable, and no notable adverse events were observed.

Case 3

The patient was a 51-year-old man with genotype 3a HCV and HIV coinfection. After being diagnosed with hemophilia A, he had been administrated clotting factor. When he was 20 years old, he had been diagnosed with HIV infection, and ART (tenofovir disoproxil fumarate/fosamprenavir + efavirenz) had been initiated when he was 40 years old. HCV infection was diagnosed when he was 38 years old; however, no treatment for HCV infection was initiated.

In December 2017, a 12-week treatment course of glecaprevir and pibrentasvir combination therapy was initiated (Figure C). At the time of treatment initiation, the patient's platelet count was 11.7×10^4/μL, the liver stiffness obtained by Fibroscan® (transient elastography) was 8.1 kPa, the ALT levels were 96 IU/L, the HCV RNA titer was 6.7 $\log_{10}$ IU/mL, HIV RNA was negative, and the CD4+ cell count was 522 cells/μL (Table). At the time of glecaprevir and pibrentasvir treatment initiation, the patient was being treated with tenofovir alafenamide fumarate/emtricitabine + dolutegravir as ART, and no change or reduction in the dose of those drugs was required. As shown in Figure C, the HCV RNA titer decreased quickly and was non-detectable at 2 weeks after treatment initiation. The patient achieved SVR12. Similar to the HCV RNA titer, the serum ALT level quickly decreased. He completed the 12-week treatment course, during which the HIV RNA and CD4+ cell counts were stable, and no notable adverse events were observed.

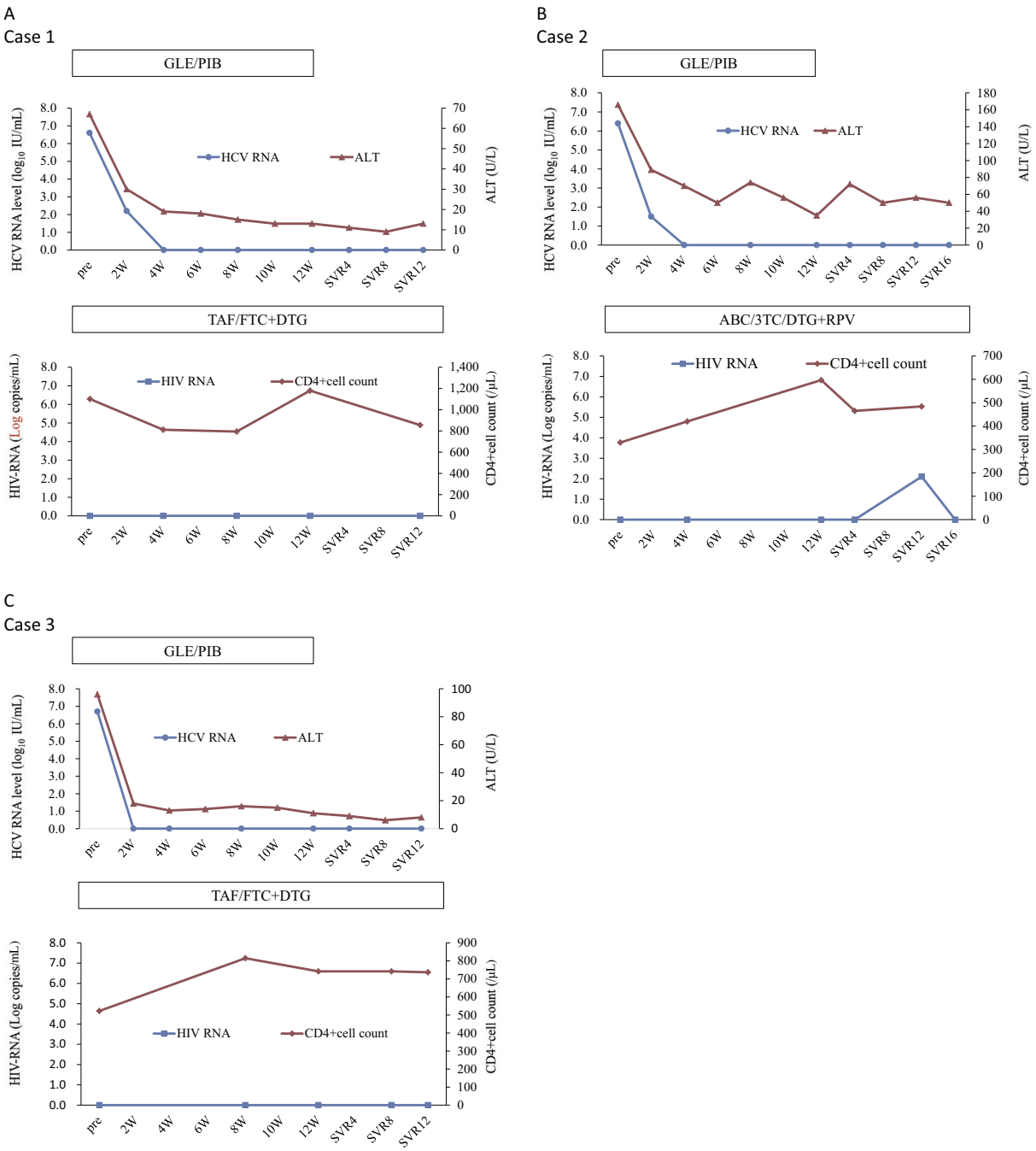

Figure. **The virologic response and clinical course of glecaprevir and pibrentasvir therapy for three Japanese patients with human immunodeficiency virus and genotype 3 hepatitis C virus coinfection. Changes in the serum hepatitis C virus (HCV) titer, human immunodeficiency virus (HIV) titer, alanine aminotransferase (ALT), and CD4+cell counts are shown. A: Clinical course of Case 1. B: Clinical course of Case 2. C: Clinical course of Case 3. HCV: hepatitis C virus, HIV: human immunodeficiency virus, IFN: interferon, ALT: alanine transaminase, TAF: tenofovir alafenamide fumarate, FTC: emtricitabine, DTG: dolutegravir, ABC: abacavir sulfate, 3TC: lamivudine, DTG: dolutegravir sodium, RPV: rilpivirine, ART: antiretroviral therapy**

Discussion

In this case report, all three patients had several difficult-to-treat factors: genotype 3 HCV infection, HIV coinfection, and hemophilia. We herein report, for the first time, the efficacy and safety of using glecaprevir and pibrentasvir in Japanese patients with genotype 3 HCV/HIV coinfection and hemophilia. All three patients completed this therapy without the occurrence of severe adverse events, and no change or dose reduction of ART was required. In addition, all three patients achieved SVR12. Thus, the administration of glecaprevir and pibrentasvir might be effective and safe, even in Japanese patients with multiple difficult-to-treat fac-

Table. Baseline Characteristics of the Three Patients Coinfected with HIV and Genotype 3 HCV.

	Case 1	Case 2	Case 3
Age (years)	48	53	51
Sex	Male	Male	Male
Baseline white blood cell count (/μL)	7,200	3,100	4,000
Baseline hemoglobin level (g/dL)	17.5	13.6	14.2
Baseline platelet count ($\times 10^3$)	16.9	7.5	11.7
Baseline ALT level (IU/L)	67	166	96
Baseline AST level (IU/L)	45	133	177
Baseline total bilirubin (mg/dL)	1.0	1.1	1.0
Baseline prothrombin time (%)	89.5	86.6	95.7
Baseline albumin (g/dL)	4.4	4.7	4.1
Baseline eGFR (mL/min/1.73 m^2)	79.4	68.8	81.2
Baseline HCV RNA level (log10 IU/mL)	6.6	6.4	6.7
HCV genotype	3a	3a	3a
FIB-4 index	1.56	7.43	7.87
Liver stiffness (kPa)	10.1	NA	8.1
Previous anti-HCV tx	naive	peg-IFN	naive
HIV RNA (copies/mL)	negative	negative	negative
ART	TAF/FTC+DTG	ABC/3TC/DTG+RPV	TAF/FTC+DTG
CD4+cell count (/μL)	1,101	330	522
Hemophilia	+	+	+

† HCV: hepatitis C virus, HIV: human immunodeficiency virus, IFN: interferon, ALT: alanine transaminase, TAF: tenofovir alafenamide fumarate, eGFR: estimated glomerular filtration rate, FTC: emtricitabine, DTG: dolutegravir, ABC: abacavir sulfate, 3TC: lamivudine, DTG: dolutegravir sodium, RPV: rilpivirine, ART: antiretroviral therapy, NA: not analysis, tx: treatment

tors.

It is estimated that a total of 20-35% of HIV-infected patients have HCV coinfection (10, 11). Importantly, thanks to progress in ART development, the numbers of acquired immune deficiency syndrome (AIDS)-related deaths in HIV/HCV-coinfected patients have been decreasing (12); thus, the management of non-AIDs-related deaths is an important issue in HIV patients. Liver-related death is the second cause of non-AIDS-related deaths in HIV-infected patients (12). In HIV/HCV-coinfected patients, liver fibrosis progresses more rapidly than it does in patients with HCV monoinfection (13). Thus, urgent intervention is required in these patients. However, the SVR rate was lower in HIV/HCV-coinfected patients than in HCV-monoinfected patients during treatment with IFN, partially because of the high rate of adverse events. IFN-free DAA therapy has dramatically changed the safety and efficacy of anti-HCV therapy in HIV/HCV coinfected patients (14). However, drug-drug interactions between ART and DAA should still be monitored. For example, the coadministration of the HCV NS5A inhibitor ledipasvir and tenofovir disoproxil fumarate (TDF) as part of the ART regimen caused an increase in the TDF serum concentration, which can worsen the renal function in patients. However, no clinically significant drug-drug interactions have been observed between glecaprevir/pibrentasvir and commonly used antiretroviral agents (15). In the present report, no patients experienced severe adverse events, including renal dysfunction or worsening of HIV titers, during the therapy. Thus, this regimen is likely to be useful for HIV/HCV-coinfected patients.

In the present case report, all three patients had genotype 3 HCV infection. Although this type of HCV infection is rare in Japan, it is the second-most common HCV genotype worldwide (16). Importantly, it has been reported that infection with genotype 3 HCV is more likely to lead to hepatic steatosis, liver cirrhosis, and hepatocellular carcinoma than infection with other HCV genotypes (17). Until recently, in Japan, treatment options for patients with genotype 3 HCV infection were limited to peg-IFN and ribavirin combination therapy and 24-week sofosbuvir and ribavirin combination therapy. The SVR rate of sofosbuvir and ribavirin was reported to be 85% (18); however, this regimen requires a relatively long duration of standard IFN-free DAA therapy and cannot be administered to patients with renal dysfunction. In contrast, glecaprevir and pibrentasvir have pangenotypic HCV anti-viral activity, and with a treatment duration of just 12 weeks, it can be used in patients with genotype 3 HCV infection and administrated to those with renal dysfunction. The Japanese phase 3 trial for glecaprevir and pibrentasvir included only 12 patients with genotype 3 HCV infection, and the SVR rate was 83.3% (n=10/12). In the present report, all three patients achieved SVR12. In the Japanese phase 3 trial, two HCV genotype 3-infected patients failed to respond to glecaprevir and pibrentasvir. The HCV subgenotypes carried by those patients were genotype 3b and genotype 3k (one patient each). All seven patients

with genotype 3a HCV infection achieved SVR12. Thus, the genotype 3 HCV subgenotype might also affect the treatment outcome (9). A durther analysis is required to reproduce these observations.

Two of the patients described in the present report with advanced liver fibrosis (FIB-4 index >3.25) were able to complete glecaprevir and pibrentasvir treatment without severe adverse events and achieved SVR12. This result was consistent with that of the Japanese phase 3 trial, which found that glecaprevir and pibrentasvir are highly effective and safe in patients with compensated liver cirrhosis (7).

One patient experienced intermittent HIV viremia after the completion of the glecaprevir and pibrentasvir course. Such intermittent HIV viremia during ART is reported to occur frequently and is not associated with virologic failure (19). In addition, it occurred 12 weeks after glecaprevir and pibrentasvir treatment completion; thus, this intermittent HIV viremia might not be associated with the treatment.

In the present report, all patients had hemophilia. Given that HCV is transmitted mainly through the blood, the HCV coinfection rates are higher in HIV-infected patients with hemophilia than in patients without hemophilia (60-97%) (11, 20). Such patients sometimes have mixed-genotype HCV infection; thus, a treatment regimen that has pangenotypic HCV antiviral activity, such as glecaprevir and pibrentasvir, is ideal.

In conclusion, this case report indicates that glecaprevir and pibrentasvir combination therapy is safe and effective for Japanese patients with genotype 3 HCV and HIV coinfection. Future studies using a large number of patients will be required to corroborate these observations.

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

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Takuya Sho and Goki Suda equally contributed to this study.

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