Original Research Report

Pan-Genotypic DAA Therapy for HCV Genotypes Not Covered by Health Insurance for Hemophilia Patients with or without HIV in Japan : Report of a Joint Multi-Institutional Study of the Clinical Study Group for AIDS Drugs

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Background : A number of patients with hemophilia were infected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) via imported unheated plasma products before mid 1980s. And the genotypes (GTs) of the HCV infected were various due to contaminated products which were made from pooled human plasma. Although hepatitis C treatment has advanced dramatically with oral direct-acting antivirals (DAA), in Japan as of 2016, DAAs are only indicated for GT 1 or 2. In Europe and the United States, pan-genotypic treatment with daclatasvir+sofosbuvir±ribavirin had been recommended for hepatitis C associated with hemophilia. Many hemophilia patients in Japan had advanced liver fibrosis and could not wait for approval for pan-genotypic therapy.

Methods : We conducted a joint multi-institutional study with this pan-genotypic regimen in hemophilia patients infected with HCV GTs not covered by health insurance in Japan from 2016 to 2018 as an activity of the Clinical Study Group for AIDS Drugs.

Results : Sixteen patients enrolled, 15 were GT3a and one patient was GT4. In addition, 12 patients had HIV complications and 10 patients had compensated cirrhosis. All patients completed treatment safely, and 15 achieved sustained virologic response.

Conclusion : This study was able to provide beneficial treatment to hemophilia patients who were infected with rare HCV GTs in Japan.

Key words：chronic hepatitis C, hemophilia, human immunodeficiency virus, pan-genotype direct-acting antivirals, health insurance

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Introduction

In the 1980s, a number of patients with hemophilia were infected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) via unheated plasma products[1–4]. Chronic hepatitis C is a long-term inflammatory condition of the liver that can progress to cirrhosis and cause hepatocellular carcinoma[3–7]. Especially, when complicated by HIV infection, chronic hepatitis C progresses rapidly, and many patients with hemophilia die from end-stage liver disease, hepatocellular carcinoma, and liver failure[4–9]. Previously, chronic hepatitis C was primarily treated with interferon (IFN), but many patients failed to achieve sustained virologic response (SVR)[4, 5]. Since 2014, IFN-free direct-acting antiviral (DAA) therapy has shown high efficacy and safety in these patients[4, 10–12]. Because most hepatitis C patients in Japan were infected with HCV genotypes (GTs) 1b, 2a, or 2b, DAA therapy for other GTs was not initially approved in Japan[13, 14]. However, HCV GTs range from 1 to 6, and many patients with hemophilia have other GTs as well as GT1 and GT2 due to the use of imported plasma products[15, 16]. Treatment of hemophilia patients infected with HCV of various GTs requires a pan-genotypic DAA that is effective against all GTs. Until the approval of glecaprevir plus pibrentasvir in November 2017, there was no pan-genotypic therapy covered by Japanese health insurance[17–19]. According to the 2015 European Association for the Study of the Liver (EASL) HCV treatment guidelines, the combination of the NS5A inhibitor daclatasvir (DCV); and the nucleotide analog inhibitor sofosbuvir (SOF); was an effective pan-genotypic therapy[20]. Under these situations, to fill the drag-lag until pan-genotypic therapy was approved, we constructed a clinical trial for hemophilia patients, many of whom had advanced liver fibrosis and could not wait for treatment. We report here on a multicenter trial of the DCV+SOF ± ribavirin (RBV) regimen in patients with hemophilia who are infected with HCV GTs, which is not covered by Japanese health insurance. This study is conducted as part of the activities of the Clinical Study Group for AIDS Drugs, which is funded by the Ministry of Health, Labour and Welfare of Japan and the Japan Agency for Medical Research and Development; Grant Number : 19k0201051h0004.

Patients and Methods

1. Study Design and Patients

The study included patients who were ≥ 20 years of age with hemophilia who were HCV-RNA-positive, regardless of previous IFN-based treatment. The target number of subjects in this study was 20 because of the large budget of US$ 50,000 to US$ 100,000 per person. The inclusion criteria for patients with HIV-1 infection were as follows : maintenance of HIV-1 RNA at <50 copies/mL and CD4-positive T-lymphocyte levels of ≥ 100/μL at the time of enrollment. The exclusion criteria for patients were as follows : who were eligible for DAA treatment covered by the Japanese health insurance (i.e., cases of HCV GT1 alone or GT2 alone); presence of decompensated cirrhosis (i.e., cases of Child-Pugh C) or uncontrolled hepatocellular carcinoma (i.e., Barcelona Clinic Liver Cancer Classification, stage D); severe renal dysfunction and an estimated glomerular filtration rate of <30 mL/min/1.73 m^2; QTcF >500 ms or the presence of second- or third-degree AV block on electrocardiogram; Hb <12 g/dL in the RBV combined group; presence of active opportunistic infections in patients with HIV-1; use of drugs that were contraindicated (e.g., amiodarone, rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, dexamethasone systemic administration, and St. John's wort); and those who were deemed inappropriate for inclusion by the treating physician in charge of the patients, such as those who do not follow instructions. The enrollment period was from February 2016 through March 2018.

The major HCV GTs (i.e., 1a, 1b, 1c, 1d, 2a, 2b, 2c, 3a, 3b, 4, 5a, 6a) in each serum sample were determined by direct sequencing by LSI Medience Corporation (Tokyo, Japan).

HCV treatment was conducted in this open-label study was administered with 60 mg of DCV and 400 mg of SOF orally once daily. The dose of DCV was adjusted to 30 or 90 mg based on its interaction with other drugs[21]. Our study was initially started with a 12-week regimen of DCV+SOF without RBV for all eligible patients based on the international ALLY-2[22] and ALLY-3[23] trials. However, the ALLY-3+ trial[24] reported that patients with cirrhosis and GT3 infection did not respond adequately to DCV+SOF; therefore, patients with cirrhosis (i.e. Child-Pugh A or B) received RBV in combination with the DCV + SOF regimen for 24 weeks against HCV GT3 and for 12 weeks against other GTs. The dose of RBV was adjusted according to the weight of the subject based on the drug information[25]. For drug supply, commercially available DCV tablets (60 mg, DAKLINZA™; Bristol-Myers Squibb Company, Princeton, NJ, USA), SOF tablets (400 mg, SOVALDI®; Gilead Sciences, Inc., Foster City, CA, USA), and RBV capsules (200 mg, REBETOL®; MSD KK, Tokyo, Japan) were used. DCV tablets (30 mg) were provided free of charge by the Bristol-Myers Squibb Company because they were not commercially available in the domestic market. During the administering of the therapeutic drugs, we confirmed the occurrence of adverse events every 4 weeks by vital, hematological, biochemical, and virologic examinations and by electrocardiogram. Patients were followed for an additional 12 weeks after the end of drug administration.

2. Safety Assessment

Withdrawal was considered in the following cases :

progression of liver failure; ALT greater than 5-fold from baseline level or greater than 10-fold from the upper limit of normal; platelet count <25,000/μL; other laboratory abnormalities possibly due to the study drug, such as a Grade 4 in the Division of AIDS Table[26]; if the patient withdrew his/her consent; if the investigator determined that it was disadvantageous for the subject to continue with the study drug; or if the study treatment could not be continued for any reason (e.g., swallowing difficulties, transfer).

3. Efficacy Assessment

Treatment efficacy was assessed at 12 weeks after the end of drug administration. Patients whose sera were negative for HCV-RNA were considered to have achieved SVR at 12 weeks after treatment (SVR12), and those who were positive were deemed as failures in the trial.

4. Ethics

The clinical trial was approved by the independent ethics committees at the clinical sites and was conducted in compliance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, published by the Ministry of Health, Labor, and Welfare, Japan. The accession numbers were 3,264, 3,373, 3,439, 3,535, and 3,792. All patients provided written informed consent to participate in the study.

Results

1. Patient Demographics and Disposition

The trial entry began in 2016, with 16 individuals from nine facilities participating in the study. The baseline characteristics of the patients are presented in Table 1. The median age was 47 years, with 13 patients with hemophilia A and 3 patients with hemophilia B. There were 15 patients with HCV GT3a and a remaining patient was with HCV GT4. Ten of them had developed compensated cirrhosis and 1 patient had undergone liver transplantation. Ten patients had treatment experience, 9 patients had been treated with IFN-based therapy, and 1 patient had been treated with DAA. For the patient who had been treated with DAA, the initial combination therapy of peg-IFN+RBV+telaprevir had been ineffective. Subsequent therapy with SOF+RBV had also proved ineffective for the patient. Four patients had been treated for hepatocellular carcinoma, prior to entering the study. One of the patients was treated for hepatocellular carcinoma prior to liver transplantation.

DCV+SOF was provided for the six patients who did not have cirrhosis (five with GT3a, one with GT4) for 12 weeks. Among the 10 patients with liver cirrhosis (all with GT3a infections), 2 were treated with DCV+SOF for 12 weeks, 7 underwent DCV+SOF+RBV treatment for 24 weeks, and 1 was treated with DCV+SOF without RBV, due to renal impairment, for 24 weeks.

Twelve patients had HIV infection complicated due to the use of unheated plasma products. The median CD4 number was 545/μL, and the control of viral load was stable. The antiretroviral therapy (ART) regimen is presented in Table 1. One untreated patient was a long-term non-progressive state case.

2. Virologic Response

The scheduled treatment was completed by all the patients in this study. The virologic responses to the treatment are presented in Table 2. Fifteen patients achieved SVR12, with an effective rate of 93.8%. One patient who failed to respond to treatment had compensated cirrhosis with GT3a infection and was HIV positive; this patient had previously been treated for hepatocellular carcinoma. This patient had received the DCV+SOF without RBV regimen for 12 weeks, which was the regimen used prior to the revision of the protocol. Although the patient was HCV-RNA-negative at the end of the administration of the drug regimen, 6.2 log copies/mL was detected 12 weeks later, indicating a relapse. The patients without cirrhosis presented a 100% SVR12 rate. Regardless of the presence of liver cirrhosis, the SVR12 was 93% (14/15) when limited to GT3a infections and 90% (9/10) in patients with GT3a liver cirrhosis. All seven patients with GT3a liver cirrhosis who were treated with SOF+DCV+RBV for 24 weeks achieved SVR12.

The patient who suffered a relapse was re-administered with DCV+SOF+RBV for 24 weeks after completion of the 12-week treatment with DCV+SOF (with a 28-week interval between the two treatments). Although the patient was negative for HCV-RNA at the 12th week of administration, the treatment was discontinued due to the occurrence of pneumonia and gastrointestinal bleeding, and HCV-RNA levels were not tested after the treatment.

3. Adverse Events

Mild anemia occurred in patients receiving RBV concomitant therapy, but no dose modification was required. Severe adverse events that did not appear to be related to the treatment were a suspected recurrence of hepatocellular carcinoma at week 19 of administration; a fracture of the left upper trochanter due to a fall at week 20 of administration; re-exacerbation of pulmonary aspergillosis at week 22 of administration; and a gastrointestinal bleeding complicated by pneumonia at week 12 of re-administration. The patient who received re-administration of the drugs developed a portal vein tumor embolism due to the recurrence of hepatocellular carcinoma, which occurred 12 weeks after discontinuation of the treatment, and died due to progressed liver failure. No adverse events due to concomitant ART were reported in HIV cases.

Discussion

In the 2003 hemophilia cohort survey in Japan, the distribution of HCV GTs among 1,366 subjects with

Table 1 Clinical characteristics of patients at baseline

HIV positivity	Positive	Negative	Total
N (% of total)	12 (75)	4 (25)	16
Median age, year (IQR)	46.6 (43.8–49.0)	47.5 (45.3–51.8)	47.0 (43.8–49.0)
Male, *n* (%)	12 (100)	4 (100)	16 (100)
Japanese, *n* (%)	12 (100)	4 (100)	16 (100)
Bleeding disorder, *n* (%)			
Hemophilia A	10 (83)	3 (75)	13 (81)
Hemophilia B	2 (17)	1 (25)	3 (19)
Prior HCV therapy, *n* (%)			
IFN-based	5 (42)	3 (75)	8 (50)
DAA	1 (8)	0 (0)	1 (6)
Liver transplantation	1 (8)	0 (0)	1 (6)
HCV RNA, log IU/mL ± SD	5.71 ± 0.91	6.73 ± 0.13	6.03 ± 0.86
HCV genotype, *n* (%)			
3a	11 (92)	4 (100)	15 (94)
4	1 (8)	0 (0)	1 (6)
Cirrhosis, *n* (%)	8 (67)	2 (50)	10 (63)
History of HCC treatment	4 (33)	0 (0)	4 (25)
Median $CD4^+$ count, cells/μL (IQR)	545 (319 ～ 590)	–	–
ART regimen (*n*=11), *n* (%)			
ABC + 3TC + DTG	3 (27)		
TDF + FTC + RAL	3 (27)		
TDF + FTC + DRV + rtv	1 (9)	–	–
TDF + FTC + LPV + rtv	1 (9)		
TDF + FTC + EVG + cobi	1 (9)		
d4T + ABC + RAL	1 (9)		
3TC + RAL + MVC	1 (9)		

HIV, human immunodeficiency virus ; IQR, interquartile range ; HCV, hepatitis C virus ; IFN, interferon ; DAA, direct acting antiviral ; HCC, hepatocellular carcinoma ; ART, antiretroviral therapy ; ABC, abacavir ; 3TC, lamivudine ; DTG, dolutegravir ; TDF, tenofovir ; FTC, emtricitabine ; RAL, raltegravir ; DRV, darunavir ; riv, ritonavir boost ; LPV, lopinavir ; EVG, elvitegravir ; cobi, cobicistat boost ; d4T, stavudine ; MVC, maraviroc.

hemophilia with hepatitis C was 1a (24.5%), 1b (26%), 2a (12.8%), 2b (10.6%), 3a (12.5%), 3b (0.1%), 4a (1.5%), and mixed (11.8%)[27]. In contrast, the distribution of HCV GTs among patients without hemophilia with hepatitis C in Japan was 1b (72%), 2a (18%), 2b (7%), and others (3%)[13]. DAA treatment in Japan had limited insurance coverage depending on the genotype until glecaprevir plus pibrentasvir was approved as a pan-genotypic treatment in November 2017[17–19]. Many hemophilia patients had advanced liver fibrosis and could not wait for approval of pan-genotypic therapy. In our study, 15 of 16 patients had HCV GT3a, and one was a patient with HCV GT4 after liver transplantation. HCV GT3 is common worldwide, particularly in parts of Europe and South Asia, where approximately 30% of HCV infections are GT3[28,29]. In Japan, however, it is a rare GT and is found only in individuals with hemophilia infected with imported blood products. Moreover, GT3 has a higher incidence of hepatocellular carcinoma in patients with cirrhosis than other GTs, as well as accelerated development of fibrosis[30, 31]. The EASL 2015 and the WHO 2016 guidelines recommend DCV+SOF ± RBV as the first line of treatment for HCV GT3[20, 32]. Although there are insufficient research reports on DAA treatment for mixed types of HCV GTs, such as patients with hemophilia, the EASL and American Association for the Study of Liver Diseases (AASLD) recommend pan-genotypic DAA regimens [33, 34]. Recently, as a pan-genotypic DAA regimen, the combination of the NS3/4 protease inhibitor, glecaprevir, and the NS5A inhibitor, pibrentasvir[32], and the combination of SOF and the NS5A inhibitor, velpatasvir, have been recomended[35–37]. The clinical trial ENDURANCE-3

Table 2 Treatment response

	HIV-positive			HIV-negative		Total
	Without cirrhosis		Cirrhosis	Without cirrhosis	Cirrhosis	
HCV genotype	3a (n = 3)	4 (n = 1)	3a (n = 8)	3a (n = 2)	3a (n = 2)	n = 16
HCV RNA undetectable						
During treatment						
Week 2	2/3	1/1	2/7	1/2	0/2	6/15
Week 4	3/3	1/1	6/8	2/2	1/2	13/16
Week 8	3/3	1/1	8/8	2/2	2/2	16/16
Week 12	3/3	1/1	8/8	2/2	2/2	16/16
Week 16	−	−	7/7	−	1/1	8/8
Week 20	−	−	7/7	−	1/1	8/8
Week 24	−	−	7/7	−	1/1	8/8
SVR12	3/3	1/1	7/8	2/2	2/2	15/16
Virologic failure on treatment	0	0	0	0	0	0
Relapse	0	0	1	0	0	1

HIV, human immunodeficiency virus ; HCV, hepatitis C virus ; SVR12, sustained virologic response at 12 weeks after treatment.

compared a 12-week course of glecaprevir plus pibrentasvir with a 12 week course of DCV+SOF in GT3-infected patients without cirrhosis. The rates of SVR12 in the two groups were 95% and 97%, respectively, in the study, indicating that treatment with glecaprevir plus pibrentasvir was not inferior to that with DCV+SOF[38]. In Japan, the combination of glecaprevir and pibrentasvir was approved in November 2017[17–19]. Furthermore, the combination of SOF and velpatasvir was approved in February 2019[39,40].

At that time, each drug of the regimen (DCV+SOF ± RBV) had been approved in Japan, but their combination use was not approved because no clinical trial had been done in Japan due to belonging to different pharmaceutical companies. Therefore, the present study of pan-genotypic therapy for HCV was beneficial for Japanese hemophilia patients who were infected with the rare HCV-GTs and who could not have access to the treatment.

Conclusion

We conducted a joint multi-institutional study of the DCV+SOF ± RBV regimen in Japanese hemophilia patients who could not receive treatment for chronic hepatitis C (GT3a and GT4) by their health insurance as part of the activities of The Clinical Study Group for AIDS Drugs. As a result, we reported that 16 hemophilia patients were safely treated with this pan-genotypic HCV regimen and 15 patients achieved SVR.

Conflict of Interest : DCV tablets (30 mg) were offered free of charge by Bristol-Myers Squibb Company because they were not commercially available in the domestic market. The authors declare that they have no conflicts of interests.

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