The Impact of Ledipasvir/Sofosbuvir on HIV-Positive and HIV-Negative Japanese Hemophilia Patients With 1, 4, and Mixed-Genotype HCV

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Introduction: Approximately 80% of patients with hemophilia who received nonheated coagulation factor concentrates in the early 1980s were infected with hepatitis C virus (HCV), and approximately 40% of them were infected with HIV.

Aim: We evaluated the efficacy and safety of administering ledipasvir (LDV)/sofosbuvir (SOF) to Japanese patients with hemophilia.

Methods: Forty-three patients with hemophilia with genotype 1 or 4 HCV were treated with LDV/SOF for 12 weeks. The efficacy, safety, and results of the laboratory tests were evaluated.

Results: Twenty patients were coinfected with HIV and HCV. The sustained virological response (SVR) at 12 weeks after therapy was 90% in HIV-positive patients and 100% in HIV-negative patients. The efficacy of LDV/SOF was not significantly different between HIV-positive and HIV-negative patients ($P = 0.12$). However, the rate of SVR at 12 weeks after therapy in the patients with cirrhosis was significantly lower than that in patients without cirrhosis ($P = 0.005$). Overall, 20 patients (46%) had adverse events, and while the severity of most was mild to moderate, 3 were serious, including 1 death in the HIV-positive group. All patients completed treatment with no alterations in the antiretroviral regimen. No significant abnormalities in the renal function were detected in patients taking an antiretroviral regimen of tenofovir disoproxil fumarate.

Conclusions: In this cohort study, LDV/SOF was effective and safe, but the SVR in patients with cirrhosis was lower than that in the noncirrhosis group. Thus, patients with hemophilia with genotype 1/4 HCV should be treated as early as possible before the onset of cirrhosis.

Key Words: HCV, HIV coinfection, SVR, ledipasvir/sofosbuvir, hemophilia, pan-genotype

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INTRODUCTION

In the early 1980s, many patients with hemophilia worldwide became accidentally infected with HIV and hepatitis C virus (HCV). In Japan, 1432 patients with hemophilia A/B were infected with HIV through imported coagulation factor concentrates, and 51% of them are still alive. More than 90% of patients who had used nonheated plasma-derived coagulation factor concentrates were infected with HCV.[1] Long-term infection with HCV in patients with hemophilia severely affects their liver status.[2,3] Given that HIV is known to exacerbate cirrhosis, hepatocellular carcinoma, and hepatic decompensation,[4–9] HCV now represents a leading cause of mortality in patients with hemophilia.[10,11]

Because a sustained virological response (SVR) of HCV is associated with a lower rate of mortality, early treatment and the achievement of an SVR are crucial for obtaining a long-term survival in these patients.[12] However, the treatment of HCV with polyethylene glycol–interferon and ribavirin (peg-IFN/RBV) in patients who are coinfected with HIV has been historically associated with low rates of SVR.[13–15] We previously reported the increasing genetic diversity of HCV in patients with hemophilia with HIV coinfection.[16]

The combination of the NS5A inhibitor ledipasvir (LDV) with the NS5B polymerase inhibitor sofosbuvir (SOF) has recently been approved for the treatment of genotype 1 HCV infection.[17] The ION-4 study investigated the safety and efficacy of the LDV/SOF regimen in patients coinfected with HIV and genotype 1 or 4 HCV who were receiving an antiretroviral regimen of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) with efavirenz (EFV), rilpivirine (RPV), or raltegravir (RAL).[18] The outcomes of this study showed that 96% of the patients had an SVR at 12 weeks after therapy (SVR12), and none had confirmed HIV virologic rebound or severe adverse events. Although drug interaction studies have suggested that some patients receiving LDV might have elevated TDF levels, which can increase the risk of TDF-associated renal tubular toxicity, no clinically significant changes in the renal function were observed in the ION-4 study.[18] We previously reported the usefulness of urinary beta-2 microglobulin (Uβ2MG) levels for monitoring the renal tubular toxicity of TDF.[19] Because the Uβ2MG level was not monitored in these reports, signs suggesting early-stage renal failure might have been missed. Furthermore, the increase in the TDF levels by other concomitant antiretroviral drugs [ie, EFV[20] and dolutegravir (DTG)[21]] was not discussed. In addition, some patients

TABLE 1. Hepatitis C Virologic Response During and After Therapy

Response	HIV				Liver Cirrhosis		
	Total (n = 43)	Positive (n = 20)	Negative (n = 23)	*P*	Positive (n = 9)	Negative (n = 34)	*P*
HCV RNA <LLOQ							
4 wk into treatment	30 (70)	15 (75)	15 (65)	0.49	6 (67)	24 (70)	0.8
8 wk into treatment	43 (100)	20 (100)	23 (100)		9 (100)	34 (100)	
12 wk into treatment	43 (100)	19 (95)	23 (100)		9 (100)	34 (100)	
12 wk after treatment (SVR12)	41 (95)	18 (95)	23 (100)	0.12	7 (78)	34 (100)	0.005
Virologic breakthrough during treatment	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	
Relapse in patients with HCV RNA <LLOQ at the end of therapy	0 (0)	1 (5)	0 (0)		1 (8)	0 (0)	

The values are represented as n (%).
LLOQ, lower limit of quantification (1.2 Log IU/mL).

with hemophilia who received nonheat-treated coagulation factor concentrates were found to be infected with a mixture of HCV serotypes.[22,23] The renal toxicity of TDF in combination with DTG and its efficacy and safety in patients with hemophilia with mixed HCV infection are unknown.

We herein report the findings of a cohort study that evaluated and compared the efficacy and safety of LDV/SOF in Japanese patients with hemophilia with 1, 4, and mixed-genotype HCV coinfected or noninfected with HIV.

MATERIALS AND METHODS

Patients

This cohort study comprised 43 male patients with hemophilia A or B treated with LDV/SOF at the Department of Hematology, Ogikubo Hospital, from September 2015 to April 2016. The CD4 cell counts and HIV viral loads were irrelevant for starting LDV/SOF; however, a minimum estimated glomerular filtration rate (eGFR) of >30 mL·min^{-1}·1.73 m^{-2} was required for all patients. A few patients underwent a liver biopsy because of the risk of hemorrhaging, so the noninvasive index for predicting liver cirrhosis was estimated based on 3 fibro scores combined with the gamma-globulin Fibro Index score,[24] the platelet count for Ikeda score,[25] and the aspartate aminotransferase-to-platelet ratio index.[26] Cirrhosis was determined when 3 estimated formulae simultaneously indicated cirrhosis. Informed consent in writing was obtained from each patient, and the study protocol conformed to the appropriate institutional review committee.

HCV Treatment

The patients received LDV (90 mg) and SOF (400 mg) in a fixed-dose combination (Gilead Sciences, Foster City, CA) orally once daily for 12 weeks, regardless of the cirrhosis status.

Study Assessments

The screening assessments included an evaluation of the serum HCV RNA levels, medical history, and content of antiretroviral therapy (ART) for HIV infection, in addition to the standard laboratory and clinical tests. The serum HCV RNA was measured using the COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Diagnostics K.K., Basel, Switzerland), with a lower limit of quantification of 1.2 Log IU/mL. The HCV core genotype was determined using the Gene Amp PCR system 9600 (Perkin Elmer, Inc., MA).

On-treatment assessments included standard laboratory testing, along with the measurement of the serum HCV RNA levels and HIV RNA levels and the recording of vital signs and weight at baseline; at 4, 8, and 12 weeks into treatment; and at 12 weeks after treatment. All adverse events were recorded and graded according to standardized scales. Monitoring of the renal function and the renal tubular function was performed in all patients (serum creatinine level, eGFR, and Uβ2MG level).

Statistical Analyses

This study was not designed to evaluate any formal statistical hypotheses, and no sample size calculations were performed. We compared the SVR12 and safety between the HIV-positive and HIV-negative groups and between the cirrhosis and noncirrhosis groups using chi-squared tests for detecting statistical significance. Differences were considered to be statistically significant if the *P* value was <0.05.

RESULTS

Patient Characteristics

Our population comprised 43 male Japanese patients with hemophilia A (number, n:38) or B (n:5). Twenty patients were coinfected with HIV. The patients were all chronically infected with genotype 1a (n = 25), 1b (n = 12), 4 (n = 5), or 1a + 2b (n = 1) HCV, including those with compensated (n = 8) or decompensated cirrhosis (n = 1). The prevalence of cirrhosis was significantly higher in patients with HIV (6/8 with compensated and 1 with decompensated cirrhosis) than in those without ($P = 0.03$). Although 18 patients (8 HIV-negative and 10 HIV-positive) were treatment-experienced with IFN-containing regimens, SVR could not be obtained in

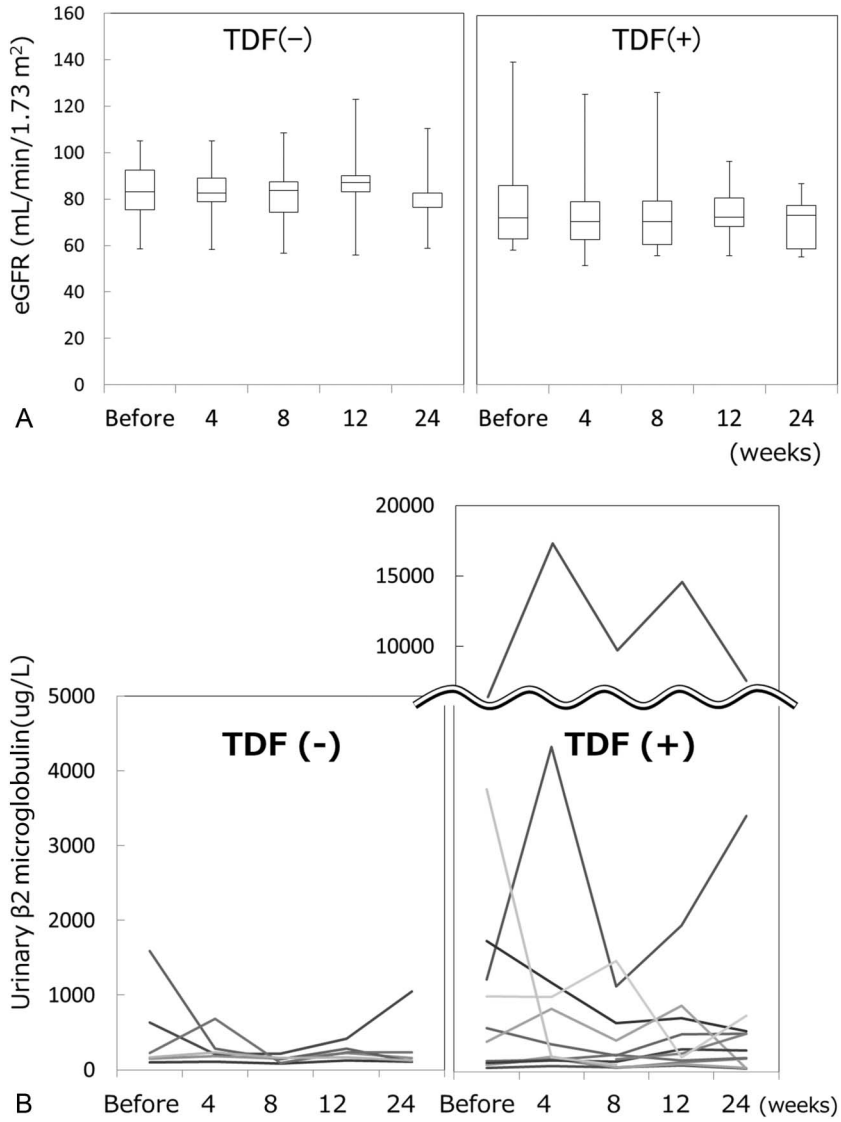

FIGURE 1. Evaluation of renal function between HIV-positive patients with and without TDF intake. A, A box and Whiskers plot of the value of eGFR in HIV patient. B, The value of UB2MG in each HIV patient.

any patients. Three of 18 patients were treatment-experienced with peg-IFN/RBV/simeprevir (2 HIV-positive patients had received this triple therapy twice). Although 41.8% of patients had CC of *IL28B* genotype, CC genotype are more likely to be cured by IFN, half of them had failed previous treatment with peg-IFN/RBV (data not shown).

The median CD4 cell count at the baseline was 616 cells per microliter. One patient with HIV infection had a CD4 cell count of 70 cells per microliter and was classified as A3 under the Centers for Disease Control and Prevention classification system,[27] 6 had CD4 counts of 300–500 cells per microliter and were classified as A2, and the others had CD4 counts exceeding 500 cells per microliter and were classified as A1. ART was commenced in most patients with HIV; however, 2 patients who had shown no progression over a long period were not on ART at the time of the study. Fourteen patients were receiving TDF/FTC, and the majority (75%) had originally received integrase inhibitors (DTG or RAL). ART was not changed before HCV treatment. The HIV RNA in all patients who were receiving ART was undetectable. There were no patients with positive hepatitis B antigens or hepatitis B viral DNA.

Efficacy

The efficacy is shown in Table 1. The rate of SVR12 with LDV/SOF was not significantly different between the HIV-negative and HIV-positive patients ($P = 0.12$). In total, 2 patients with HIV infection did not achieve SVR12; 1 died 8 weeks after the end of therapy, and the other had an HCV relapse 8 weeks after the end of therapy. The patient with a virologic relapse was infected with HCV type 1a and HIV (ART: TDF/FTC+RAL). The rate of SVR12 in the patients with cirrhosis was significantly lower than that in the patients without cirrhosis ($P = 0.005$).

Safety

None of the 43 patients in the study discontinued treatment prematurely due to an adverse event. Overall, 20

patients (46%) had adverse events, most of which were mild to moderate in severity. The following serious adverse events occurred in 3 patients: sudden deafness (1 patient), prosthetic replacement arthroplasty in a patient with severe arthropathy of the left hip joint (1 patient), and death (1 patient). The patient who died was infected with HIV and HCV type 1a with compensated cirrhosis. His complications were uncontrolled diabetes mellitus (HbA1c >13%) and hypertension. Postmortem cross-sectional whole-body imaging showed no remarkable observations.

Although the observed laboratory abnormalities were primarily hepatic and renal impairments, no patients had grade 3 or 4 elevations in any of the laboratory findings. The $CD4^+$ cell counts were stable during treatment, and no patients had HIV-1 virologic failure. All patients completed treatment with no alterations in the antiretroviral regimen.

No anticipated significant abnormalities with respect to the renal or renal tubular function were detected (Fig. 1). In the HIV-positive group, the Uβ2MG levels were higher in patients taking TDF than in those not taking it but were not significantly changed during LDV/SOF treatment, except in 1 patient with a transient high level of Uβ2MG (17,300 μg/L) 4 weeks into the study (Fig. 1B). This patient was taking TDF +EFV. His Uβ2MG level declined to 7540 μg/L at 12 weeks after LDV/SOF, and his serum creatinine level, eGFR, serum phosphate level, and proteinuria did not change significantly during LDV/SOF treatment.

DISCUSSION AND CONCLUSION

The efficacy and safety were not significantly different between the HIV-positive and HIV-negative patients. No modification of the HIV treatment was required, and no marked changes in the CD4 count or HIV RNA level in blood were noted. SVR12 was achieved even in patients with resistance-associated variants of HCV for LDV or SOF (data not shown). The failure history of previous IFN treatment and *IL28B* genotype did not affect the SVR success. The degree to which low CD4 counts (under 200 μL^{-1}) influence SVR remains controversial.[18,28–30] In this study, 1 patient with a CD4 count under 100 μL^{-1} achieved SVR12. A larger study or the accumulation of more case reports evaluating the efficacy of direct-acting antiviral (DAA) regimens in patients with low CD4 counts are necessary to clarify this issue.

A decline in the renal function (eGFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) from the start of intake was observed in 7 patients; however, some studies have reported that chronic kidney disease is a frequent complication in hemophilia because of HIV infection, TDF, HCV infection, diabetes mellitus, and microbleeding in the kidney.[31,32] Intake modification should be considered if the renal function is aggravated during intake; however, TDF was continued in all patients in our study because no aggravation was observed. The Uβ2MG level transiently exceeded 10,000 μg/L in patients taking TDF/FTC+EFV. Although an increased TDF concentration due to LDV or EFV was suspected as one of the causes of this increase in the Uβ2MG level, no marked changes in the eGFR, tubular reabsorption of phosphate, serum phosphorus level, or alkaline phosphatase level were noted, thus making the follow-up of these cases possible.

On a background of inherited bleeding disorder, our results of SVR12 did not differ from the reports that the SVR with LDV/SOF/RBV was 100% (14/14)[33] or the SVR with elbasvir (NS5A inhibitor) and grazoprevir (NS3/4A inhibitor) was 95% (95/100). Given that all of our patients with hemophilia had a long duration (more than 30 years) of HCV infection, this group of patients is considered an ageing cohort at an increased risk of serious and life-threatening complications. Approximately 20% of them had become complicated with cirrhosis 20 years after HCV infection, and the risk of hepatocellular carcinoma increases 5% annually once 30 years have passed since HCV infection. In addition, in our study, the prevalence of cirrhosis was higher in coinfected than in monoinfected patients, and the SVR in patients with cirrhosis was lower than in those without cirrhosis. Thus, patients with hemophilia who were infected with HCV through nonheat-treated coagulation factor concentrates should, therefore, be treated with DAA as early as possible before the onset of cirrhosis. Many patients infected with types 1 and 4 HCV have previously been unable to receive IFN-based therapy because of the markedly low rate of SVR and severe adverse effects, so the development of oral DAA regimens such as LDV/SOF can afford these patients new treatment opportunities and thereby improve their clinical outcomes.

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