Liver Fibrosis Is Associated With Corrected QT Prolongation During Ledipasvir/Sofosbuvir Treatment for Patients With Chronic Hepatitis C

Yuki Tahata,[1] Ryotaro Sakamori,[1] Ayako Urabe,[1] Naoki Morishita,[1] Ryoko Yamada,[1] Takayuki Yakushijin,[1] Naoki Hiramatsu,[1] Yoshinori Doi,[2] Akira Kaneko,[3] Hideki Hagiwara,[4] Yukinori Yamada,[5] Taizo Hijioka,[6] Masami Inada,[7] Shinji Tamura,[8] Yasuharu Imai,[9] Kunimaro Furuta,[1] Takahiro Kodama,[1] Hayato Hikita ,[1] Tomohide Tatsumi,[1] and Tetsuo Takehara[1]

Combination treatment of ledipasvir and sofosbuvir (LDV/SOF) is first-line treatment for patients with chronic hepatitis C genotype 1 in the United States, Europe, and Japan. However, the influence of LDV/SOF on the cardiovascular system is poorly characterized. A total of 470 chronic hepatitis C patients who started LDV/SOF treatment between September 2015 and February 2016 at nine hospitals in Japan were prospectively enrolled in this study. Corrected QT (QTc) prolongation was defined as a QTc interval ≥450 milliseconds. The sustained virologic response rate was 96.0% (451/470), and the discontinuance rate due to adverse effects was 0.9% (4/470). Among 395 patients whose electrocardiogram was evaluated over time and compared with baseline, the QTc interval was significantly prolonged during treatment and returned to baseline levels 12 weeks after the end of treatment. Twenty-four of 376 patients with baseline QTc intervals <450 milliseconds experienced on-treatment QTc prolongation. Higher aspartate aminotransferase-to-platelet ratio index scores (≥0.76; odds ratio, 4.375; *P* = 0.005) and longer QTc intervals (≥416 milliseconds; odds ratio, 4.823; *P* = 0.003) at baseline were significantly associated with on-treatment QTc prolongation on multivariate analysis. Patients with cirrhosis showed significantly longer QTc intervals than those without cirrhosis during treatment but not at baseline, and they developed on-treatment QTc prolongation at a higher rate than patients without cirrhosis. No cardiovascular events occurred, except for 1 patient who developed paroxysmal supraventricular tachycardia. *Conclusion*: Newly developed QTc prolongation was observed in 6.4% of Japanese patients during treatment and was associated with more advanced fibrosis. (*Hepatology Communications* 2018;2:884-892).

Antiviral treatments for patients with chronic hepatitis C virus (HCV) infection have changed from interferon-based treatment to interferon-free treatment using multiple direct-acting antivirals. Ledipasvir (LDV; an HCV nonstructural protein 5A protease inhibitor) plus sofosbuvir (SOF; an HCV nonstructural protein 5B polymerase inhibitor) treatment is a once daily medical compound for oral use and shows high sustained virologic response (SVR) rates and low discontinuous rates for patients with

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; EOT, end of treatment; HCV, hepatitis C virus; LDV, ledipasvir; QTc, corrected QT; SOF, sofosbuvir; SVR, sustained virologic response.

Received February 26, 2018; accepted May 15, 2018.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1206/full.

Supported by a Grant-in-Aid for Research on Hepatitis from the Ministry of Health, Labor, and Welfare of Japan and the Japan Agency for Medical Research and Development (JP18fk0210021 to T.T., R.S., and H.H.; JP18fk0210025 to R.S.).

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1206

Potential conflict of interest: Dr. Takehara is on the speakers' bureau and received grants from Gilead. Dr. Kodama received grants from Gilead. The other authors have nothing to report.

chronic HCV genotype 1 infection in clinical trials.[1-4] LDV/SOF treatment is one of the first-line choices for patients with chronic HCV genotype 1 infections in the United States, Europe, and Japan.[5-7]

SOF was approved in December 2013 for patients with HCV infections by the U.S. Food and Drug Administration, and an SOF-based regimen has been shown to be relatively safe. However, in the combination treatment of SOF and another direct-acting antiviral for patients with chronic HCV infection, 9 patients experienced extreme bradycardia in postmarketing reports.[8] All 9 patients took amiodarone by mouth; 1 patient died and 3 patients needed a pacemaker insertion. European guidelines for hepatitis C recommend that amiodarone and SOF should not be co-administered.[6] Regarding the adverse cardiac events in phase 3 trials, 1 patient experienced unstable angina during LDV/SOF treatment.[1-3] In a Japanese phase 3 trial, 2 patients receiving LDV/SOF plus ribavirin treatment among 341 patients receiving LDV/SOF with or without ribavirin treatment experienced severe adverse cardiac events (including cardiac arrest and acute myocardial infarction).[4] Regarding electrocardiography, Hagiwara et al.[9] reported that corrected QT (QTc) prolongation during LDV/SOF treatment was observed in 2 out of 17 patients who were able to be evaluated by electrocardiography over time. However, the patient sample size was small, the factors associated with QTc prolongation were not investigated, and data on the QTc interval during LDV/SOF treatment were not examined in phase 3 trials.

In the present study, we investigated the effect of antiviral treatments on the QTc interval as well as the overall efficacy and safety of treatment in a prospective cohort of patients with chronic HCV genotype 1 infection who were treated in general practice.

Patients and Methods

STUDY PATIENTS

This study is a multicenter prospective study conducted by Osaka University Hospital and other hospitals affiliated with the Osaka Liver Forum. A total of 470 consecutive patients with chronic HCV genotype 1 infection who started the fixed-dose LDV/SOF combination treatment between September 2015 and February 2016 at 9 institutions were enrolled in this study.

Inclusion criteria were patients aged 20 years old or more and infected with HCV genotype 1. Patients with decompensated cirrhosis (Child-Pugh grade B or C), signs of liver failure, hepatocellular carcinoma (HCC), hepatitis B virus or human immunodeficiency virus co-infection, other causes of liver disease (e.g., primary biliary cholangitis or autoimmune hepatitis), and comorbidities, such as immunodeficiency or severe chronic renal failure (estimated glomerular filtration rate under 30 mL/minute/1.73 m^2), were excluded. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and the Ethics Committee of Osaka University Hospital and institutional review boards of all hospitals affiliated with the Osaka Liver Forum approved this study (UMIN000018561). Written informed consent was obtained from all study patients.

TREATMENT PROTOCOL AND DATA COLLECTION

Patients received a fixed dose, once daily, oral tablet of LDV (90 mg/day) plus SOF (400 mg/day) (HARVONI; Gilead Science, Foster City, CA) for 12 weeks. For safety

ARTICLE INFORMATION:

From the [1]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Suita, Japan; [2]Otemae Hospital, Osaka, Japan; [3]NTT West Osaka Hospital, Osaka, Japan; [4]Kansai Rosai Hospital, Amagasaki, Japan; [5]Kaizuka City Hospital, Kaizuka, Japan; [6]National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan; [7]Toyonaka Municipal Hospital, Toyonaka, Japan; [8]Minoh City Hospital, Minoh, Japan; [9]Ikeda Municipal Hospital, Ikeda, Japan.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Tetsuo Takehara, M.D., Ph.D.
Department of Gastroenterology and Hepatology
Osaka University Graduate School of Medicine
2-2 Yamadaoka
Suita, Osaka 565-0871, Japan
E-mail: takehara@gh.med.osaka-u.ac.jp
Tel: +81-6-6879-3621

evaluation, physical examinations and blood tests were performed at 1 week, 2 weeks, and every 2 weeks until the end of treatment (EOT). A liver biopsy was performed prior to initiating LDV/SOF treatment. Trained liver pathologists confirmed diagnoses and scored the grade of activity and fibrosis of liver tissues based on the meta-analysis of histological data in viral hepatitis (METAVIR) histological score.[10] Liver cirrhosis was diagnosed according to a METAVIR score of F4 in cases when liver biopsy was performed and according to clinical findings in cases without liver biopsy. Clinical findings included characteristics of liver cirrhosis on a liver imaging test or blood test or physical findings and gastroesophageal varix by gastroendoscopy. We evaluated serum levels of creatinine, alanine aminotransferase, total bilirubin, neutrophil, and hemoglobin and platelet counts as laboratory adverse events according to the Common Terminology Criteria for Adverse Events version 4.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

ELECTROCARDIOGRAM EXAMINATION

Electrocardiography was performed at baseline, 4 weeks, 8 weeks, 12 weeks, and 12 weeks after the EOT. QTc interval measurements were automatically calculated according to Bazett's formula ($QTc = QT/\sqrt{RR}$) or ECAPS, which is a correction formula based on a linear regression technique, ($QTc = QT + (1–RR)/7$) by the electrocardiogram machine. The maximal value of QTc intervals ≥450 milliseconds was defined as QTc prolongation because QTc intervals ≥450 milliseconds were considered grade 1 adverse events in the Common Terminology Criteria for Adverse Events version 4.0. Patients with a history of atrial fibrillation were excluded from the analysis by electrocardiogram.

ASSESSMENT OF THE VIROLOGIC RESPONSE

Serum HCV-RNA levels were routinely monitored during and after the treatment by using real-time polymerase chain reaction (COBAS TaqMan HCV version 2.0; quantitative range 1.2 to 8.0 $\log_{10}$ IU/mL; Roche Diagnostics K.K., Tokyo, Japan). Serum HCV-RNA negativity at 24 weeks after the EOT was classified as SVR24.

STATISTICAL ANALYSIS

The continuous baseline variables were described as the median value and range, and categorical baseline variables were described as absolute frequencies. The Wilcoxon signed-rank test was used to analyze the differences in the QTc interval during and after treatment, and the Mann-Whitney test was used to analyze the differences in the QTc interval and delta QTc interval for patients with chronic hepatitis and liver cirrhosis at each time point. Fisher's exact test or the chi-square test was used to analyze categorical data. Univariate and multivariate logistic regression analyses were used, and all continuous variables were divided according to the median value in the analyses of factors associated with QTc prolongation (QTc interval ≥450 milliseconds). All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, NY), and a two-tailed P value of <0.05 was considered statistically significant.

Results

BASELINE CHARACTERISTICS OF STUDY PATIENTS

The median age was 70 years, and 22.1% (104/470) of patients were diagnosed with liver cirrhosis (Table 1). Among the 104 patients with liver cirrhosis, 33 were diagnosed by liver histology (F4) and 71 were diagnosed clinically. Fifty-three patients (11.3%) had a history of HCC treatment. These 53 patients received curative treatment for HCC before LDV/SOF treatment, and signs of HCC recurrence were not observed on liver imaging. Additionally, 51.1% (240/470) of patients had never received antiviral therapy.

TREATMENT EFFECT

Virologic responses were assessed using intention-to-treat analysis. HCV-RNA negativity rates at the EOT and 12 and 24 weeks after the EOT were 98.1% (461/470), 97.9% (460/470), and 96.0% (451/470), respectively (Supporting Fig. S1). Two patients died before being classified as SVR12, and 4 patients relapsed after the EOT. Thirteen patients were lost to follow-up on classification as SVR24 and were counted as non-SVR.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

Factor	All (N = 470)	CH (n = 366)	LC (n = 104)
Age (years)	70 (26-92)	68 (26-92)	72 (43-85)
Sex, male/female	211/259	175/191	36/68
BMI (kg/m^2)*	22 (15-34)	22 (16-34)	23 (15-31)
Diabetes mellitus, no/yes	386/84	312/54	74/30
Hypertension,† no/yes	285/167	227/123	58/44
Previous antiviral treatment,‡ naive/IFN/IFN and RBV/Peg-IFN and RBV/PI, Peg-IFN, and RBV	240/33/14/124/54	193/25/8/95/42	47/8/6/29/12
Cirrhosis, no/yes	366/104	366/0	0/104
Child-Pugh score, 5/6	59/45	-	59/45
History of HCC treatment, no/yes	417/53	342/24	75/29
HCV-RNA (median, $\log_{10}$ IU/mL)	6.1 (2.0-8.0)	6.1 (2.0-8.0)	6.0 (3.0-7.0)
Liver histology: activity, A0/1/2/3	10/156/43/0	10/133/30/0	0/23/13/0
fibrosis, F0/1/2/3/4	9/104/41/19/33	9/104/41/19/0	0/0/0/0/33
White blood cell (/μL)	4,395 (1,730-9,400)	4,505 (1,730-9,400)	3,800 (1,930-7,800)
Hemoglobin (g/dL)	13.5 (8.2-17.8)	13.6 (8.2-17.8)	13.1 (9.0-16.9)
Platelets (×10^4/μL)	14.5 (2.5-47.6)	16.1 (5.9-47.6)	10.4 (2.5-21.7)
Total bilirubin (mg/dL)	0.7 (0.2-2.7)	0.7 (0.2-2.7)	0.9 (0.3-1.8)
AST (U/L)	42 (13-230)	39 (13-230)	50 (18-164)
ALT (U/L)	38 (9-338)	37 (9-338)	41 (9-148)
Creatinine (mg/dL)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.7 (0.4-1.4)
Albumin (g/dL)	3.9 (2.9-5.0)	4.0 (2.9-4.9)	3.7 (2.9-5.0)
APRI score	0.76 (0.13-7.70)	0.62 (0.13-6.18)	1.29 (0.48-7.70)
FIB-4 index	3.18 (0.55-22.72)	2.79 (0.55-13.31)	5.52 (2.30-22.72)
BNP (ng/mL)§	27.4 (3.3-483.5)	24.5 (3.9-483.5)	35.7 (3.3-286.6)
QTc interval (milliseconds)‖	416 (334-492)	417 (334-474)	416 (338-492)

*BMI data were missing in 22 patients; †hypertension data were missing in 18 patients; ‡previous antiviral treatment data were missing in 5 patients; §BNP data were missing in 39 patients; ‖QTc interval data were missing in 16 patients.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; CH, chronic hepatitis; FIB-4, fibrosis 4; IFN, interferon; LC, liver cirrhosis; Peg-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin.

SAFETY AND CHARACTERISTICS OF PATIENTS LEADING TO DISCONTINUATION

Nine patients experienced an increase in creatinine levels (1.5-3 times baseline values) (Table 2). One patient discontinued treatment after 4 weeks because of renal impairment. One patient experienced an increase in alanine aminotransferase (3-5 times upper limit of normal), and 10 other patients experienced an increase in bilirubin (1.5-3 times upper limit of normal); however, none of these patients discontinued treatment or experienced signs of liver failure. Regarding cardiovascular events, 1 patient developed a paroxysmal supraventricular tachycardia at week 1 and was treated with verapamil hydrochloride but safely completed LDV/SOF treatment. The patient who developed a paroxysmal supraventricular tachycardia was a 56-year-old woman who was clinically diagnosed with liver cirrhosis (liver biopsy was not examined).

TABLE 2. SAFETY DURING TREATMENT

	N = 470
Adverse events leading to discontinuation	4 (0.9%)
Reasons	
Sudden death	1 (0.2%)
Renal impairment	1 (0.2%)
Hyperkalemia	1 (0.2%)
Pneumonia	1 (0.2%)
Laboratory abnormalities	
Increased creatinine	
1.5-3 times BL	9 (1.9%)
Increased ALT	
3-5 times ULN	1 (0.2%)
Increased bilirubin	
1.5-3 times ULN	10 (2.1%)
Decreased neutrophil count	
500-1,000/μL	10 (2.1%)
Decreased hemoglobin	
8.0-10.0 g/dL	13 (2.8%)
<8.0 g/dL	1 (0.2%)
Decreased platelet count	
2.5-5.0 × 10^4/μL	7 (1.5%)

Abbreviations: ALT, alanine aminotransferase; BL, baseline; ULN, upper limit of normal.

TABLE 3. CHARACTERISTICS OF PATIENTS LEADING TO DISCONTINUATION

	Age (Years)	Sex	Cirrhosis	Previous Antiviral Treatment	Comorbidity	Past Medical History	Reasons Leading To Discontinuation	Administration Period (Weeks)
Case 1	81	female	no	naive	hypertension	sepsis	hyperkalemia	6
Case 2	84	male	yes	naive	COPD	-	pneumonia	1
Case 3	72	female	yes	naive	-	-	sudden death	2
Case 4	81	female	yes	naive	CKD	-	renal impairment	4

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IFN, interferon.

She had a history of cancer of the ovary; however, she had no history of cardiovascular disease and was not receiving any medication at the time she started LDV/SOF treatment. Other patients did not develop cardiac events needing medical treatment, such as severe heart failure or arrhythmia. None of the study patients took amiodarone by mouth.

Four patients discontinued LDV/SOF treatment due to adverse events, and the discontinuous rate was 0.9%. In the 4 patients who discontinued LDV/SOF treatment, 3 patients were aged 80 years or more, 3 patients had liver cirrhosis, and all 4 patients were treatment naive (Table 3). Reasons leading to discontinuation were hyperkalemia, pneumonia, sudden death, and renal impairment. Two out of 4 patients died (cases 2 and 3). One patient was an 84-year-old man with underlying chronic obstructive pulmonary disease and liver cirrhosis who died because of pneumonia 10 weeks after a 1-week administration of LDV/SOF (case 2). The other patient was a 72-year-old woman with underlying liver cirrhosis; she died at week 2 from a sudden unexplained death (case 3).

EFFECT OF LDV/SOF TREATMENT ON QTC PROLONGATION

Electrocardiography could be evaluated in 395 patients at baseline, 4 weeks, 8 weeks, 12 weeks, and 12 weeks after the EOT (Supporting Fig. S2). The QTc interval during treatment was significantly longer than baseline during treatment and returned to the same level as baseline 12 weeks after the EOT (Fig. 1A). The QTc interval was prolonged to 481-500 milliseconds during treatment (grade 2 adverse event) in 2 patients and to 501 milliseconds or more (grade 3 adverse event) in 1 patient; however, all 3 patients completed LDV/SOF treatment without cardiovascular events. No patient experienced grade 4 QTc prolongation.

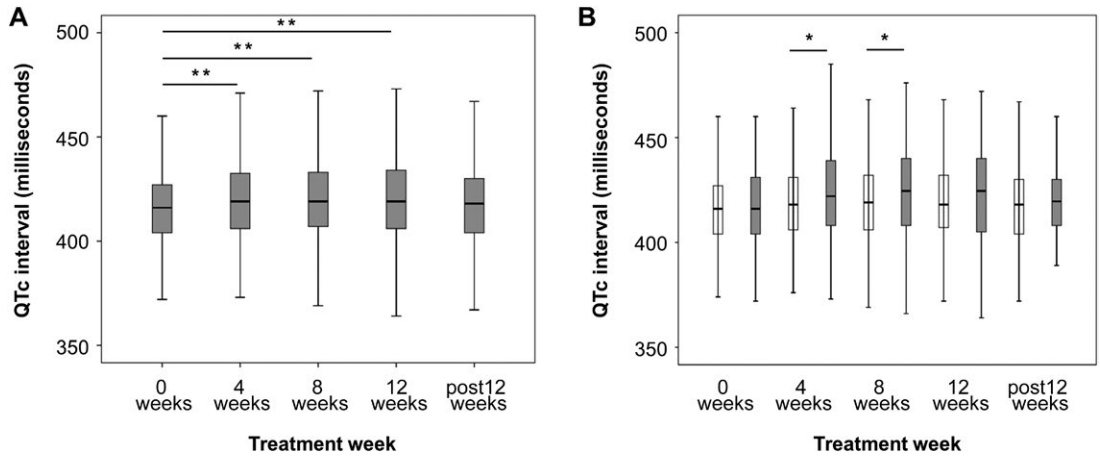

FIG. 1. Changes in QTc interval during treatment and 12 weeks after the EOT. (A) All patients; (B) patients with chronic hepatitis and liver cirrhosis. White box, patients with chronic hepatitis; gray box, patients with liver cirrhosis. Boxes represent twenty-fifth to seventy-fifth percentiles; lines within the boxes represent median values. The lower and upper lines outside the boxes represented tenth to ninetieth percentiles, respectively. $^{*}P < 0.05$, chronic hepatitis versus liver cirrhosis at each time point; $^{**}P < 0.01$, 0 week versus each value at each time point.

TABLE 4. FACTORS ASSOCIATED WITH QTC PROLONGATION (QTC INTERVAL ≥450 MILLISECONDS) DURING TREATMENT AMONG PATIENTS WHOSE QTC INTERVAL WAS <450 MILLISECONDS AT BASELINE

		Univariate Analysis			Multivariate Analysis		
Factor	Category	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (years)	<70/≥70	0.966	0.423-2.210	0.936			
Sex	Male/Female	1.610	0.672-3.860	0.286			
BMI (kg/m^2)	<22/≥22	0.862	0.364-2.042	0.736			
Fibrosis	F0-2/F3,4	2.723	0.811-9.149	0.105			
Total bilirubin (mg/dL)'	<0.7/≥0.7	2.789	1.018-7.639	0.046	2.336	0.831-6.569	0.108
ALT (U/L)	<38/≥38	1.223	0.533-2.803	0.635			
Creatinine (mg/dL)	<0.7/≥0.7	0.457	0.190-1.094	0.079			
Albumin (g/dL)	<3.9/≥3.9	0.692	0.303-1.584	0.384			
APRI score	<0.76/≥0.76	4.258	1.555-11.657	0.005	4.375	1.566-12.226	0.005
FIB-4 index	<3.18/≥3.18	2.093	0.873-5.016	0.098			
BNP (ng/mL)	<27.4/≥27.4	1.025	0.432-2.430	0.956			
QTc interval (milliseconds)	<416/≥416	4.356	1.591-11.926	0.004	4.823	1.734-13.413	0.003

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; FIB-4, fibrosis 4.

Twenty-four (6.4%) out of 376 patients with QTc intervals <450 milliseconds at baseline experienced on-treatment QTc prolongation (QTc interval ≥450 milliseconds) during treatment (Table 4). We collected data on co-administered drugs on the 24 patients who experienced on-treatment QTc prolongation. With the exception of 1 patient who was treated for a paroxysmal supraventricular tachycardia, there were no changes in other drugs for these patients after starting administration of LDV/SOF.

In univariate analysis, total bilirubin levels (P = 0.046), aspartate aminotransferase-to-platelet ratio index (APRI) scores (P = 0.005), and QTc intervals at baseline (P = 0.004) correlated with on-treatment QTc prolongation. Multivariate analysis using these three factors revealed that higher APRI scores (≥0.76; odds ratio, 4.375; P = 0.005) and longer QTc intervals at baseline (≥416; odds ratio, 4.823; P = 0.003) were significant independent factors associated with on-treatment QTc prolongation. No patient met a diagnostic criterion for long QT syndrome.

Because the noninvasive indicator of liver fibrosis, the APRI score, independently correlated with QTc prolongation during treatment, we compared the rate of QTc prolongation during treatment in patients with or without cirrhosis. The QTc prolongation rate during treatment was much higher in patients with cirrhosis than in patients without cirrhosis (Fig. 2). The QTc interval was significantly longer in patients with cirrhosis than in patients without cirrhosis during treatment, but this difference was not observed before treatment and disappeared after treatment (Fig. 1B). In addition, we investigated the delta QTc interval (changes in the QTc interval between baseline and each time point). At 8 weeks, the delta QTc interval was longer in patients with cirrhosis than in patients without cirrhosis (Supporting Fig. S3).

Discussion

The present study revealed a high SVR24 rate of 96.0% and demonstrated that the discontinuous rate

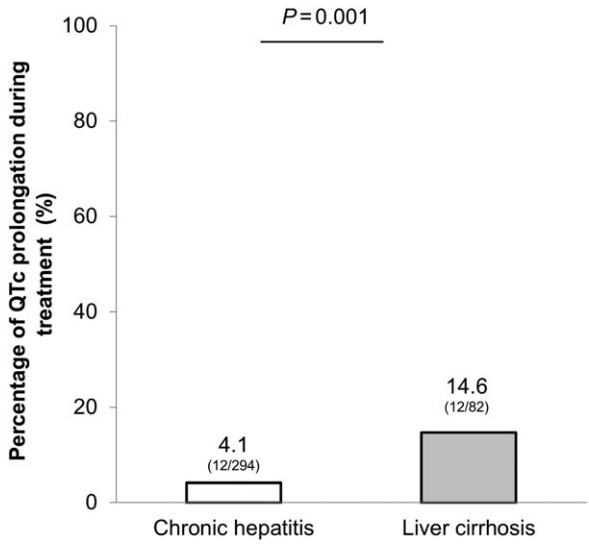

FIG. 2. Incidence of on-treatment QTc prolongation (QTc interval ≥450 milliseconds) during treatment in patients with chronic hepatitis and liver cirrhosis.

was only 0.9% for Japanese patients with chronic HCV genotype 1 infection in clinical practice. Although the age of this cohort was older than that of previous clinical trials (mean age in previous trials, 51-60 years old), the effect and safety of LDV/SOF treatment in clinical practice were very high and of similar magnitude to clinical trials that implemented LDV/SOF treatment with or without ribavirin.[1-4] The present study demonstrated for the first time that the QTc interval was significantly prolonged during LDV/SOF treatment and then returned to a baseline level after treatment. In addition, this study revealed that newly developed QTc prolongation (QTc ≥450 milliseconds) was observed in 6.4% of patients and was associated with liver fibrosis. According to a safety test on healthy subjects, the administration of SOF for a single therapeutic (400 mg) or supratherapeutic (1,200 mg) dose or supratherapeutic doses of LDV (120 mg twice daily) for 10 days alone did not prolong the QTc interval.[11] The difference in the duration of administration, the administration of multiple direct-acting antivirals, and lack of any liver disease may be possible reasons for the difference between the present study and the previous safety test.

QTc prolongation is an important electrocardiogram finding.[12-14] According to reports of patients with or without cardiac disease, patients with QTc prolongation had a 2-fold to 3-fold effect on sudden death compared with patients without QTc prolongation.[13,14] A QTc interval >450 milliseconds has been reported as a risk factor for all-cause and cardiovascular mortality in several populations.[15,16] QTc prolongation was divided into congenital or acquired factors, such as an electrolyte abnormality, or taking certain types of drugs.[17-20] A variety of drugs, including anti-arrhythmic drugs, histamine H_2 receptor antagonists, hypocholesterolemic agents, and psychotropic drugs, were reported to prolong the QTc interval.[21-23] Morganroth et al.[21] reported that 1.1% (4/360) of patients experienced QT prolongation (QT interval >550 milliseconds) after the administration of quinidine. Yun et al.[22] reported that 15.5% (56/362) of patients experienced QTc prolongation (QTc interval >450 milliseconds) after the administration of famotidine. Reinoehl et al.[23] reported that 16% (58/359) of patients experienced QTc prolongation (QTc interval ≥450 milliseconds) after the administration of probucol, and predrug QTc interval and female sex were significantly associated with QTc prolongation. In the present study, QTc prolongation (QTc interval ≥450 milliseconds) was observed during SOF/LDV treatment in 6.4% (24/376) of patients whose baseline QTc interval was <450 milliseconds.

In this study, baseline APRI scores and QTc intervals were significantly associated with QTc prolongation during LDV/SOF treatment (Table 4). The APRI score is a noninvasive fibrosis diagnostic tool that can be calculated using routine laboratory data (aspartate aminotransferase level and platelet count) and was widely recognized as correlating with liver fibrosis in patients with chronic hepatitis C.[24,25] Therefore, we examined the association between QTc prolongation and liver fibrosis. The QTc interval and delta QTc interval from baseline were significantly longer in patients with cirrhosis than in patients without cirrhosis during treatment (Fig. 1B; Supporting Fig. S3), and the QTc prolongation rate during treatment was much higher in patients with cirrhosis than in patients without cirrhosis (Fig. 2). In patients with liver cirrhosis, the QTc interval was reported to be longer than in patients without cirrhosis.[26,27] The underlying mechanism was not fully investigated, but activation of sympathetic nerves was reported as a possible mechanism.[26,28] For the metabolism of LDV/SOF, the plasma exposure of LDV or SOF in subjects with severe liver impairment was similar to or modestly higher than that in patients with normal liver function.[11] These factors might be part of the cause of QTc prolongation during LDV/SOF treatment in patients with liver cirrhosis, but the specific mechanism is unclear. On the other hand, baseline QTc intervals were similar among patients with cirrhosis and patients without cirrhosis in the present study. Bernardi et al.[26] reported that the QTc interval was prolonged along with an increased Child-Pugh score. In the present study, patients with cirrhosis with only a Child-Pugh grade A score were enrolled, and this may be a possible reason why the baseline QTc interval did not change between patients with cirrhosis and patients without cirrhosis at baseline.

There are several limitations of the present study. First, this is an observational study and includes some missing values. Among 470 patients, electrocardiography was not evaluated in 75 patients (16%) over time. However, electrocardiography could be evaluated in about 400 patients over time, and the present study is the first report to describe changes in the QTc interval during LDV/SOF treatment. Second, several conditions with electrolyte abnormalities and co-administered drugs may affect the QTc interval. However, serum electrolyte levels were not studied in the present study and co-administered drugs were

examined only in patients with on-treatment QTc prolongation. Third, the present study was conducted only in Japanese patients and the influence of race could therefore not be examined. Fourth, our cohort was older than those typically studied in clinical trials and the proportion of younger patients was relatively small.

In conclusion, the QTc interval is slightly but significantly prolonged during LDV/SOF treatment. In our cohort, the incidence of QTc prolongation during treatment was 6.4% and no cardiovascular events occurred, except for one case of arrhythmia. During treatment, the QTc interval and the delta QTc interval from baseline were longer and the incidence of on-treatment QTc prolongation was higher in patients with cirrhosis than in those without cirrhosis. Clinicians need to be aware of the potential for QTc prolongation with LDV/SOF, especially in those with cirrhosis, and should consider monitoring on a case-by-case basis.

Acknowledgment: Other institutions that enrolled patients in this study were as follows: Osaka International Cancer Institute, K. Katayama; National Hospital Organization Osaka National Hospital, E. Mita; Osaka Rosai Hospital, A. Hosui; National Hospital Organization Minami Wakayama Medical Center, I. Yabuuchi; Osaka Police Hospital, M. Oshita; Japan Community Healthcare Organization Osaka Hospital, T. Ito; Osaka General Medical Center, A. Inoue; Yao Municipal Hospital, H. Fukui; Nishinomiya Municipal Central Hospital, H. Ogawa; Suita Municipal Hospital, Y. Yoshida; Kinki Central Hospital of Mutual Aid Association of Public School Teachers, M. Yamamoto; Sumitomo Hospital, A. Yamada; Itami City Hospital, S. Tsutsui; Hyogo Prefectural Nishinomiya Hospital, S. Iio; and Saso Hospital, M. Nishiuchi. Author names in bold designate shared co-first authorship.

REFERENCES

1) Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al.; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-1898.
2) Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al.; ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-1493.
3) Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al.; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-1888.
4) Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis 2015;15:645-653.
5) Asahina Y, Izumi N, Hiromitsu K, Kurosaki M, Koike K, Suzuki F, et al. JSH Guidelines for the management of hepatitis C virus infection: a 2016 update for genotype 1 and 2. Hepatol Res 2016;46:129-165.
6) European Association for the Study of the Liver (EASL). EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2016;65:146-181.
7) AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932-954.
8) Dear Healthcare Provider letter: serious and life-threating cases of symptomatic bradycardia as well as one case of fatal cardiac arrest reported with coadministration of amiodarone with either Harvoni® (ledipasvir and sofosbuvir fixed-dose combination) or with Sovaldi® (sofosbuvir) in combination with another direct acting antivilar. Foster City, CA: Gilead Sciences, Inc.; March 20, 2015.
9) Hagiwara S, Nishida N, Watanabe T, Sakurai T, Ida H, Minami Y, et al. Outcome of combination therapy with sofosbuvir and ledipasvir for chronic type C liver disease. Oncology 2017;92(Suppl. 1):3-9.
10) Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289-293.
11) German P, Mathias A, Brainard D, Kearney BP. Clinical pharmacokinetics and pharmacodynamics of ledipasvir/sofosbuvir, a fixed-dose combination tablet for the treatment of hepatitis C. Clin Pharmacokinet 2016;55:1337-1351.
12) Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136-1144.
13) Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074-1077.
14) Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83:1888-1894.
15) Cox AJ, Azeem A, Yeboah J, Soliman EZ, Aggarwal SR, Bertoni AG, et al. Heart rate-corrected QT interval is an independent predictor of all-cause and cardiovascular mortality in individuals with type 2 diabetes: the Diabetes Heart Study. Diabetes Care 2014;37:1454-1461.
16) Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. Am J Med 2003;115:689-694.
17) Schwartz PJ. Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;109:399-411.
18) Moss AJ. Prolonged QT-interval syndromes. JAMA 1986;256:2985-2987.
19) Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013-1022.
20) Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. Eur Heart J 2000;21:1216-1231.

21) Morganroth J, Horowitz LN. Incidence of proarrhythmic effects from quinidine in the outpatient treatment of benign or potentially lethal ventricular arrhythmias. Am J Cardiol 1985;56:585-587.
22) **Yun** J, **Hwangbo** E, Lee J, Chon CR, Kim PA, Jeong IH, et al. Analysis of an ECG record database reveals QT interval prolongation potential of famotidine in a large Korean population. Cardiovasc Toxicol 2015;15:197-202.
23) Reinoehl J, Frankovich D, Machado C, Kawasaki R, Baga JJ, Pires LA, et al. Probucol-associated tachyarrhythmic events and QT prolongation: importance of gender. Am Heart J 1996;131:1184-1191.
24) European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. JHepatol 2015;63:237-264.
25) Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.
26) Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology 1998;27:28-34.
27) Ytting H, Henriksen JH, Fuglsang S, Bendtsen F, Moller S. Prolonged Q-T(c) interval in mild portal hypertensive cirrhosis. JHepatol 2005;43:637-644.
28) Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. JHepatol 2006;44:994-1002.

Author names in bold designate shared co-first authorship.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1206/full.