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BRIEF REPORT

Successful Re-treatment of Hepatitis C Virus in Patients Coinfected With HIV Who Relapsed After 12 Weeks of Ledipasvir/Sofosbuvir

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We assessed the efficacy and safety of ledipasvir/sofosbuvir plus ribavirin for 24 weeks in 9 human immunodeficiency virus/hepatitis C virus–coinfected patients who relapsed after receiving 12 weeks of treatment with ledipasvir/sofosbuvir. Eight of 9 (89%) achieved sustained virologic response 12 weeks after the end of treatment. One patient relapsed at posttreatment week 4. These results suggest an effective salvage therapy for patients for whom direct-acting antiviral treatment has failed.

Clinical Trials Registration. NCT02073656.

Keywords. HCV/HIV coinfection; direct-acting antiviral agents; HCV NS5B polymerase inhibitor; re-treatment; NS5A resistance.

All-oral, interferon-free therapy has substantially improved hepatitis C virus (HCV) management in recent years. Safe and well-tolerated regimens with cure rates of >90% are available for most patients, even those with characteristics historically associated with poor response to treatment [1–3]. However, for those failing to achieve sustained virologic response (SVR), re-treatment options remain uncertain. The emergence of long-lasting NS5A resistance-associated variants (RAVs) after exposure to NS5A inhibitors raises concerns about re-treatment with NS5A inhibitors [4–6]. For patients needing re-treatment, the optimal combinations of direct-acting antivirals (DAAs), duration of salvage therapy, and the role of ribavirin are unknown.

In the ION-4 phase 3 trial, HCV/human immunodeficiency virus (HIV)–coinfected patients receiving ledipasvir/sofosbuvir for 12 weeks had an SVR rate of 96% [7]. For 9 study patients who experienced HCV virologic relapse, we assessed the efficacy and safety of 24 weeks of ledipasvir/sofosbuvir plus weight-based ribavirin.

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METHODS

Study Design and Participants

This open-label, re-treatment substudy was conducted at 9 sites in the United States. We enrolled 9 of the 10 patients with HIV/HCV coinfection who had virologic failure after treatment with ledipasvir/sofosbuvir in the ION-4 study within 60 days from confirmed virologic failure (ClinicalTrials.gov identifier NCT02073656). One patient who had virologic relapse after a full course of treatment in ION-4 was not enrolled in this substudy due to hepatocellular carcinoma.

All patients provided written informed consent before any study procedures were undertaken. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Study Procedures

All patients received the fixed-dose combination tablet of ledipasvir/sofosbuvir once daily plus weight-based ribavirin (1000 mg in patients with a body weight of <75 kg, and 1200 mg in patients with a body weight of ≥75 kg) in a divided dose for 24 weeks.

Deep sequencing of the NS5A and NS5B regions of the HCV RNA using MiSeq technology (DDL Diagnostic Laboratory, Rijswijk, the Netherlands) was performed for all patients at baseline prior to the primary treatment course and at the time of virologic failure in the primary study, and at the time of virologic failure in the re-treatment substudy. Presence of variants was evaluated by deep sequencing assay cutoffs of 1% of the viral population. NS5A RAVs, defined as those that confer >2.5-fold reduced susceptibility to ledipasvir in vitro, include specific substitutions at the following positions: K24G/N/R, M28A/G/T, Q30E/G/H/L/K/R/T, L31I/F/M/V, P32L, S38F, H58D, A92K/T, and Y93C/F/H/N/S for genotype 1a and L31I/F/M/V, P32L, P58D, A92K, and Y93C/H/N/S for genotype 1b. NS5B RAVs include the specific substitutions at the following positions: S96T, N142T, L159F, S282T, any S282 variant other than T, M289L/I, L320V/I/F, and V321A/I.

All patients were assessed for safety by physical examination and by review of adverse events and clinical laboratory testing of blood samples on the first day of re-treatment, at weeks 2, 4, 8, 12, 16, and 20 on treatment, and at the end of treatment.

Statistical Analysis

The statistical analysis was performed on all enrolled and treated patients. The safety data were assessed descriptively. Formal statistical hypothesis testing was not conducted.

RESULTS

Baseline Characteristics

Nine patients were enrolled and completed study treatment (Table 1). All patients were black, had non-CC *IL28B* genotype, and were receiving antiretroviral regimens with suppressed HIV RNA. They had a median baseline $CD4^+$ count of 785 cells/μL (interquartile range, 404–971 cells/μL). The mean age was 57 years (range, 35–65 years), 7 were male, and 7 had genotype 1a infection. Two had cirrhosis. The median time from virologic failure in the primary study to dosing in the re-treatment study was 40 days (range, 34–70 days). The mean re-treatment baseline HCV RNA was 6.4 $\log_{10}$ IU/mL (range, 4.4–7.1 $\log_{10}$ IU/mL), compared with 7.0 $\log_{10}$ IU/mL (range, 6.5–7.5 $\log_{10}$ IU/mL) in the primary study. HIV antiretroviral regimens were the same as in the primary study, and included tenofovir and emtricitabine with either efavirenz (n = 7) or raltegravir (n = 2).

Seven of the 9 patients had NS5A RAVs detected at the time of relapse using deep sequencing with assay cutoff of 1%, including L31M/V/I, H58D, and Y93N/H (Table 1). Four of the patients had NS5A RAVs at entry to the primary study that were still present at the time of virologic relapse, and 3 patients had newly emergent NS5A RAVs. No patient had the S282T variant associated with phenotypic resistance to sofosbuvir.

Efficacy

By week 4 of re-treatment, all patients had HCV RNA <25 IU/mL (target not detected). No patients experienced virologic breakthrough or nonresponse. Of the 9 patients enrolled and treated, 8 (89%) achieved SVR 12 weeks after the end of treatment (SVR_{12}) (Table 1). Six of the 7 patients (86%) with NS5A RAVs at the time of relapse in the primary study achieved SVR_{12}.

The patient who experienced virologic relapse by posttreatment week 4 was a 55-year-old black man. This patient had no baseline NS5A RAVs at entry to the primary study. At the time of relapse in the primary study, the NS5A RAV L31M (>99%) had emerged. At relapse following re-treatment, the patient was observed to have L31M (98%) and L31V (2%). Following re-treatment, this patient had the L159F NS5B sofosbuvir treatment-emergent variant in 10.8% of the viral population. The patient was adherent to the study drugs as measured by pill count at study visits.

Safety

No patient discontinued study treatment due to an adverse event, and all adverse events experienced were nonserious (Supplementary Table 1). Four patients required modification or interruption of their ribavirin dose. No patient had confirmed HIV virologic rebound (HIV type 1 RNA ≥ 400 copies/mL), and $CD4^+$ cell counts were stable on treatment.

DISCUSSION

In this open-label study of patients with HCV/HIV coinfection who relapsed following 12 weeks of ledipasvir/sofosbuvir in the

Table 1. Patient Characteristics at Baseline and Beginning of Re-treatment, Resistance-Associated Variants, and Re-treatment Outcomes

	Patient Characteristics at Baseline and Beginning of Re-treatment											RAVs at:			
								$CD4^+$ Count, cells/mL		HCV RNA, $\log_{10}$ IU/mL					
Pt	Age	Sex	BMI	GT	Cirrhosis	*IL28B*	Antiviral Regimen	BL	Retxt	BL	Retxt	Baseline	Relapse	Re-treatment Relapse	Re-treatment Outcome
1	35	M	23.9	1a	No	CT	EFV + FTC + TDF	320	308	6.3	7.3	None	None	. . .	SVR_{12}
2	61	F	23.1	1a	Yes	CT	RAL + FTC + TDF	158	144	4.4	6.4	None	None	. . .	SVR_{12}
3	51	M	30.0	1a	No	TT	EFV + FTC + TDF	930	964	6.3	6.5	L31 M (>99%) H58D (92.1%)	L31 M (>99%) H58D (99%)	. . .	SVR_{12}
4	63	M	43.7	1a	No	TT	EFV + FTC + TDF	785	690	6.6	7.3	Y93F (1.2%) Y93N (9.9%)	Y93N (9.9%)	. . .	SVR_{12}
5	60	M	32.5	1a	No	TT	RAL + FTC + TDF	404	435	6.6	3.4	L31 M (98.8%) Y93N (24.8%)	L31 M (99%) Y93N (99%)	. . .	SVR_{12}
6	58	M	28.0	1a	No	TT	EFV + FTC + TDF	480	553	7.0	7.5	None	Y93N (>99%)	. . .	SVR_{12}
7	65	F	24.8	1b	Yes	TT	EFV + FTC + TDF	971	904	7.1	7.0	None	L31 V (>99%)	. . .	SVR_{12}
8	58	M	25.0	1b	No	TT	EFV + FTC + TDF	1625	2069	6.9	7.3	Y93H (>99%)	L31I (11.12%) Y93H (>99%)	. . .	SVR_{12}
9	55	M	31.7	1a	No	CT	EFV + FTC + TDF	1108	933	6.6	6.7	None	L31 M (>99%)	L31 M (97.5%) L31 V (2.1%)	Relapse PT Week 4

Abbreviations: BL, baseline; BMI, body mass index; EFV, efavirenz; FTC, emtricitabine; GT, genotype; HCV, hepatitis C virus; Pt, patient; PT, posttreatment; RAL, raltegravir; RAV, resistance-associated variant; Retxt, re-treatment; SVR_{12}, sustained virologic response 12 weeks after the end of treatment; TDF, tenofovir disoproxil fumarate.

ION-4 trial, 8 of the 9 patients (89%) achieved SVR_{12} following 24 weeks of treatment with the fixed-dose combination of ledipasvir/sofosbuvir plus ribavirin. Adherence was not identified as a factor contributing to virologic relapse of patients in either the primary study or the current substudy. Therefore, we do not believe that improved adherence with the re-treatment regimen explains the outcome.

The presence of RAVs—particularly of those within the NS5A gene—is of concern to clinicians when considering re-treatment of patients who have not achieved SVR after prior treatment with an NS5A inhibitor. In this trial, 6 of 7 patients with NS5A RAVs at the time of relapse of the primary study achieved SVR_{12} after re-treatment. Although the small sample size precludes any definite conclusions concerning the effect of NS5A resistance on response to this regimen, the result suggests that SVR is possible with the 24-week re-treatment regimen with ledipasvir/sofosbuvir with ribavirin in the presence of an NS5A RAV. We used a 1% cutoff for identification of NS5a RAVs. Of note, the specific RAVs identified in our relapsers are well established to be clinically relevant.

The relevance of these outcomes may extend beyond HIV/HCV coinfection. Although confirmation in larger populations is necessary, these findings suggest that re-treatment of NS5A-experienced patients with a regimen containing an NS5A inhibitor is feasible, particularly if the duration is extended and if ribavirin is added. Prior evaluation of 24 weeks of ledipasvir/sofosbuvir salvage treatment in prior relapses compared with 8 or 12 weeks of ledipasvir/sofosbuvir in HCV-monoinfected patients suggests the longer course of treatment alone without the addition of ribavirin is insufficient as the SVR_{12} rate was 100% in those without baseline NS5A RAVs and 60% in those with baseline NS5A RAVs [8]. Ribavirin has been shown to decrease HCV relapse and prevent the emergence of RAVs in other study populations. In the PROtease Inhibition for Viral Eradication-2 study of the NS3 protease inhibitor telaprevir plus peginterferon, the rate of HCV breakthrough due to RAVs was 26% in patients receiving telaprevir and peginterferon without ribavirin, compared with 2% in patients who received telaprevir, peginterferon, and ribavirin [9]. The addition of ribavirin to ledipasvir/sofosbuvir in this re-treatment substudy may account for the improved SVR outcome in our study; however, the small sample size precludes definitive conclusion.

The benefit of ribavirin in HCV treatment has been explored in many other studies of interferon-based and DAA-based regimens [10–12]. The mechanism of action of ribavirin remains unknown, but increased viral replicative infidelity, viral and host enzymatic inhibition, and immune modulation have all been proposed as possibly contributing to the effect of ribavirin on treatment outcomes [13–19]. Gene expression analysis of patients receiving sofosbuvir plus ribavirin indicates that restoration of endogenous interferon-α2 and decreased aberrant expression of type II and III interferons, their receptors, and interferon signaling genes correlates with achievement of SVR and prevents virus relapse [18]. Ribavirin may also contribute to HCV inhibition by augmenting plasmacytoid dendritic cell–derived type I interferon production [19]. Despite the uncertainty of its mechanism of action, current HCV treatment guidelines recommend the use of ribavirin for the re-treatment of patients who have not achieved SVR after prior treatment with NS5A inhibitors [2]. In this study, the dose of ribavirin—either 1000 mg or 1200 mg daily—was determined by weight. The optimal dose and possible impact of dose reduction on outcomes is unknown in interferon-free, combination DAA regimens.

This high SVR_{12} rate was achieved in patients harboring high fold-change NS5A RAVs and provides proof of concept for re-treatment strategies in patients failing NS5A regimens.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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