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MAJOR ARTICLE

Successful Retreatment of Chronic HCV Genotype-1 Infection With Ledipasvir and Sofosbuvir After Initial Short Course Therapy With Direct-Acting Antiviral Regimens

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Background. The optimal retreatment strategy for chronic hepatitis C virus (HCV) patients who fail directly-acting antiviral agent (DAA)-based treatment is unknown. In this study, we assessed the efficacy and safety of ledipasvir (LDV) and sofosbuvir (SOF) for 12 weeks in HCV genotype-1 (GT-1) patients who failed LDV/SOF–containing therapy.

Methods. In this single-center, open-label, phase 2a trial, 34 participants with HCV (GT-1) and early-stage liver fibrosis who previously failed 4–6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks. The primary endpoint was HCV viral load below the lower limit of quantification 12 weeks after completion of therapy (sustained virological response $[SVR]_{12}$). Deep sequencing of the NS3, NS5A, and NS5B regions were performed at baseline, at initial relapse, prior to retreatment, and at second relapse with Illumina next-generation sequencing technology.

Results. Thirty-two of 34 enrolled participants completed therapy. Two patients withdrew after day 0. Participants were predominantly male and black, with median baseline HCV viral load of 1.3×10^6 IU/mL and Metavir fibrosis stage 1 and genotype-1a. Median time from relapse to retreatment was 22 weeks. Prior to retreatment, 29 patients (85%) had NS5A-resistant variants. The SVR_{12} rate was 91% (31/34; intention to treat, ITT) after retreatment. One patient relapsed.

Conclusions. In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants.

Clinical Trials Registration. NCT01805882.

Keywords. hepatitis C; direct-acting antiviral agents; retreatment; sofosbuvir; ledipasvir.

Recent advances in therapy have dramatically improved the prognosis for patients with chronic hepatitis C virus (HCV) infection. The safety and efficacy of combination directly-acting antiviral agents (DAAs) have been demonstrated in patients with a broad range of disease stages, from those naive to HCV therapy with minimal liver fibrosis to those with advanced fibrosis or cirrhosis who have failed previous interferon (IFN)-based therapies [1–4].

While DAA-only regimens have dramatically improved treatment of chronic HCV, they are expensive, and treatment still requires several months of therapy. As a result, there has been intense interest in shortening courses of DAA therapy in patients with favorable baseline characteristics, including those without advanced fibrosis. Kowdley et al demonstrated similar rates of sustained virological response (SVR) after 8 weeks compared with 12 weeks of ledipasvir (LDV) and sofosbuvir (SOF) [5] for patients without cirrhosis and naive to HCV treatment. Encouraged by high rates of response to these new shorter DAA regimens, our group has studied whether adding additional DAAs can further reduce the treatment duration in select patients [6,7].

Combination DAA therapy for 6 weeks was successful in select populations (treatment naive and noncirrhotic patients) [6], while treatment for 4 weeks was successful for only a minority of patients [7]. Retreatment options for patients who fail short-course therapies have not been well defined.

One study of LDV and SOF for retreatment of patients who failed early, single DAA therapies in combination with IFN and ribavirin demonstrated high SVR rates [8], with an excellent safety profile [9,10]. However, data from one study of patients with

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and without cirrhosis who failed 8 to 12 weeks of LDV/SOF and were retreated with 24 weeks of LDV/SOF demonstrated varied efficacy, from 100% (in patients without resistance-associated variants [RAVs]) to as low as 60% in patients who had RAVs to NS5A inhibitors [11]. Other recent data from large trials of combination DAA therapy showed that the kinetics of HCV RAVs varied by the selective pressure exerted by the drug as well as overall viral fitness [12, 13]. NS5A mutations persisted out to at least post-treatment week 48 in patients who had been treated with the NS5A inhibitor ombitasvir and up to 96 weeks after completion in patients who had failed therapy with LDV in the absence of SOF. The persistence of these RAVs for almost 2 years in the absence of selective pressure exerted by DAAs indicates that these variants replicate well and that these resistance mutations exert little fitness cost. The response of preexisting or emergent NS5A mutants to retreatment with DAA therapy is unknown. Here, we report, for the first time, highly successful retreatment with LDV/SOF in patients without liver cirrhosis who had previously failed short-course combination DAA-only LDV/SOF–containing regimens, despite high frequencies of NS5A RAVs.

METHODS

Study Design

This study was conducted as a separate arm of an ongoing, phase 2a, open-label study, the National Institute of Allergy and Infectious Diseases (NIAID) SYNERGY study (Clinical Trials.gov number NCT01805882). Patients who relapsed after 6 weeks of treatment with LDV/SOF plus GS-9669, an investigational nonnucleoside NS5B inhibitor (n = 1); after 4 weeks of LDV/SOF plus GS-9451, an investigational NS3 protease inhibitor (n = 14); or after 4 weeks of LDV/SOF plus GS-9451 and GS-9669 (n = 19) were screened at the Clinical Research Center of the National Institutes of Health (NIH) between September 2014 and December 2014. Written informed consent was attained from all study participants. Key eligibility criteria were documented infection with HCV genotype-1 (GT-1) and treatment relapse in earlier arms of the SYNERGY study, details previously published [6, 7]. The absence of cirrhosis was determined by liver biopsy within 3 years or a combination of FibroTest of <0.48 [14] and aspartate transaminase-to-platelet ratio index <1 [15] within 6 months of enrollment into the initial short course treatment arms of the NIAID SYNERGY study. Study visits were conducted primarily at the NIAID/CCMD HIV/Hepatitis C Clinic and also in community clinics in the District of Columbia as part of the Washington, DC, Partnership for AIDS Progress.

Study Oversight

The study was approved by the NIAID institutional review board and was conducted in compliance with the Good Clinical Practice Guidelines, the Declaration of Helsinki, and regulatory requirements. The Regulatory Compliance and Human Participants Protection Branch of NIAID served as the study sponsor and medical monitor. Gilead Sciences, Inc. provided drug and scientific input.

Efficacy Assessment

Plasma HCV RNA levels were measured using the RealTime HCV Assay (Abbott), with a lower limit of quantification (LLOQ) of 12 IU/mL. Serum HCV RNA levels were also measured at select time points using the COBAS TaqMan HCV RNA assay, version 2.0 (Roche), with an LLOQ of 25 IU/mL.

Safety Assessment

All study participants were monitored frequently for adverse events, and clinical laboratory results were recorded while on study drugs (weeks 4, 8, and 12 after initiation of study drugs) and afterward (weeks 2, 4, 8, and 12 after stopping therapy). Adverse events were graded from 1 (mild) to 4 (severe) according to the NIAID Division of AIDS toxicity table (version 1.0) [16]. Adherence was measured throughout the study using pill counts obtained by the study team members. Adherence was measured at 4-, 8-, and 12-week (end of treatment) time points.

Interleukin-28B and Interferon-Lambda 4 Genotyping

Interleukin-28B (IL-28B) genotype (rs12979860) and IFN-lambda 4 (IFN-L 4) genotype (rs368234815) were determined as previously described [17].

Deep Sequencing

Deep sequencing of the HCV NS3/NS4, NS5A, and NS5B genes (at a minimum of 5000 reads) was performed by DDL (DDL Diagnostics Laboratory, Rijswijk, Netherlands) to identify RAVs. This sequencing was completed using samples collected at baseline in all patients, at the time of relapse after short-course therapy, prior to retreatment, and at time of virologic failure in the patient who relapsed. All 3 regions were amplified by reverse-transcription polymerase chain reaction (RT-PCR) using genotype-specific primers. PCR products were further deep-sequenced using Illumina MiSeq technology as previously described [17].

Clinical Endpoints

The primary study endpoint was the proportion of participants with plasma HCV viral load below the level of quantification 12 weeks after treatment completion (SVR_{12}) as measured using the Roche assay. Secondary efficacy endpoints included the proportion of participants with unquantifiable HCV viral load at specified time points during and after treatment. Safety endpoints included frequency and severity of adverse events, discontinuations due to adverse events, and safety laboratory changes.

Statistical Analyses

The primary safety and efficacy data were analyzed using an intention-to-treat population (all patients who received at least 1 dose of study medication). All missing data points were counted as successful only if the preceding and succeeding time points

were obtained. Baseline demographics were described using frequency statistics. Comparisons were calculated using nonparametric tests and *t* tests. Data analysis was performed using PRISM 6.0 software.

RESULTS

Thirty-four patients were screened and enrolled in this study (Figure 1).

Baseline Characteristics of Participants

Baseline characteristics of study participants are shown in Table 1. Study participants were primarily African American (28/34, 82.4%) and male (28/34, 82.4%), with IL-28B unfavorable non-CC genotype (30/33, 90.9%). Twenty-six (76.5%) participants were infected with HCV GT-1a, and 4 (11.8%) had baseline HCV RNA >6 000 000 IU/mL. The majority of patients (33/34, 97.1%) had early-stage liver disease (stage 0–2), predominantly determined by biopsy (31/33, 93.9%). One patient (2.9%) had stage 3 fibrosis by liver biopsy. Patients initiated retreatment at an average of 25.1 (range 5–32) weeks after the end of initial therapy.

Virologic Response

Thirty-one participants (91.2%) treated with LDV/SOF had HCV RNA levels below LLOQ at week 4 as measured by the Roche assay (Supplementary Table 1). Two patients were lost to follow-up after their day 0 visit and subsequently withdrew from the study. One patient had HCV RNA below LLOQ at week 4 followed by a quantifiable HCV RNA of 48 886 IU/mL at week 8 but went on to achieve SVR_{12}. This patient admitted to nonadherence to at least 2 doses of study medication prior to the week 8 visit and did not return for a week 12 end-of-treatment visit. At the end of treatment (week 12), 31 patients (91.2%) had HCV RNA levels below LLOQ as measured by the Roche assay. Three patients did not attend the week 12 visit, including the 2 patients who were lost to follow-up. The third patient (described above) had transitory viral rebound at week 8 but went on to achieve SVR_{12}.

Overall, 91.2% (31/34) of patients retreated with 12 weeks of LDV/SOF achieved SVR_{12}. One patient experienced viral relapse (Supplementary Table 1). The participant who relapsed had suppressed HCV viremia by week 4 on therapy, maintained through the end of treatment and week 4 post-treatment, but

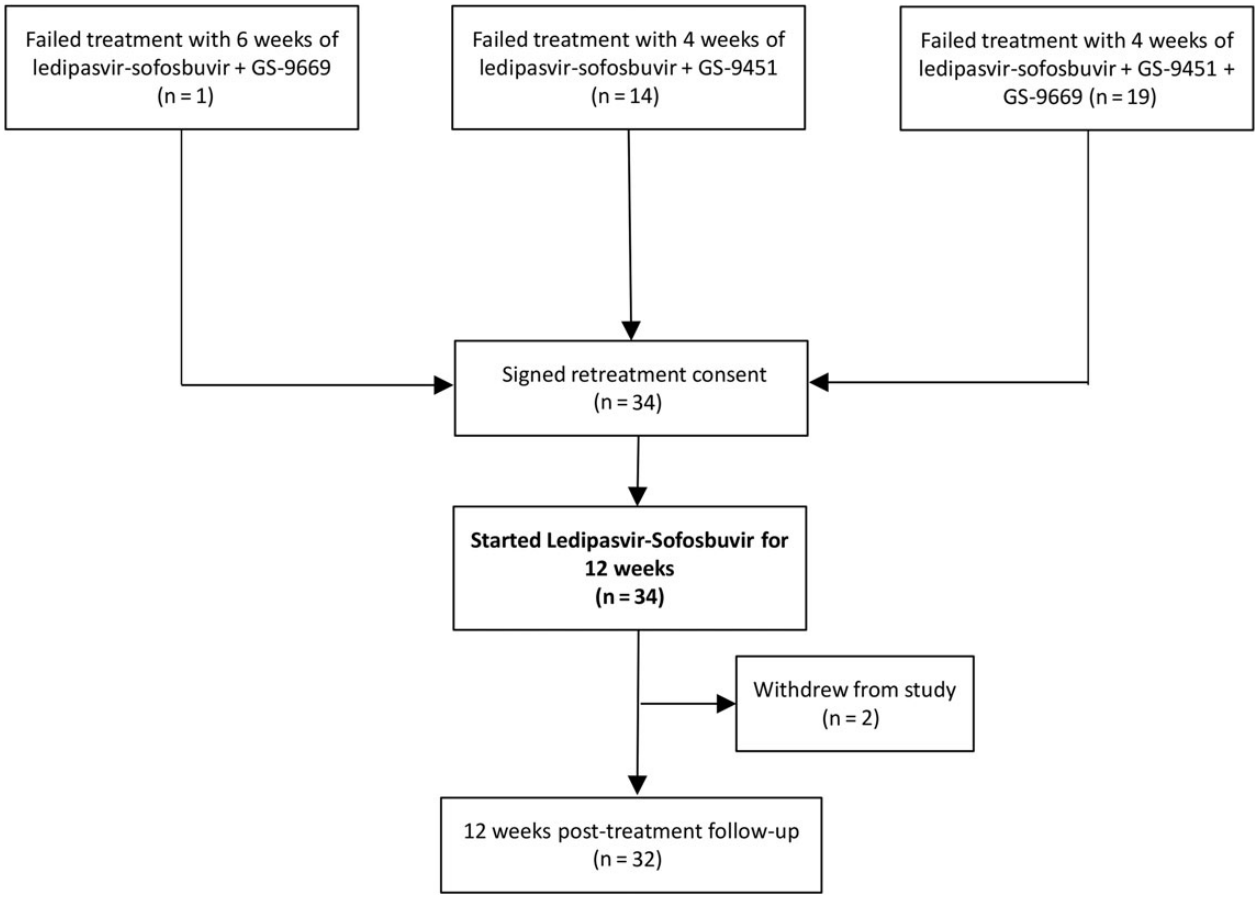

Figure 1. Study flow diagram.

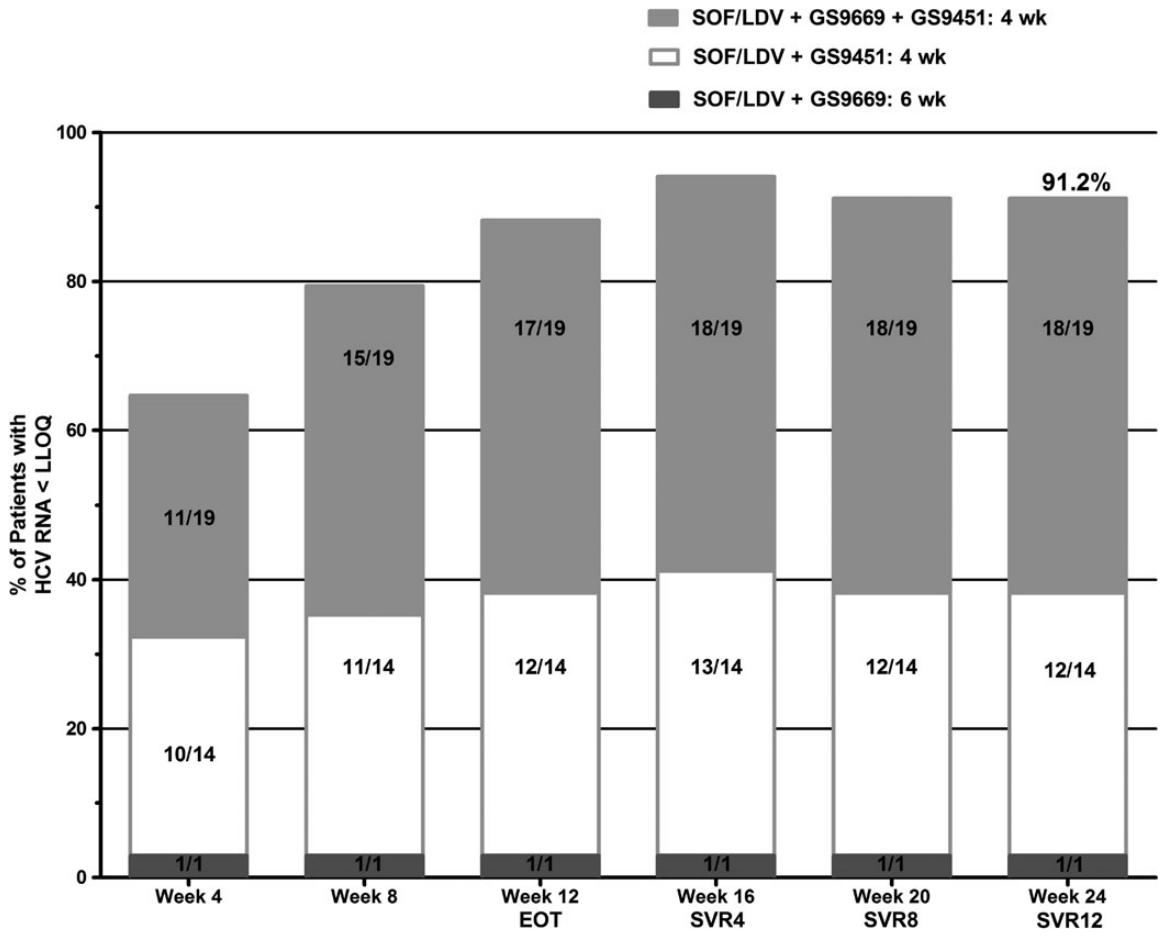

Figure 2. Patients with hepatitis C virus (HCV) RNA lower than the level of quantification (LLOQ). Treatment response, as measured by HCV RNA <LLOQ by the Abbott assay, was included in this intention-to-treat analysis of all 34 participants. Note: Two patients were lost to follow-up after their day 0 visits and were categorized as having HCV RNA >LLOQ at all subsequent visits. One patient missed the week 12, end-of-treatment (EOT), visit. Because that patient's HCV viral load was detectable at the preceding visit, the HCV viral load was counted as detectable at week 12. This participant did go on to achieve sustained virological response (SVR) 12. Abbreviations: LDV, ledipasvir; SOF, sofosbuvir.

had quantifiable HCV RNA of 181 737 IU/mL at week 8 post-treatment (only Abbott assay available). This patient denied any reexposure or high-risk behavior and reported 100% adherence with study medications.

For treatment response, as measured by the Abbott assay, by original short-course combination DAA regimen in an intention-to-treat analysis, see Figure 2.

Analysis of HCV Resistance–Associated Variants

Prior to initial therapy, 9 (9/33, 27.3%) participants had NS5A RAVs, although in only 6 (6/33, 18.2%) did this comprise a majority of the viral population. Prior to retreatment with LDV/SOF, and similar to the time of initial relapse, the NS5A RAVs K24R, M28T, Q30H/R/L/T, L31M/V/I, and Y93H/N were observed in 29/34 patients (85%). These NS5A RAVs have been reported to confer high levels of resistance (>25-fold in all 29, >100-fold in 28/29, and >1000 in 8/29 patients, respectively) to LDV in vitro [18]. All but 3 of these 29 patients with baseline RAVs went on to achieve SVR_{12}. Two of these 3 patients withdrew from the study prior to week 4. Among the 27 patients who had NS5A RAVs prior to retreatment and completed the study, SVR was achieved in 20/20 and 6/7 patients with NS5A RAVs conferring <1000-fold and >1000-fold reduced susceptibility to LDV, respectively. The patient who experienced viral relapse had an L31M NS5A RAV at baseline and developed a Y93H NS5A RAV in addition to maintaining the L31M at relapse after short-course therapy. The double-mutant L31M/Y93H confers >1000-fold reduced susceptibility to LDV. Both of these mutations persisted for 23 weeks in the absence of therapy and were detected again prior to retreatment. At relapse, these RAVs were again documented along with 2 emergent NS5B RAVs: S282T and V321I at 17.7% and 9.3% of viral sequence reads, respectively. Selected NS5A and NS5B resistance profiles to LDV and SOF of all study participants are shown in Table 2. Of note, variants within NS3/4 were unchanged throughout retreatment (data not shown).

Safety

Of the 34 patients who started study medications, 2 were lost to follow-up after day 0 and later withdrew. Eighty-eight percent (30/34) of patients experienced adverse events, most of which were mild in severity. The most common adverse event was grade 1 constipation (n = 2, 5.9%; Table 3). One serious adverse event occurred: a single episode of chest pain in a patient who had used cocaine. This was deemed to be unrelated to the study drug.

No grade 4 laboratory abnormalities occurred, but 3 patients experienced grade 3 laboratory abnormalities. Hyperglycemia was detected while on study medications in one patient with a history of type 2 diabetes mellitus. Two patients, one of whom had an elevated cholesterol measurement at baseline, developed grade 3 cholesterol elevations while on study medications.

DISCUSSION

In this proof-of-concept study, patients with HCV (GT-1) infection who had accumulated RAVs during previous short-course combination DAA therapy containing LDV/SOF achieved an SVR_{12} rate of 91% when retreated with 12 weeks of LDV/SOF. Presence of high-level RAVs, regardless of their proportion of the overall viral population, has been associated with reduced efficacy of short-course therapy [19, 20]. Here, the response rate was high in patients with NS5A RAVs. Of the 27 patients with mutations associated with >25-fold baseline NS5A resistance in vitro who completed 12 weeks of therapy, 26 (96.2%; n = 20 <1000-fold and n = 6 >1000-fold reduced susceptibility to LDV) went on to achieve SVR_{12}. These specific RAVs have been previously identified in patients who failed LDV-containing regimens [21, 22] and also demonstrated in in vitro phenotypic assays to have diminished binding to LDV [23]. The patient who relapsed had HCV with >1000-fold NS5A RAVs L31M and Y93H prior to retreatment and NS5B RAVs S282T and V321I emerged following retreatment, both of which have been shown to reduce in vitro susceptibility to SOF [18, 24]. The S282T, in particular, has rarely been reported in clinical trials in patients who failed SOF-based regimens in clinical trials [24, 25].

Retreatment was safe and extremely well tolerated. No patient discontinued the drugs due to adverse events. Side effects were generally mild and consistent with previously published studies of LDV/SOF [1, 2].

Our patient population was predominantly composed of black men, a population often underrepresented in clinical trials, and an important population to confirm efficacy of HCV therapeutic options. Our cohort also was predominantly (>70%) infected with genotype-1a infection, the predominant HCV genotype in the US HCV epidemic and 91% IL-28B non-CC genotype.

As DAAs are used more widely, the relevance of NS5A RAVs will have to be better delineated. Some of these RAVs will be preexisting and part of the natural variation (quasispecies) that exist within an infected but DAA-naive patient and some will be the result of selection, that is, RAVs that emerge in patients who relapse. Whether RAVs will be important for determining the success of specific drug therapies or will influence the optimal duration of therapy remains to be seen. This study did not assess the efficacy of retreatment for patients with cirrhosis or for patients who failed 8, 12, or 24 weeks of therapy. The influence of duration of initial treatment on emergence or persistence of RAVs, which was shown to be a factor in the success of retreatment by Lawitz et al [11], could predict response to retreatment regimens. Our data do suggest, however, that the presence of RAVs identified here do not preclude successful retreatment with some or all of the drugs used in the initial regimen.

In summary, our data support that retreatment with LDV/SOF is a safe, effective, and tolerable option for HCV-infected patients with early-stage hepatic fibrosis who have previously

Table 1. Baseline Demographics and Clinical Characteristics of Study Participants

Characteristic	Ledipasvir–Sofosbuvir (N = 34)
Age, mean ± SD	58.9 ± 7.5
Gender, n (%)	
Male	28 (82.3)
Female	6 (17.7)
Race,[a] n (%)	
Black	28 (82.3)
White	6 (17.7)
Ethnicity,[a] n (%)	
Hispanic	0
Non-Hispanic	34 (100)
Body mass index, mean ± SD	27.3 ± 4.2
HCV genotype, n (%)	
1a	26 (76.5)
1b	8 (23.5)
HCV RNA >800 000 IU/mL, n (%)	21 (61.8)
Interleukin-28B genotype, n (%)	
CC	3 (9.1)
CT, TT	30 (90.9)
Interferon-lambda 4 genotype, n (%)	
TT/TT	1 (3.0)
ΔG/TT, ΔG/ΔG	32 (97.0)
HAI-Knodell, Metavir, or Fibrosure Fibrosis Score,[b] n (%)	
0–2	33 (97.1)
3	1 (2.9)
Weeks to retreatment, mean ± SD	25.1 ± 5.5
Resistance-associated variants ≥25-fold resistance, n (%)	N = 34
NS5A, n (%)	29 (85.3)
NS5B, n (%)	1 (2.9)
NS5A and NS5B, n (%)	1 (2.9)

Abbreviations: HCV, hepatitis C virus; SD, standard deviation.

[a] Race and ethnicity were self-reported.

[b] Two (5.9%) patients had FibroTest/aspartate aminotransferase to platelet ratio index for eligibility, 32 (94.1%) patients completed liver biopsies scored using the histology activity index-Knodell or Metavir systems.

Table 2. Selected NS5A and NS5B Resistance-Associated Variants by Study Participant

			NS5A Mutant (% Population)					NS5B Mutant (% Population)				
					Prior to Retreatment							
Patient	Genotype	Previous Treatment	Baseline	Relapse	Resistance-Associated Variants	Fold Resistance	Relapse	Baseline	Relapse	Prior to Retreatment	Relapse	Outcome
D15	1b	LDV/SOF + GS-9451 + GS-9669	None	Y93H (1.1%) Y93C (2.0%)	Y93H (1.0%) Y93C (3.9%)	>1000	N/A	None	None	None	N/A	SVR_{12}
D16	1a	LDV/SOF + GS-9669	ND	ND	K24R (8.0%) M28T (75.0%) Q30L (24.5%) Q30H (74.4%)	>100	N/A	ND	ND	None	N/A	SVR_{12}
D17	1a	LDV/SOF + GS-9451	None	Q30R (28.4%) L31M (70.9%)	Q30R (17.1%) L31M (79.8%)	>100	N/A	None	None	None	N/A	Withdrawn
D18	1a	LDV/SOF + GS-9451	None	None	None	N/A	N/A	None	None	None	N/A	SVR_{12}
D19	1a	LDV/SOF + GS-9451	None	L31M (98.7%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D20	1a	LDV/SOF + GS-9451	None	Q30H (>99%) Y93H (>99%)	Q30H (>99%) Y93H (97.0%)	>1000	N/A	None	None	None	N/A	SVR_{12}
D21	1a	LDV/SOF + GS-9451	None	None	None	N/A	N/A	None	None	None	N/A	SVR_{12}
D22	1b	LDV/SOF + GS-9451	None	L31V (6.2%) L31M (45.9%) L31I (47.9%)	L31I (31.9%) L31M (67.0%)	>25	N/A	None	None	None	N/A	SVR_{12}
D23	1a	LDV/SOF + GS-9451	None	Q30R (10.5%) Q30K (13.1%) L31V (2.3%) L31M (74.7%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D24	1a	LDV/SOF + GS-9451	None	Q30R (20.1%) L31M (70.8%)	Q30R (3.4%)	>100	N/A	None	None	None	N/A	SVR_{12}
D25	1b	LDV/SOF + GS-9451[a]	L31M (94.1%)	L31M (>99%) Y93H (>99%)	L31M (>99%) Y93H (28.6%)	>1000	L31M (>99%) Y93H (>99%)	None	None	None	S282T (17.7%) V321I (9.3%)	Relapse
D26	1a	LDV/SOF + GS-9451 + GS-9669	None	None	None	N/A	N/A	None	None	None	N/A	SVR_{12}
D27	1a	LDV/SOF + GS-9451	None	L31M (>99%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D28	1b	LDV/SOF + GS-9451 + GS-9669	Y93H (>99%)	Y93H (>99%)	Y93H (>99%)	>1000	N/A	None	None	None	N/A	Withdrawn
D29	1b	LDV/SOF + GS-9451	None	None	None	N/A	N/A	None	None	None	N/A	SVR_{12}
D30	1a	LDV/SOF + GS-9451 + GS-9669	None	L31M (>99%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D31	1a	LDV/SOF + GS-9451 + GS-9669	None	M28T (1.4%) Q30H (2.6%) Q30R (56.8%) L31M (34.3%) S38F (2.3%)	Q30H (1.2%) Q30R (57.8%) L31M (11.9%)	>100	N/A	None	None	None	N/A	SVR_{12}
D32	1a	LDV/SOF + GS-9451 + GS-9669	None	Q30R (89.2%)	Q30R (4.4%)	>100	N/A	None	None	None	N/A	SVR_{12}

Table 2 continued.

			NS5A Mutant (% Population)					NS5B Mutant (% Population)				
					Prior to Retreatment							
Patient	Genotype	Previous Treatment	Baseline	Relapse	Resistance-Associated Variants	Fold Resistance	Relapse	Baseline	Relapse	Prior to Retreatment	Relapse	Outcome
D33	1a	LDV/SOF + GS-9451 + GS-9669	None	Q30R (1.2%) Q30H (22.7%)	Q30R (1.7%) Q30H (60.8%)	>100	N/A	None	None	None	N/A	SVR_{12}
D34	1a	LDV/SOF + GS-9451	L31M (65.8%)	L31M (>99%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D35	1a	LDV/SOF + GS-9451 + GS-9669	L31M (14.3%)	L31M (>99%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D36	1a	LDV/SOF + GS-9451 + GS-9669	Y93N (45.0%)	Y93N (>99%)	Y93N (>99%)	>1000	N/A	None	None	None	N/A	SVR_{12}
D37	1a	LDV/SOF + GS-9451 + GS-9669	None	Q30H (1.2%)	Q30H (2.7%)	>100	N/A	None	None	None	N/A	SVR_{12}
D38	1a	LDV/SOF + GS-9451 + GS-9669	L31M (>99%)	L31M (>99%)	L31M (98.9%)	>100	N/A	None	None	None	N/A	SVR_{12}
D39	1b	LDV/SOF + GS-9451 + GS-9669	L31M (8.1%) Y93H (>99%)	Y93H (>99%)	Y93H (>99%)	>1000	N/A	None	None	None	N/A	SVR_{12}
D40	1a	LDV/SOF + GS-9451	None	None	None	N/A	N/A	None	None	None	N/A	SVR_{12}
D41	1b	LDV/SOF + GS-9451 + GS-9669	None	Y93H (>99%)	Y93H (>99%)	>1000	N/A	None	None	None	N/A	SVR_{12}
D42	1a	LDV/SOF + GS-9451 + GS-9669	None	M28T (1.6%) Q30H (45.9%) Q30R (53.9%)	Q30R (24.9%) Q30H (74.6%)	>100	N/A	None	None	None	N/A	SVR_{12}
D43	1a	LDV/SOF + GS-9451	None	L31M (98.9%)	Q30H (56.1%) L31M (43.8%)	>100	N/A	None	None	None	N/A	SVR_{12}
D44	1a	LDV/SOF + GS-9451 + GS-9669	None	K24R (89.5%) L31M (>99%)	K24R (75.6%) L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D45	1a	LDV/SOF + GS-9451 + GS-9669	L31M (1.9%)	L31M (98.9%)	L31M (>99%)	>100	N/A	None	None	None	N/A	SVR_{12}
D46	1a	LDV/SOF + GS-9451 + GS-9669	None	Q30R (>99%)	Q30R (8.6%) L31M (26.7%)	>100	N/A	None	None	None	N/A	SVR_{12}
D47	1a	LDV/SOF + GS-9451 + GS-9669	None	Q30H (1.4%) Q30R (10.9%) L31M (84.4%)	Q30R (1.2%) L31M (98.1%)	>100	N/A	None	None	None	N/A	SVR_{12}
D48	1b	LDV/SOF + GS-9451 + GS-9669	Q30T (>99%) L31V (>99%) Y93H (>99%)	Q30T (>99%) L31V (>99%) Y93H (>99%)	Q30T (>99%) L31V (>99%) Y93H (>99%)	>1000	N/A	None	None	L159F (3.1%)	N/A	SVR_{12}

Abbreviations: LDV, ledipasvir; N/A, not applicable; ND, not done; SOF, sofosbuvir; SVR, sustained virological response.

[a] Received therapy for 6 weeks; all others treated for 4 weeks.

Table 3. Adverse Events and Laboratory Abnormalities Related to Study Drug During Treatment Period

Adverse Event or Laboratory Abnormality	Ledipasvir and Sofosbuvir (n = 34)
Any AE during treatment,[a] n (%)	30 (88)
Grade 3	7 (21)
Grade 2	21 (62)
Treatment-related AE[b]	
Grade 3	3 (9)
Grade 2	7 (21)
Any serious AE during treatment, n (%)	1 (3)
Treatment-related[b]	0 (0)
AE leading to permanent study drug discontinuation	0 (0)
Death	0 (0)
Common AE,[c] n (%)	
Constipation	2 (6)
All graded lab abnormalities during treatment, n (%)	30 (88)
Elevated cholesterol	9 (29)
Hypophosphatemia	3 (9)
Hypoglycemia	4 (12)
Hyperglycemia	6 (18)
Elevated serum creatinine	3 (9)
Blood pancreatic amylase increased	3 (9)
Absolute neutrophil count decreased	2 (6)

Abbreviation: AE, adverse event.

[a] Treatment period includes time on study medication and 30 days after discontinuation.

[b] As assessed by the study team.

[c] Common AEs were those occurring in ≥5% of patients in any treatment group.

failed short-course combination DAA therapy containing LDV/SOF. If successful, short 4–6 week durations of combination DAA therapy are developed and approved, retreatment of select failures with 12 weeks of LDV and SOF may be part of a reasonable treatment strategy.

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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Contributors. E. M. W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E. M. W. and S. Kattakuzhy searched the published literature. A. K., S. Kottilil, A. N., M. M., and H. M. contributed to the study design. E. M. W., S. Kattakuzhy, A. K., Z. S., M. M., S. S., A. P., A. N., R. S., C. G., and E. A. collected data. E. M. W., S. Kattakuzhy, A. K., S. S., Z. S., and M. M. analyzed the data. E. M. W., S. Kattakuzhy, A. K., H. Mo, A. O., and H. Masur interpreted the data. E. M. W., Z. S., M. M., and S. S. contributed to the figure design. E. M. W. wrote the first draft of the manuscript and all authors participated in the review of the article.

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