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CLINICAL—LIVER

Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection

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BACKGROUND & AIMS: We performed a phase 2 clinical trial to evaluate the efficacy and safety of ledipasvir and sofosbuvir, with or without ribavirin, in patients infected with hepatitis C virus (HCV) genotype 3 or 6. **METHODS:** We performed an open-label study of 126 patients with HCV genotype 3 or 6 infections at 2 centers in New Zealand from April 2013 through October 2014. Subjects were assigned 1 of 4 groups that received 12 weeks of treatment. Previously untreated patients with HCV genotype 3 were randomly assigned to groups given fixed-dose combination tablet of ledipasvir and sofosbuvir (n = 25) or ledipasvir and sofosbuvir along with ribavirin (n = 26). Treatment-experienced patients with HCV genotype 3 (n = 50) received ledipasvir and sofosbuvir and ribavirin. Treatment-naïve or treatment-experienced patients with HCV genotype 6 (n = 25) received ledipasvir and sofosbuvir. The primary end point was the percentage of patients with HCV RNA ≤15 IU/mL 12 weeks after stopping therapy (sustained virologic response at 12 weeks [SVR12]). **RESULTS:** Among treatment-naïve genotype 3 patients, 16 of 25 (64%) receiving ledipasvir and sofosbuvir alone achieved SVR12 compared with all 26 patients (100%) receiving ledipasvir and sofosbuvir and ribavirin. Among treatment-experienced patients with HCV genotype 3, forty-one of fifty achieved an SVR12 (82%). Among patients with HCV genotype 6, the rate of SVR12 was 96% (24 of 25 patients). The most common adverse events were headache, upper respiratory infection, and fatigue. One patient with HCV genotype 3 discontinued ledipasvir and sofosbuvir because of an adverse event (diverticular perforation), which was not considered treatment related. **CONCLUSIONS:** In an uncontrolled, open-label trial, high rates of SVR12 were achieved by patients with HCV genotype 3 infection who received 12 weeks of ledipasvir and sofosbuvir plus ribavirin, and by patients with HCV genotype 6 infection who received 12 weeks of sofosbuvir and ledipasvir without ribavirin. Current guidelines do not recommend the use of ledipasvir and sofosbuvir, with or without ribavirin, in patients with HCV genotype 3 infection. ClinicalTrials.gov Number: NCT01826981.

Keywords: Drug; DAA; Direct-Acting Antiviral Agents; Clinical Trial Result.

Genotype 3 hepatitis C virus (HCV) accounts for approximately 20% of all HCV infections globally and 40% of infections in Asia.[1] Although it is frequently grouped with genotype 2 HCV, genotype 3 HCV is associated with greater risk of steatosis,[2] fibrosis progression,[3] hepatocellular carcinoma,[4,5] and all-cause mortality.[4] Genotype 6 HCV constitutes about 1% of HCV infections globally and is found mainly in Southeast Asia and Southern China.[6] Genotype 6 HCV is genetically diverse, with 23 subtypes,[7] many of which have not been cloned, limiting in vitro testing of antiviral agents. Due to its genetic diversity and relatively low prevalence, genotype 6 HCV is not as well characterized as the other genotypes, but long-term infection appears to be associated with the similar risk of cirrhosis and hepatocellular carcinoma as genotype 1 HCV.[8]

Sofosbuvir is a potent inhibitor of the HCV NS5B polymerase with a favorable safety profile and a high genetic barrier to resistance.[9,10] In the VALENCE study of treatment-naïve and previously treated patients with and without cirrhosis, sofosbuvir plus ribavirin for 24 weeks resulted in a sustained virologic response at 12 weeks (SVR12) rate of 94% in treatment-naïve patients and 79% in treatment-experienced patients with genotype 3 HCV infection.[11] The NEUTRINO study, which evaluated sofosbuvir plus peginterferon-ribavirin in treatment-naïve patients with genotype 1, 4, 5, or 6 HCV, enrolled 6 patients with genotype 6 HCV; all achieved SVR12. The fixed-dose combination of sofosbuvir with ledipasvir, an inhibitor of the HCV NS5A protein, was recently approved for the treatment of treatment-naïve and previously treated patients chronically infected with genotype 1 hepatitis C virus (HCV).[12] The efficacy and safety of ledipasvir and sofosbuvir in patients with non−genotype 1 HCV is unknown. In the ION phase 3 trials in which patients with genotype 1 HCV received ledipasvir and sofosbuvir with and without ribavirin for 12 or 24 weeks, patients receiving ledipasvir and sofosbuvir alone had rates of SVR12 similar to those receiving ledipasvir and sofosbuvir plus ribavirin.[13–15] The elimination of ribavirin from the treatment of HCV is desirable due to the adverse events associated with ribavirin therapy.

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; EC_{50}, 50% effective concentration; FDA, US Food and Drug Administration; FDC, fixed-dose combination; HCV, hepatitis C virus; LLOQ, lower limit of quantification; SVR, sustained virologic response.**

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We evaluated the efficacy and safety of a fixed-dose combination (FDC) tablet of ledipasvir and sofosbuvir administered with or without ribavirin for 12 weeks in treatment-naïve and treatment-experienced patients with genotype 3 or 6 HCV. We included treatment arms with and without ribavirin for treatment-naïve patients with genotype 3 HCV to determine if ribavirin can be omitted from the regimen without a loss of efficacy. At the time the trial was designed, there was no information concerning the efficacy of ledipasvir and sofosbuvir in patients with genotype 3 HCV, so the trial was designed so that the easier-to-treat patients—those naïve to HCV treatment—initiated treatment first, and patients with more difficult to treat genotype 3 HCV—those who had not achieved SVR after previous treatment—would begin ledipasvir and sofosbuvir plus ribavirin only if 90% of the treatment-naïve patients had HCV RNA less than lower limit of quantification (LLOQ) at post-treatment week 4.

Methods

Patients

We enrolled patients at 2 centers in New Zealand during the period from April 2013 to October 2014. Eligible patients were at least 18 years old and had chronic infection with genotype 3 or 6 HCV, with plasma HCV RNA $\geq 10^4$ IU/mL. The first 2 groups enrolled treatment-naïve patients with genotype 3 HCV, the third group, previously treated patients with genotype 3 HCV, and the fourth group included both treatment-naïve and previously treated patients with genotype 6 HCV. Up to 40% of patients in each group could have compensated cirrhosis, as determined by the following: biopsy, Fibroscan >12.5 kPa, or FibroTest >0.75 and aspartate aminotransferase to platelet ratio index >2. Patients with any of the following characteristics or conditions were excluded from participation: body mass index <18 kg/m^2; decompensated liver disease; electrocardiogram with clinically significant abnormalities; chronic use of systemic immunosuppressive or immunomodulatory agents; human immunodeficiency virus infection; hepatitis B virus infection; creatinine clearance <60 mL/min as calculated by the Cockcroft-Gault equation; albumin <3 g/dL; international normalized ratio >1.5 × upper limit of normal unless the patient had known hemophilia or was stable on an anticoagulant regimen affecting international normalized ratio; hemoglobin <11 g/dL for females and <12 g/dL for males; platelets <50,000/mm^3; direct bilirubin >1.5 × upper limit of normal, except for patients with Gilbert's syndrome; alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >10 × upper limit of normal. All patients provided written informed consent before undertaking any study-related procedures.

Study Design

This was a phase 2, multi-center, open-label study. Patients with HCV genotype 3 were enrolled in 2 parts (Supplementary Figure 1). First, previously untreated patients were randomly assigned in a 1:1 ratio to receive 12 weeks of treatment with ledipasvir and sofosbuvir FDC (90 mg ledipasvir, 400 mg sofosbuvir) once daily or ledipasvir and sofosbuvir FDC once daily plus ribavirin 1000 or 1200 mg/d divided twice daily. The study statistician produced the computer-generated randomization sequence using SAS software (SAS Institute, Cary, NC). Allocation to treatment was done sequentially and Gilead Clinical Operations communicated the randomization sequence to the site by e-mail. If >90% of patients receiving ledipasvir and sofosbuvir plus ribavirin had HCV RNA below the LLOQ at treatment week 4, a third group of HCV genotype 3 patients was to be enrolled. This group of 50 patients who had been previously treated with peginterferon plus ribavirin received 12 weeks of ledipasvir and sofosbuvir FDC once daily plus ribavirin 1000 or 1200 mg/d in a divided dose. A fourth treatment group included treatment-naïve or treatment-experienced patients with HCV genotype 6 who received 12 weeks of ledipasvir and sofosbuvir FDC once daily. Treatment-experienced patients with HCV genotype 3 and patients with HCV genotype 6 were sequentially assigned to their respective therapies.

The study protocol was approved by each institution's review board or ethics committee before study initiation. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The study was designed and conducted by the sponsor in collaboration with the principal investigators. The sponsor collected the data and monitored the study conduct. All authors had access to the study data and reviewed and approved the final article.

Study Assessments

Plasma HCV RNA was analyzed by using the COBAS AmpliPrep/COBAS TaqMan HCV Test, version 2.0 (Roche Molecular Systems, Inc., Branchburg, NJ), which has a LLOQ of 15 IU/mL.

Plasma samples for viral sequencing were collected at the same time points as for HCV RNA levels. Deep sequencing of the HCV NS5A and NS5B-encoding regions was performed for viral samples with HCV RNA ≥1000 IU/mL. Safety data were collected during treatment and for 4 weeks after stopping treatment. The data included reported adverse events, physical examinations, clinical laboratory tests, vital signs, and electrocardiography recordings. Treatment-emergent clinical and laboratory adverse events were summarized using the Medical Dictionary for Regulatory Activities (version 17.0). Virologic relapse was defined as HCV RNA equal to or more than the LLOQ during the post-treatment period in a patient who had HCV RNA less than LLOQ at end of treatment.

End Points and Statistical Analyses

The primary efficacy end point was the percentage of patients in each study group with SVR12, defined as HCV RNA less than LLOQ (15 IU/mL) 12 weeks after stopping study drug. In the primary efficacy analysis, the SVR12 rate was calculated with a 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method. We calculated that with 25 patients in a treatment group, a 2-sided 95% exact CI would extend at most 42% in length. With 50 subjects in a treatment group, a 2-sided 95% exact CI will extend at most 29% in length. This study was not designed to evaluate formal statistical hypotheses. No inferential statistics or statistical comparisons were planned.

Results

Study Population

In total, 126 patients were enrolled and treated at 2 sites in New Zealand between April 2013 and October 2014.

Overall, 71% of patients were white and 63% were male (Table 1). In patients with genotype 3 HCV, the presence of cirrhosis was more common among treatment-experienced (44%) than treatment-naïve (20%) patients. Among the 25 patients with genotype 6 HCV, only 2 had been treated previously and 2 had cirrhosis at baseline. Patients with genotype 6 HCV infection were from the following countries of origin: Cambodia (n = 11), China (n = 7), Myanmar (n = 3), Vietnam (n = 1), and other (n = 3). Figure 1 shows patient disposition throughout the study.

Antiviral Response

Among treatment-naïve genotype 3 patients, the overall rates of SVR12 were 64% (16 of 25) in those receiving ledipasvir and sofosbuvir alone (95% CI: 43%−82%) and 100% (26 of 26) in those receiving ledipasvir and sofosbuvir plus ribavirin (95% CI: 87%−100%), including 6 patients with cirrhosis (Table 2). Two patients with genotype 3 HCV who were receiving ledipasvir and sofosbuvir plus ribavirin had their participation in the study halted after completing at least 8 weeks of treatment due to nonadherence with the visit schedule and dosing requirements; both achieved SVR12. Table 3 shows the baseline characteristics of the 8 patients receiving ledipasvir and sofosbuvir without ribavirin who relapsed.

Of the 50 treatment-experienced patients with genotype 3 HCV receiving 12 weeks of ledipasvir and sofosbuvir plus ribavirin, 41 (82%) achieved SVR12 (95% CI: 69%−91%). The rate of SVR12 was 73% (95% CI: 50%−89%) and 89% (95% CI: 72%−98%) in those with and without cirrhosis, respectively. Of the 9 patients who did not have SVR12, 1 had virologic breakthrough on treatment after having HCV RNA less than LLOQ, and 8 had virologic relapse after treatment. Baseline characteristics of these patients are given in Table 3.

Among the 25 patients with genotype 6 HCV, 24 (96%; 95% CI: 80%−100%) reached SVR12 with ledipasvir and sofosbuvir without ribavirin. The single patient who did not reach SVR12 was a 34-year-old male who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment. He relapsed by post-treatment week 4.

Viral Sequencing

Sequencing of the NS5B region was successfully carried out on baseline samples from 98 of the 101 genotype

Table 1. Patient Demographics and Baseline Characteristics

Characteristics	HCV genotype 3			HCV genotype 6
	Treatment naïve		Treatment experienced	Treatment naïve or experienced
	LDV and SOF (n = 25)	LDV and SOF + RBV (n = 26)	LDV and SOF + RBV (n = 50)	LDV and SOF (n = 25)
Age, *y*, mean (SD)	43 (10.2)	48 (9.2)	52 (8.2)	51 (13.9)
Male, n (%)	13 (52.0)	11 (42.3)	39 (78.0)	16 (64.0)
Race, n (%)				
White	22 (88.0)	23 (88.5)	40 (80.0)	4 (16.0)
Asian	1 (4.0)	1 (3.8)	3 (6.0)	21 (84.0)
Native Hawaiian or Pacific Islander	1 (4.0)	1 (3.8)	5 (10.0)	—
New Zealand Maori	1 (4.0)	1 (3.8)	2 (4.0)	—
BMI <30 kg/m^2, n (%)	19 (76.0)	18 (69.2)	42 (84.0)	23 (92.0)
Genotype, n (%)				
3	1 (4.0)	—	3 (6.0)	—
3a	24 (96.0)	25 (96.2)	47 (94.0)	—
3k	—	1 (3.8)	—	—
6 (subtypes c−1)	—	—	—	17 (68.0)
6a or 6b	—	—	—	8 (32.0)
HCV RNA, *log$_{10}$ IU/mL*, mean (SD)	6.3 (0.88)	6.3 (0.87)	6.3 (0.76)	6.7 (0.67)
Prior HCV treatment, n (%)				
Treatment naïve	25 (100)	26 (100)	—	23 (92.0)
Nonresponse	—	—	10 (20.0)	—
Relapse/breakthrough	—	—	40 (80.0)	2 (8.0)
IL-28B, n (%)				
CC	9 (36.0)	15 (57.7)	18 (36.0)	20 (80.0)
CT	10 (40.0)	6 (23.1)	27 (54.0)	5 (20.0)
TT	6 (24.0)	5 (19.2)	5 (10.2)	—
Cirrhosis present, n (%)	4 (16.0)	6 (23.1)	22 (44.0)	2 (8.0)
ALT, *U/L*, median (range)	48 (25−291)	75 (25−365)	88 (24−369)	61 (15−264)
Creatinine clearance,[a] *mL/min*, median (range)	123.7 (56.2−181.5)	120.4 (58.1−241.1)	112.9 (62.0−218.4)	97.0 (60.9−159.4)

ALT, alanine aminotransferase; BMI, body mass index; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.
[a]Estimated by Cockroft-Gault.

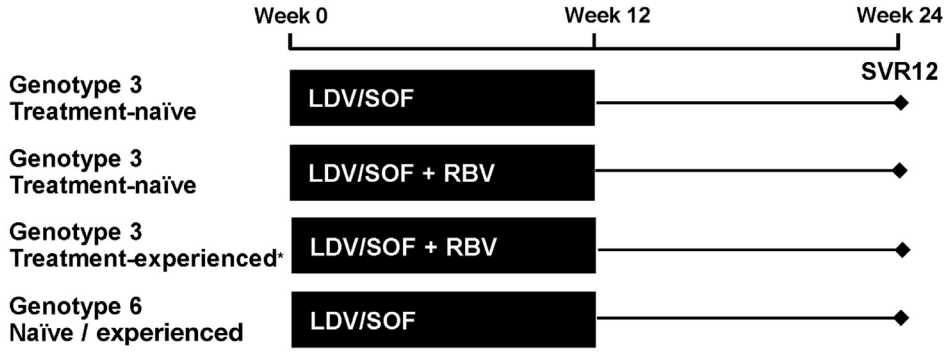

Figure 1. Patient disposition. *This group will only be enrolled if the SVR4 rate among treatment-naive patients with genotype 3 HCV receiving SOF/LDV FDC + RBV exceeds 90%

3 patients (3 samples could not be amplified for sequencing). Of these 98 patients, 96 were infected with genotype 3a HCV and 2 with genotype 3k HCV. Baseline sequencing of the NS5B region was successful for all 25 patients infected with genotype 6 HCV. The subtype distribution of patients with genotype 6 HCV was as follows: 8 patients had genotype 6a, 6 had genotype 6e, 3 had genotype 6l, 2 had genotype 6m, 3 had genotype 6p, 2 had genotype 6q, and 1 had genotype 6r. The NS5B variants S282T, V321A, and L159F were not observed at baseline in any patient. Sequencing of the NS5A region was successfully carried out on baseline samples from 100 of the 101 patients with genotype 3 HCV and 23 of the 25 patients with genotype 6 HCV. Common NS5A resistance-associated polymorphisms detected at baseline included 30A/V/S/R/T in genotype 3 and 30R/S/A/L and 93T/S in genotype 6. All patients had at least one common NS5A polymorphism at baseline. In addition, L31M and Y93H were observed in 1 and 8 baseline samples, respectively, of the 100 we were able to sequence. A patient with genotype 3k HCV who had been previously treated with pegylated interferon plus ribavirin and who had the L31M variant at baseline experienced post-treatment relapse. Only 1 of the 8 patients with Y93H at baseline experienced post-treatment relapse. This treatment-naïve patient had genotype 3a HCV and received ledipasvir and sofosbuvir alone.

Deep sequencing of the NS5A and NS5B regions was successfully carried out in samples taken at time of virologic failure from 17 and 18, respectively, of the 19 patients who experienced relapse or breakthrough or had detectable HCV after early discontinuation. The NS5A variant Y93H was not detected in any patient who experienced virologic failure. The NS5B variant S282T, which is associated with resistance to sofosbuvir, was detected at relapse in 2 patients who received ledipasvir and sofosbuvir—1 treatment-naïve patient with

Table 2. Treatment Response

	HCV genotype 3			HCV genotype 6
	Treatment naïve		Treatment experienced	Treatment naïve
HCV RNA <15 IU/mL	LDV and SOF (n = 25)	LDV and SOF + RBV (n = 26)	LDV and SOF + RBV (n = 50)	LDV and SOF (n = 25)
During treatment, n/n (%)				
Week 2	16/25 (64)	16/26 (62)	26/50 (52)	14/25 (56)
Week 4	23/24 (96)	23/26 (88)	48/50 (96)	24/25 (96)
Week 6	24/24 (100)	26/26 (100)	24/25 (96)	50/50 (100)
Week 8	24/24 (100)	26/26 (100)	25/25 (100)	50/50 (100)
Post treatment, n/n (%)				
Week 4	17/25 (68)	26/26 (100)	42/50 (84)	24/25 (96)
Week 8	16/25 (64)	26/26 (100)	41/50 (82)	24/25 (96)
Week 12 (SVR)	16/25 (64)	26/26 (100)	41/50 (82)	24/25 (96)
95% CI	43–82	87–100	69–91	80–100
Virologic failure, n (%)				
On treatment	0	0	1	0
Relapse	8 (32)	0	8 (16)	1 (4)
Discontinued due to AE, n	1[a] (4)	0	1[b] (2)	0

AE, adverse event; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.
[a]Patient discontinued after 2 weeks of treatment because of the adverse event diverticular perforation.
[b]Patient reached SVR12.

Table 3. Baseline Characteristics of Patients With Virologic Failure

Treatment group	Age, *y*	Sex	Race	BMI, *kg/m²*	HCV genotype	IL28B status	HCV RNA, *log₁₀ IU/mL*	ALT × ULN	Cirrhosis	HCV RNA <LLOQ, *wk*	Response
Treatment-naïve	53	F	White	36.7	3a	CC	6.9	1.1	No	2	Relapse
patients with	56	M	White	27.9	3a	CT	7.1	4.3	Yes	4	Relapse
genotype 3	58	M	White	18.7	3a	CC	7.0	1.3	Yes	4	Relapse
HCV	39	F	White	24.2	3a	TT	4.0	0.8	No	1	Relapse
receiving	46	M	White	27.2	3a	CT	6.9	2.7	No	4	Relapse
LDV and SOF	46	M	White	31.3	3a	CT	7.1	1.8	No	6	Relapse
for 12 wk	45	M	White	27.9	3a	CC	6.0	6.5	Yes	4	Relapse
	58	M	White	27.4	3a	TT	5.5	1.1	No	2	Relapse
Previously	61	M	White	25.0	3a	CC	5.4	3.1	Yes	2	Relapse
treated	59	M	White	30.4	3a	CT	6.4	2.4	Yes	2	Relapse
patients with	47	M	White	28.9	3a	CT	5.9	1.9	Yes	4	Relapse
genotype 3	57	M	White	30.4	3a	CC	6.2	2.8	Yes	2	Relapse
HCV	55	M	White	28.4	3a	CT	5.6	6.7	Yes	2	Relapse
receiving	65	M	Pacific Islander	31.0	3a	CC	6.8	1.4	Yes	2	Relapse
LDV and SOF + RBV	57	M	White	29.2	3a	CT	5.9	1.6	No	1	Relapse
for 12 wk	48	M	Pacific Islander	34.1	3a	CC	6.8	2.5	No	4	Breakthrough
	61	M	White	24.5	3	CT	6.4	1.5	No	4	Relapse

ALT, alanine aminotransferase; BMI, body mass index; F, female; LDV, ledipasvir; M, male; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal.

genotype 3a HCV at week 2 post treatment (90%) and 1 treatment-naïve patient with genotype 6l at week 12 post treatment (98%). Variants associated with NS5A resistance were not detected in either patient. The variant L159F was detected at time of virologic failure in one treatment-experienced patient with genotype 3a HCV at week 12 of treatment with ledipasvir and sofosbuvir plus ribavirin.

Safety

The adverse events reported in this study were consistent with those reported in prior studies of ledipasvir and sofosbuvir and ribavirin.[12–16] The most common adverse events among all treatment groups were headache and upper respiratory tract infection, followed by fatigue and nausea (Table 4). Six patients experienced serious adverse events. Two of the events, upper abdominal pain and abdominal pain, were considered related to treatment. Only 1 patient, a 38-year-old treatment-naïve male with genotype 3 HCV receiving ledipasvir and sofosbuvir alone, discontinued treatment because of an adverse event. The event, diverticular perforation, was not considered related to treatment. Another patient, a 49-year-old, treatment-experienced woman with genotype 3 HCV, discontinued ribavirin after an event of acute agitation. Seven patients experienced anemia; all were taking ribavirin. Six patients had their dose of ribavirin reduced and one had ribavirin interrupted.

Discussion

In this open-label, phase 2 study, all 26 (100%) treatment-naïve patients with genotype 3 HCV who were randomized to receive 12 weeks of ledipasvir and sofosbuvir plus ribavirin achieved SVR12 as compared with only 16 of 25 (64%) patients who were randomized to receive 12 weeks of ledipasvir and sofosbuvir alone. Although this study was not powered for formal comparisons between these groups, these results suggest that the addition of ribavirin improves the efficacy of ledipasvir and sofosbuvir in treatment-naïve patients with genotype 3 HCV.

Less clear is the benefit ledipasvir adds to the efficacy of sofosbuvir with or without ribavirin. Ledipasvir's lower potency in replicons containing HCV genotype 3a (50% effective concentration [EC_{50}] = 168 nM) as compared with those containing genotype 1a (EC_{50} = 0.031 nM) or 1b (EC_{50} = 0.004 nM) suggest that it would have minimal activity against genotype 3 HCV (unpublished data).

In the current trial of 12 weeks of ledipasvir and sofosbuvir plus ribavirin in patients with HCV genotype 3 infection, the SVR12 rate was 100% in treatment-naïve and 82% in treatment-experienced patients. In contrast, in the phase 3 studies of 12 weeks of sofosbuvir plus ribavirin in patients with genotype 3 HCV infection, the SVR12 rate was 56% in treatment-naïve patients and only 30% in treatment-experienced patients.[17,18] While cross-study comparisons are not ideal, the higher SVR rates observed in the current trial support further evaluation of the safety and efficacy of ledipasvir-sofosbuvir plus ribavirin in patients with HCV genotype 3 infection. This would test the hypothesis that the in vitro activity of ledipasvir may not capture in its entirety the efficacy of ledipasvir in patients. At any rate, the reason for the higher rates of SVR in patients who received ledipasvir is not clear and warrants further evaluation.

No Y93H variants associated with NS5A resistance emerged in any genotype 3 or 6 patient with virologic failure, in contrast to previous findings in genotype 1 HCV. The S282T variant was detected in 2 of the 18 patients

Table 4. Treatment-Emergent Adverse Events and Laboratory Abnormalities

Adverse events and laboratory abnormalities	HCV genotype 3			HCV genotype 6
	Treatment naïve		Treatment experienced	Treatment naïve or experienced
	LDV and SOF, 12 wk (n = 25)	LDV and SOF + RBV, 12 wk (n = 26)	LDV and SOF + RBV, 12 wk (n = 50)	LDV and SOF, 12 wk (n = 25)
Patients with any AE, n (%)	25 (100)	23 (89)	45 (90)	21 (84)
Patients with SAE, n (%)	4 (16)	0	1 (2)	1 (4)
AE leading to d/c of LDV and SOF, n (%)	1 (4)	0	0	0
Deaths, n	0	0	0	0
AEs in ≥10% of patients in any treatment group, n (%)				
Headache	10 (40)	8 (31)	13 (26)	2 (8)
Upper respiratory tract infection	9 (36)	9 (35)	9 (18)	6 (24)
Fatigue	5 (20)	2 (8)	13 (26)	6 (24)
Nausea	9 (36)	4 (15)	5 (10)	0
Insomnia	3 (12)	3 (12)	10 (20)	0
Rash	1 (4)	1 (4)	7 (14)	2 (8)
Diarrhea	2 (8)	0	4 (8)	4 (16)
Constipation	3 (12)	2 (8)	1 (2)	1 (4)
Gastroenteritis	2 (8)	3 (12)	2 (4)	0
Anxiety	3 (12)	1 (4)	1 (2)	0
Cough	3 (12)	0	2 (4)	0
Hemolytic anemia	0	4 (15)	1 (2)	0
Vomiting	3 (12)	1 (4)	1 (2)	0
SAEs, n (%)				
Abdominal pain	1 (4)	—	—	—
Abdominal pain upper	1 (4)	—	—	—
Agitation	—	—	1 (2)	—
Choroidal effusion	1 (4)	—	—	—
Diverticular perforation	1 (4)	—	—	—
Hemorrhagic shock	—	—	—	1 (4)
Hemorrhoidal hemorrhage	—	—	—	1 (4)
Lens dislocation	1 (4)	—	—	
Urinary tract infection	—	—	—	1 (4)
Selected laboratory abnormalities, n (%)				
Hemoglobin (7.0 to <9.0 g/dL)	—	5 (19)	3 (6)	—
Total bilirubin (>2.5 to 5.0 × ULN)	—	2 (8)	—	—
ALT (>5.00 to 10.00 × ULN)	—	—	1 (2)	1 (4)
AST (>5.00 to 10.00 × ULN)	—	—	—	1 (4)
Lipase (>3.0 to 5.0 × ULN)	1 (4)	1 (4)	1 (2)	—
Lymphocytes (350 to <500/mm^3)	—	—	1 (2)	—
Neutrophils (500 to <750 × mm^3)	—	—	1 (2)	—

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; d/c, discontinuation; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir; ULN, upper limit of normal; WBC, white blood cells.

who experienced virologic failure at time of failure. Both of these observations support the lower potency of ledipasvir against genotype 3 and 6 HCV as compared with genotype 1 HCV.

In vitro studies suggest that the antiviral potency of the HCV NS5A inhibitor daclatasvir against genotype 3 HCV is superior to that of ledipasvir.[19] In a recent nonrandomized early access program in patients with genotype 3 HCV and decompensated cirrhosis, the SVR rate among a small number of patients receiving ledipasvir and sofosbuvir was 43% (3 of 7), while the SVR rate among an equally small number receiving daclatasvir and sofosbuvir was 71% (5 of 7).[20] When ribavirin was added, the SVR12 rate for patients receiving ledipasvir and sofosbuvir was raised to 59% (36 of 61), but the rate among patients receiving daclatasvir and sofosbuvir plus ribavirin was still significantly higher (70% [80 of 114]; $P < .05$). Current European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines recommend daclatasvir and sofosbuvir with or without ribavirin, but not ledipasvir and sofosbuvir with or without ribavirin in patients with GT 3 infection.[21,22] For patients with genotype 6 HCV infection, the results of this study suggest that ledipasvir and sofosbuvir for 12 weeks may be a safe and effective treatment.

This study was limited by the small size of its treatment arms, the small number of sites (n = 2), and by the lack of

a control group. The open-label design is not likely to have had any effect on the assessment of efficacy because the end point of SVR is not subject to bias, but it is conceivable that it biased the reporting of safety events. Another limitation of the study was geographic: all patients were enrolled at 2 sites in New Zealand. In light of these limitations, our results, which are not entirely consistent with previous observations, require further confirmation in a larger clinical trial. An open-label trial of 12 weeks of ledipasvir and sofosbuvir plus ribavirin in approximately 100 treatment-naïve patients with genotype 3 HCV has begun enrollment in Canada (NCT02413593).

In summary, this uncontrolled exploratory study of 12 weeks of treatment with the all-oral regimen of ledipasvir and sofosbuvir with ribavirin resulted in a high rate of SVR among treatment-naïve patients with genotype 3 HCV. Treatment-naïve and treatment-experienced patients with genotype 6 HCV achieved a high rate of SVR with 12 weeks of ledipasvir and sofosbuvir alone.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.07.063.

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Conflicts of interest
These authors disclose the following: Edward J. Gane served on the advisory board at AbbVie, Boehringer Ingelheim, Gilead, Janssen, Novartis, Roche, and Tibotec; was a speaker for Gilead, Novartis, Roche, and Tibotec; has patents from Gilead. Catherine A. Stedman received grant/research support from Gilead and served on the advisory board at Janssen, MSD, and Gilead. Robert H. Hyland, Di An, Evguenia Svarovskaia, Phillip S. Pang, and Diana Brainard are current employees of Gilead Sciences.

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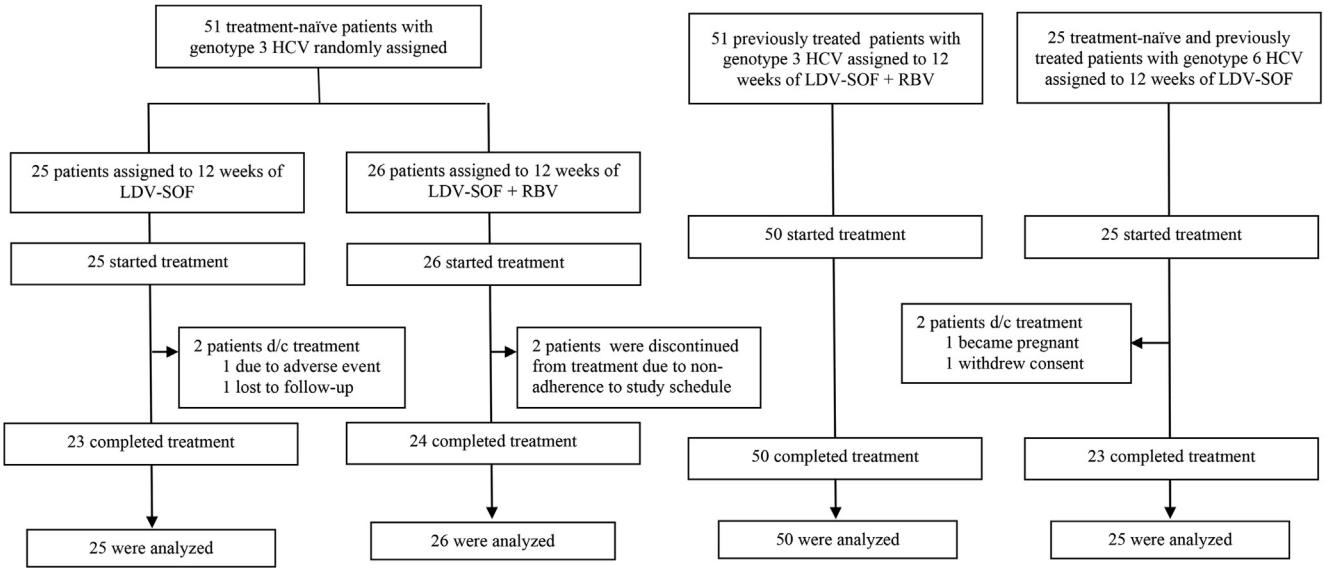

Supplementary Figure 1. Study design.