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Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease

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BACKGROUND & AIMS: There are no effective and safe treatments for chronic hepatitis C virus (HCV) infection of patients who have advanced liver disease. **METHODS:** In this phase 2, open-label study, we assessed treatment with the NS5A inhibitor ledipasvir, the nucleotide polymerase inhibitor sofosbuvir, and ribavirin in patients infected with HCV genotypes 1 or 4. Cohort A enrolled patients with cirrhosis and moderate or severe hepatic impairment who had not undergone liver transplantation. Cohort B enrolled patients who had undergone liver transplantation: those without cirrhosis; those with cirrhosis and mild, moderate, or severe hepatic impairment; and those with fibrosing cholestatic hepatitis. Patients were assigned randomly (1:1) to receive 12 or 24 weeks of a fixed-dose combination tablet containing ledipasvir and sofosbuvir, once daily, plus ribavirin. The primary end point was sustained virologic response at 12 weeks after the end of treatment (SVR12). **RESULTS:** We enrolled 337 patients, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection. In cohort A (nontransplant), SVR12 was achieved by 86%–89% of patients. In cohort B (transplant recipients), SVR12 was achieved by 96%–98% of patients without cirrhosis or with compensated cirrhosis, by 85%−88% of patients with moderate hepatic impairment, by 60%–75% of patients with severe hepatic impairment, and by all 6 patients with fibrosing cholestatic hepatitis. Response rates in the 12- and 24-week groups were similar. Thirteen patients (4%) discontinued the ledipasvir and sofosbuvir combination prematurely because of adverse events; 10 patients died, mainly from complications related to hepatic decompensation. **CONCLUSION:** The combination of ledipasvir, sofosbuvir, and ribavirin for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation. ClinTrials.gov: NCT01938430.

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Abbreviations used in this paper: **CPT, Child–Pugh–Turcotte; FCH, fibrosing cholestatic hepatitis; HCV, hepatitis C virus; MELD, model for end-stage liver disease; RAV, resistance-associated variant; SVR12, sustained virologic response at 12 weeks after the end of treatment.**

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Patients with chronic hepatitis C virus (HCV) infection and advanced liver disease—especially patients with decompensated cirrhosis—have a poor prognosis and limited treatment options.[1,2] Liver failure and hepatocellular carcinoma related to HCV infection are the most common indications for liver transplantation in North America and Europe.[3,4] In patients with detectable virus at the time of transplantation, recurrent HCV infection is universal and 30% of patients have an aggressive clinical and histologic course with increased morbidity, mortality, and graft loss.[5–7] There is an urgent medical need for safe and effective treatments for patients with advanced liver disease. To date, few clinical trials have included patients with decompensated liver disease and the effect of sustained virologic response on liver-related function and outcomes is not known.

Sofosbuvir is a nucleotide analogue inhibitor approved for the treatment of HCV.[8] In phase 2 trials, sofosbuvir plus ribavirin was used to treat patients both before and after liver transplantation, including those with compensated cirrhosis, with moderate efficacy after prolonged (24–48 wk) administration.[9,10] Sofosbuvir plus ribavirin also has been used successfully in a subgroup of patients with decompensated cirrhosis in a compassionate-use program, with similarly moderate efficacy.[11] A fixed-dose combination of sofosbuvir with the HCV NS5A inhibitor ledipasvir recently was approved in the United States and Europe for the treatment of chronic genotype 1 HCV infection.[12] The safety and efficacy of ledipasvir-sofosbuvir among patients with compensated cirrhosis has been established,[13] but this combination has not been evaluated previously in patients with more advanced liver disease. We conducted an open-label, phase 2 study to determine the efficacy and safety of ledipasvir-sofosbuvir with ribavirin in patients with advanced liver disease, including patients who have undergone liver transplantation.

Materials and Methods

Patients

Between September 6, 2013, and January 11, 2014, patients were enrolled at 29 clinical sites in the United States. Eligible patients were at least 18 years of age and chronically infected with genotypes 1 or 4 HCV. Patients co-infected with human immunodeficiency virus or hepatitis B virus or with prior exposure to an NS5a inhibitor were not eligible for enrollment. Patients with any of the following laboratory abnormalities also were excluded from enrollment: hemoglobin level less than 10 g/dL, platelet level of 30,000/mm^3 or less, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase level 10 times or more the upper limit of normal, total bilirubin level greater than 10 mg/dL (except for the fibrosing cholestatic hepatitis [FCH] cohort), serum creatinine level greater than 2.5 times the upper limit of normal, and/or evidence of renal impairment (creatinine clearance, $<$40 mL/min).

Patients were enrolled in 2 cohorts. Cohort A consisted of 2 groups of patients with advanced cirrhosis (Child–Pugh class B and C, Supplementary Table 1) caused by chronic HCV infection who had not undergone liver transplantation: group 1 enrolled patients with cirrhosis and moderate hepatic impairment (Child–Pugh class B), and group 2 enrolled patients with cirrhosis and severe hepatic impairment (Child–Pugh class C). Cohort B consisted of 5 groups of patients, all of whom had undergone liver transplantation previously: group 3 enrolled patients without cirrhosis, group 4 enrolled patients with compensated cirrhosis and mild hepatic impairment (Child–Pugh class A), group 5 enrolled patients with cirrhosis and moderate hepatic impairment (Child–Pugh class B), group 6 enrolled patients with cirrhosis and severe hepatic impairment (Child–Pugh class C), and Supplementary group 7 enrolled patients with fibrosing cholestatic hepatitis (Supplementary Appendix).

Study Design

In this open-label, phase 2 study, patients in each of the 7 groups were randomized using a computer-generated randomization sequence generated by Bracket (San Francisco, CA) and allocated by means of an interactive web response system in a 1:1 ratio to receive either 12 or 24 weeks of treatment with ledipasvir 90 mg and sofosbuvir 400 mg in a fixed-dose combination tablet (ledipasvir-sofosbuvir) once daily plus ribavirin. For groups 3, 4, and 7, ribavirin was administered orally twice daily, with the dose determined according to body weight (1000 mg/day in patients with a body weight of $<$75 kg, and 1200 mg/day in patients with a body weight $\geq$75 kg). For groups 1, 2, 5, and 6, ribavirin was administered at a starting dose of 600 mg in a divided daily dose. Provided that the starting dose was well tolerated, and that hemoglobin levels remained higher than 10 g/dL without hematologic growth factor support, the dose could be increased to a maximum of 1000 mg/day in patients with a body weight of less than 75 kg, and 1200 mg/day in patients with a body weight of 75 kg or greater. For patients who could not tolerate the starting dose of 600 mg, the dose was reduced as necessary on the basis of hemoglobin levels or other ribavirin side effects.

Management of immunosuppression was not specified in the clinical protocol, but levels and resulting dose adjustments were recorded to assess whether the regimens required an adjustment in correlation with resolution of HCV infection or because of drug interaction with study treatment.

Study Assessments

Serum HCV-RNA level was measured using the Roche (Branchburg, NJ) COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (HCV RNA polymerase chain reaction). HCV genotype and subtype were determined using the Siemens (Tarrytown, NY) Versant HCV Genotype INNO-LiPA 2.0 Assay, the Trugene HCV 5'NC Genotyping Assay, and NS5b sequencing. The interleukin 28B genotype was determined by polymerase chain reaction amplification of the single-nucleotide polymorphism rs12979860.

For analysis of viral resistance, we collected samples at baseline from all patients. The HCV NS5A and NS5B coding regions were amplified using standard reverse-transcription polymerase chain reaction technology. Variants present at more 1% of sequence reads are reported. For patients who had virologic failure, deep sequencing was performed for the HCV NS5A and NS5B coding regions with samples collected at the first virologic failure time point. Variants in NS5A and NS5B

coding regions present in at least 1% of the viral population were compared with the respective baseline sequence.

End Points and Statistical Analysis

The primary efficacy end point was the rate of sustained virologic response, defined as the absence of quantifiable HCV RNA in serum (<15 IU/mL) at 12 weeks after the end of therapy (SVR12) among all patients who underwent randomization and received at least 1 dose of study drugs. The proportions of patients with SVR12 along with a 2-sided 90% confidence interval (using the Clopper–Pearson method) were calculated by group and treatment duration. We did not perform a formal sample size calculation. The enrolment target of 50 patients for all groups (except group 3, which had an enrolment target of 100 patients) was chosen to provide a reasonable estimate of SVR12 with appropriate 90% confidence intervals. The efficacy end point for patients who underwent liver transplantation during the study was the rate of post-transplant virologic response (defined as HCV-RNA level <15 IU/mL at 12 weeks after transplant) in all patients who have HCV-RNA level less than 15 IU/mL at their last observed HCV RNA quantification before transplantation. Six of these patients underwent liver transplantation with HCV-RNA level less than 15 IU/mL before post-treatment week 12 and were not included in the efficacy analysis for cohort A. The primary safety end point was the proportion of patients who discontinued study treatment owing to an adverse event. Secondary end points included improvements in Child–Pugh class and model for end-stage liver disease (MELD) score during treatment and follow-up evaluation. We used the Wilcoxon rank sum test to analyze the bilirubin and albumin data.

Study Oversight

The design of this study, which was in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements, was approved by the institutional review board or independent ethics committee at each participating site. This study was conducted according to the protocol by the sponsor (Gilead Sciences) in collaboration with the academic investigators.

Role of the Funding Source

The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. An independent data and safety monitoring committee reviewed the progress of the study. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors had access to the data and assume responsibility for the integrity and completeness of the data and analyses reported. The first draft of the manuscript was prepared by a professional writer who is an employee of Gilead Sciences and both corresponding authors, with input from all the authors.

Results

Patient Baseline Characteristics

Of the 417 patients screened, 337 were enrolled, 332 (99%) with HCV genotype 1 infection and 5 (1%) with HCV genotype 4 infection (Supplementary Table 2 in the Supplementary Appendix). Only 9 patients were enrolled in group 6 (patients with Child–Pugh class C liver disease who had undergone liver transplantation) and only 6 patients were enrolled in group 7 (patients with fibrosing cholestatic hepatitis). The demographic and baseline clinical characteristics of the patients generally were balanced between the 12- and 24-week treatment arms in each of the 7 patient groups (Table 1).

Seven patients in cohort A underwent liver transplantation, 4 patients during study treatment and 3 patients after completing study treatment (Figure 1).

Efficacy

Nontransplanted Patients With Decompensated Cirrhosis: Groups 1 and 2. Rates of sustained virologic response among patients with Child–Pugh class B disease who had not undergone transplantation were similar regardless of treatment duration: 87% in patients who received 12 weeks of treatment and 89% in patients who received 24 weeks of treatment (Table 2 and Supplementary Table 3). Rates of sustained virologic response also were similar among patients with Child–Pugh class C decompensated disease who had not undergone transplantation regardless of treatment: 86% and 87% in patients who received 12 and 24 weeks of treatment, respectively (Supplementary Table 4).

In the majority of patients with Child–Pugh class B and C disease, MELD and Child–Pugh–Turcotte (CPT) scores decreased between baseline and post-treatment week 4 (Figure 2, Supplementary Figures 2–5, and Supplementary Table 5). Patients with Child–Pugh class B disease had statistically significant improvements from baseline in total bilirubin and albumin levels from baseline to post-treatment week 4 (Supplementary Appendix, Supplementary Table 5).

Post-Transplant Patients With No Cirrhosis or Compensated Cirrhosis: Groups 3 and 4. Among patients with no cirrhosis or compensated cirrhosis who had undergone liver transplantation, rates of sustained virologic response ranged from 96% to 98%. Rates of response in these groups did not substantially vary by the presence or absence of cirrhosis or by treatment duration (Table 2).

Post-Transplant Patients With Decompensated Cirrhosis: Groups 5 and 6. Rates of sustained virologic response among patients with Child–Pugh class B disease who had undergone liver transplantation were similar regardless of treatment duration: 86% in those who received 12 weeks of treatment and 88% in those who received 24 weeks of treatment. Patients with Child–Pugh class C disease who had undergone transplantation (group 6) had lower rates of sustained virologic response (60% and 75%, respectively, in patients receiving 12 and 24 weeks of treatment), but the small number of patients enrolled in this group (n = 9) makes this result difficult to interpret. Similar to nontransplanted patients, the majority of patients with both Child–Pugh class B and C disease who had undergone liver transplantation had MELD and CPT scores that were improved at post-treatment week 4 compared with baseline levels (Figure 1 and Supplementary Figure 2).

FCH: Group 7. All 6 patients with fibrosing cholestatic hepatitis achieved sustained viral response. These patients

Table 1. Baseline Demographic Characteristics

Characteristic	Cohort A: pretransplantation				Cohort B: post-transplantation	
	Group 1 CTP B		Group 2 CTP C		Group 3 No cirrhosis	
	12 wk (n = 30)	24 wk (n = 29)	12 wk (n = 23)	24 wk (n = 26)	12 wk (n = 55)	24 wk (n = 56)
Median age, *y* (IQR)	60 (53–63)	58 (56–62)	58 (53–61)	59 (55–62)	59 (58–63)	58 (56–61)
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)	45 (82)	46 (82)
Race, n (%)						
White	29 (97)	26 (90)	21 (91)	24 (92)	50 (91)	49 (88)
Black	1 (3)	3 (10)	2 (9)	1 (4)	4 (7)	4 (7)
Other	0	0	0	1 (4)	1 (2)	3 (5)
HCV genotype						
1a	19 (63)	22 (76)	15 (65)	18 (69)	40 (73)	40 (71)
1b	10 (33)	7 (24)	6 (26)	8 (31)	14 (25)	16 (29)
4	1 (3)	0	2 (9)	0	1 (2)	0
HCV-RNA level, log_{10} *IU/mL* ± SD	5.9 ± 0.7	5.8 ± 0.8	5.6 ± 0.6	5.8 ± 0.7	6.5 ± 0.6	6.4 ± 0.9
HCV-RNA level ≥800,000 IU/mL	16 (53)	18 (62)	9 (39)	11 (42)	45 (82)	46 (82)
IL28B genotype CC, n (%)	4 (13)	5 (17)	6 (26)	7 (27)	11 (20)	10 (18)
Previously treated	22 (73)	19 (66)	11 (48)	18 (69)	39 (71)	48 (86)
Regimen received						
Peg/ribavirin	10 (45)	10 (53)	8 (73)	17 (94)	26 (67)	39 (81)
PI + Peg/ribavirin	9 (41)	9 (47)	2 (18)	0	9 (23)	5 (10)
Other	3 (17)	0	1 (9)	1 (6)	4 (10)	4 (8)
Prior response						
Nonresponse	15 (68)	14 (74)	7 (64)	13 (72)	23 (59)	33 (69)
Relapse/breakthrough	7 (32)	5 (26)	4 (36)	5 (28)	16 (41)	15 (31)
Median time since transplant, *y*	–	–	–	–	2.9	2.8
Median eGFR, *mL/min* (IQR)	98 (70–108)	81 (64–99)	77 (54–90)	78 (69–97)	61 (50–75)	71 (55–84)
Median platelets, (IQR)	88 (61–120)	73 (63–91)	81 (51–99)	71 (53–79)	143 (123–196)	152 (108–206)
Child–Turcotte–Pugh class						
Class A (CTP score 5–6)	0	1 (3)	0	0	–	–
Class B (CTP score 7–9)	27 (90)	27 (93)	7 (30)	4 (15)	–	–
Class C (CTP score 10–12)	3 (10)	1 (3)	16 (70)	22 (85)	–	–
MELD score						
<10	6 (20)	8 (28)	0	0	–	–
10–15	21 (70)	16 (55)	16 (70)	13 (50)	–	–
16–20	3 (10)	5 (17)	7 (30)	12 (46)	–	–
21–25	0	0	0	1 (4)	–	–

eGFR, estimated glomerular filtration rate; IQR, interquartile range; Peg, pegylated; PI, protease inhibitor.

also showed large decreases in total bilirubin level by treatment weeks 2–4, accompanied by suppression of HCV RNA (Supplementary Appendix).

Patients With Genotype 4 HCV. Results for the 5 patients with genotype 4 HCV are included in the relevant groups listed earlier, but we report them separately here. Three of the 5 patients (1 patient each in groups 1, 2, and 3) achieved SVR12, 1 patient in group 2 was lost to follow-up evaluation after achieving SVR4, and 1 patient in group 5 died of complications relating to cirrhosis on day 75 of treatment (Supplementary Appendix).

On-Study Liver Transplantation. Seven patients in cohort A underwent liver transplantation, 4 patients before the end of treatment and 3 patients in the follow-up period before post-treatment week 12. Of the 7 patients, 6 patients have achieved post-transplant virologic response. The seventh patient had undetectable HCV-RNA level at post-transplantation week 2 and died 1 day later of multiorgan failure and septic shock (Supplementary Appendix).

Post-Transplantation Immunosuppression. The most commonly used immunosuppressive agents among the 229 patients in cohort B were tacrolimus in 174 patients (76%); mycophenolate mofetil, mycophenolate sodium, or mycophenolic acid in 82 patients (36%); and cyclosporine in 34 patients (15%) (Supplementary Appendix). One patient experienced an increase in cyclosporine concentrations that the investigator attributed to an interaction with study treatment. However, increases in cyclosporine concentrations also have been reported to be a result of an improvement of organ function. No other changes to immunosuppression were reported as caused by drug interactions with the study treatment. Forty instances of adjustments to immunosuppression in 24 patients were attributed by the investigators to improvements in hepatic function after viral clearance.

Cohort B: post-transplantation							
Group 4 CTP A		Group 5 CTP B		Group 6 CTP C		Group 7 FCH	
12 wk (n = 26)	24 wk (n = 25)	12 wk (n = 26)	24 wk (n = 26)	12 wk (n = 5)	24 wk (n = 4)	12 wk (n = 4)	24 wk (n = 2)
60 (56–64)	61 (58–65)	61 (55–63)	61 58–65)	58 (58–62)	61 (60–62)	62 (59–65)	58 (52–64)
19 (73)	22 (88)	22 (85)	23 (88)	5 (100)	4 (100)	4 (100)	2 (100)
21 (81)	20 (80)	21 (81)	24 (92)	4 (80)	4 (100)	4 (100)	2 (100)
3 (12)	4 (16)	5 (19)	2 (8)	1 (20)	0	0	0
2 (8)	1 (4)	0	0	0	0	0	0
17 (65)	17 (68)	20 (77)	18 (69)	4 (80)	3 (75)	3 (75)	2 (100)
9 (35)	8 (32)	6 (23)	7 (27)	1 (20)	1 (25)	1 (25)	0
0	0	0	1 (4)	0	0	0	0
6.2 ± 0.8	6.7 ± 0.3	6.3 ± 0.6	6.2 ± 0.7	6.4 ± 0.4	6.3 ± 0.4	6.5 ± 1.2	7.1 ± 0.9
19 (73)	25 (100)	20 (77)	17 (65)	4 (80)	4 (100)	3 (75)	2 (100)
7 (27)	1 (4)	3 (12)	5 (19)	2 (40)	1 (25)	0	0
22 (85)	24 (96)	22 (85)	22 (85)	4 (80)	4 (100)	4 (100)	1 (50)
15 (68)	18 (75)	12 (55)	17 (77)	4 (100)	3 (75)	4 (100)	1 (100)
3 (14)	4 (17)	8 (36)	4 (18)	0	1 (25)	0	0
4 (18)	2 (8)	2 (9)	1 (5)	0	0	0	0
14 (64)	19 (79)	15 (68)	16 (73)	3 (75)	3 (75)	4 (100)	1 (100)
8 (36)	5 (21)	7 (32)	6 (27)	1 (25)	1 (25)	0	0
8.8	6.6	5.1	6.3	5.2	5.7	1.1	0.3
59 (55–67)	68 (57–88)	68 (53–77)	56 (51–65)	67 (54–67)	62 (47–69)	90 (36–92)	69 (n = 1)
106 (75–138)	112 (88–168)	93 (73–121)	97 (66–97)	106 (63–160)	65 (54–93)	45 (42–131)	196 (182–210)
25 (96)	22 (88)	0	2 (8)	0	0	–	–
1 (4)	3 (12)	24 (92)	24 (92)	2 (40)	1 (25)	–	–
0	0	2 (8)	0	3 (60)	3 (75)	–	–
15 (58)	13 (52)	8 (31)	5 (19)	1 (20)	0	–	–
10 (38)	10 (40)	14 (54)	19 (73)	3 (60)	2 (50)	–	–
1 (4)	2 (8)	2 (8)	2 (8)	1 (20)	1 (25)	–	–
0	0	2 (8)	0	0	1 (25)	–	–

Virologic Resistance. Overall, NS5A and NS5B pretreatment resistance analysis was conducted for 311 and 309 patients with genotype 1 HCV infection, respectively. A total of 42 of 311 patients (14%) with genotype 1 HCV infection had baseline NS5A resistance-associated variants (RAVs), which confer reduced susceptibility to ledipasvir. Of these 42 patients, 3 patients (7%) relapsed. The rate of relapse among patients without baseline NS5A RAVs was 4% (10 of 269). None of the 25 patients with NS5A RAVs who received ledipasvir-sofosbuvir plus ribavirin for 24 weeks relapsed. At virologic failure, 11 of 13 (85%) patients who relapsed were observed to have NS5A variants: M28T, Q30H/R, H58D, and Y93H/C. Neither S282T, the signature RAV associated with resistance to sofosbuvir, nor other nucleotide inhibitor RAVs were observed at pretreatment or after treatment in any of the patients with virologic failure.

Safety

Given that the study population consisted of patients with advanced liver disease, rates of adverse events were high in all patient groups (Table 3). However, only 13 patients (4%) discontinued ledipasvir-sofosbuvir prematurely secondary to adverse events. The only adverse events that led to discontinuation in more than 1 patient were sepsis (n = 2), acute renal failure (n = 2), dyspnea (n = 2), and gastrointestinal hemorrhage (n = 2). Seventy-seven patients (23%) experienced serious adverse events, the majority of which were associated with hepatic decompensation. A full list of serious adverse events is provided in Supplementary Table 7. Thirteen patients died during the study: 4 patients during treatment, 6 patients after discontinuing study treatment but within 30 days after treatment, and 3 patients at more than 30 days after the end of treatment. The most common cause of death was septic shock accompanied by

Table 2. Response During and After Treatment

	Cohort A: pretransplantation				Cohort B: post-transplantation									
	Group 1 CTP B		Group 2 CTP C		Group 3 No cirrhosis		Group 4 CTP A		Group 5 CTP B		Group 6 CTP C		Group 7 FCH	
Response	12 wk (n = 30)	24 wk (n = 29)	12 wk (n = 23)	24 wk (n = 26)	12 wk (n = 55)	24 wk (n = 56)	12 wk (n = 26)	24 wk (n = 25)	12 wk (n = 26)	24 wk (n = 26)	12 wk (n = 5)	24 wk (n = 4)	12 wk (n = 4)	24 wk (n = 2)
HCV RNA <LLOQ on treatment														
At week 2	11/30 (37)	12/29 (41)	9/23 (39)	10/26 (38)	27/55 (49)	23/55 (42)	9/26 (35)	7/25 (28)	2/25 (8)	11/26 (42)	2/5 (40)	1/4 (25)	2/4 (50)	0/2
At week 4	25/30 (83)	24/29 (83)	23/23 (100)	22/26 (85)	48/55 (87)	50/55 (91)	23/26 (88)	20/25 (80)	18/25 (72)	23/26 (88)	5/5 (100)	4/4 (100)	4/4 (100)	1/2 (50)
At week 6	30/30 (100)	29/29 (100)	22/22 (100)	25/26 (96)	53/55 (96)	55/55 (100)	25/25 (100)	25/25 (100)	25/25 (100)	26/26 (100)	5/5 (100)	4/4 (100)	4/4 (100)	1/2 (50)
HCV RNA <LLOQ after treatment														
At week 4 (SVR4)	27/30 (90)	24/27 (89)	20/22[a] (91)	22/23 (96)	53/55 (96)	55/56 (98)	25/26 (96)	25/25 (100)	23/26 (88)	24/26 (92)	5/5 (100)	3/4 (75)	4/4 (100)	2/2 (100)
At week 12 (SVR12)	26/30 (87)	24/27 (89)	19/22 (86)	20/23 (87)	53/55 (96)	55/56 (98)	25/26 (96)	24/25 (96)	22/26 (85)	23/26 (88)	3/5 (60)	3/4 (75)	4/4 (100)	2/2 (100)
90% CI	72–95	74–97	68–96	70–96	89–99	92–100	83–100	82–100	68–95	73–97	19–92	25–99	47–100	22–100
Virologic failure														
Breakthrough	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Relapse	3	1	1	2	2	0	0	0	1	0	2	1	0	0

CI, confidence interval; LLOQ, lower limit of quantification.
[a]Patients undergoing transplantation with HCV-RNA levels less than the LLOQ before the post-treatment visit window were excluded from analysis.

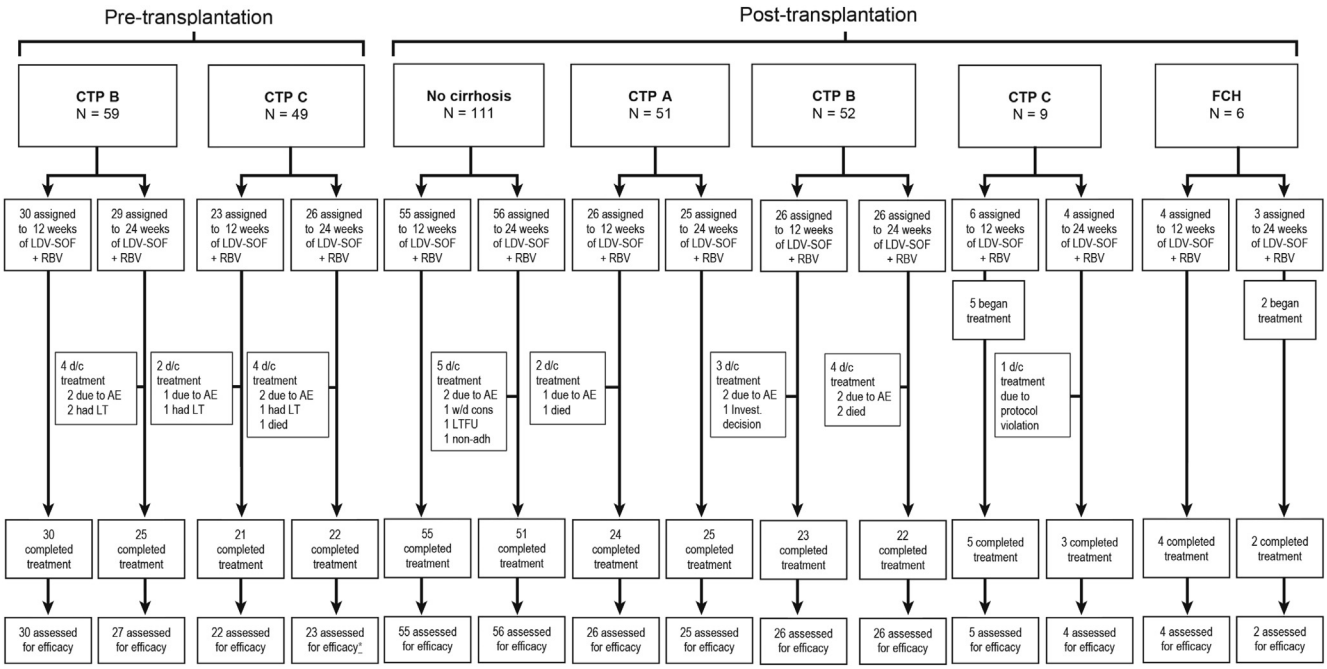

Figure 1. Patient disposition during the study. AE, adverse event; LDV, ledipasvir; SOF, sofosbuvir; LT, liver transplantation; RBV, ribavirin.

multiorgan failure (Supplementary Appendix). None of the deaths were deemed treatment-related.

Across all groups, the most common grade 3 or 4 laboratory abnormalities were decreases in hemoglobin and lymphocyte levels and increases in total bilirubin and glucose level. Decreases in hemoglobin level and hyperbilirubinemia are known to be associated with ribavirin-induced hemolysis.

The most common grade 3 or 4 laboratory abnormality for cohort A was increases in total bilirubin level followed by lymphopenia. For cohort B patients, the most common grade 3 or 4 laboratory abnormalities were decreases in hemoglobin and lymphocyte levels. Increases in serum glucose level were observed mostly among patients with increased serum glucose level at baseline. Across all groups, median creatinine values remained stable while on treatment.

A total of 132 (39%) and 44 (13%) patients experienced hemoglobin values less than 10 and 8.5, respectively. Fifty-one (15%) patients received at least 1 concomitant blood product or erythropoietin. The average daily dose of ribavirin in patients with decompensated cirrhosis (pre-transplantation or post-transplantation) was approximately 600 mg. The average daily dose of ribavirin in patients with no cirrhosis or compensated cirrhosis was approximately 1000 mg. The dose of ribavirin was reduced in 43% of patients (144 of 337) and discontinued altogether in 18% of patients (59 of 337). Discontinuation of ribavirin was more common in the 24-week groups and among patients with a worsening disease state (Supplementary Appendix).

There were 3 reports of acute cellular rejection in post-transplant patients. None of the 3 cases were thought to be related to study treatment. Two reports were in group 3, 1 on day 169 of treatment, which subsequently resolved, and 1 at 91 days after the last dose of study drug, which has not resolved. One patient in group 1 with acute cellular rejection underwent transplantation during the study and had graft loss 6 days after transplant. This patient was retransplanted 9 days later, and went on to achieve post-transplant virologic response.

Discussion

In this large-scale trial that evaluated the efficacy of all-oral direct-acting antiviral therapy in patients with HCV genotype 1 and decompensated cirrhosis, and post-transplant patients with cirrhosis, 12 or 24 weeks of treatment with ledipasvir-sofosbuvir and ribavirin resulted in high rates of response. Rates of sustained virologic response were greater than 85% in every group of patients with Child–Pugh class B decompensated cirrhosis—in patients who had and had not undergone liver transplantation, as well as in patients who were receiving 12 and 24 weeks of treatment. Similar response rates were observed in Child–Pugh class C patients who had not undergone liver transplantation. Rates of response were numerically lower in liver transplant recipients with Child–Pugh class C disease, but the small sample size (n = 9) make this a preliminary observation. Our results also show that SVR12 in patients with decompensated cirrhosis is associated with early improvements in CPT and MELD scores, suggesting that eradication of the virus can improve hepatic function rapidly by attenuating the injury and inflammation caused by HCV replication. Similar effects have been described for suppression of hepatitis B virus in patients with decompensated disease.[14,15] Long-term follow-up evaluation of

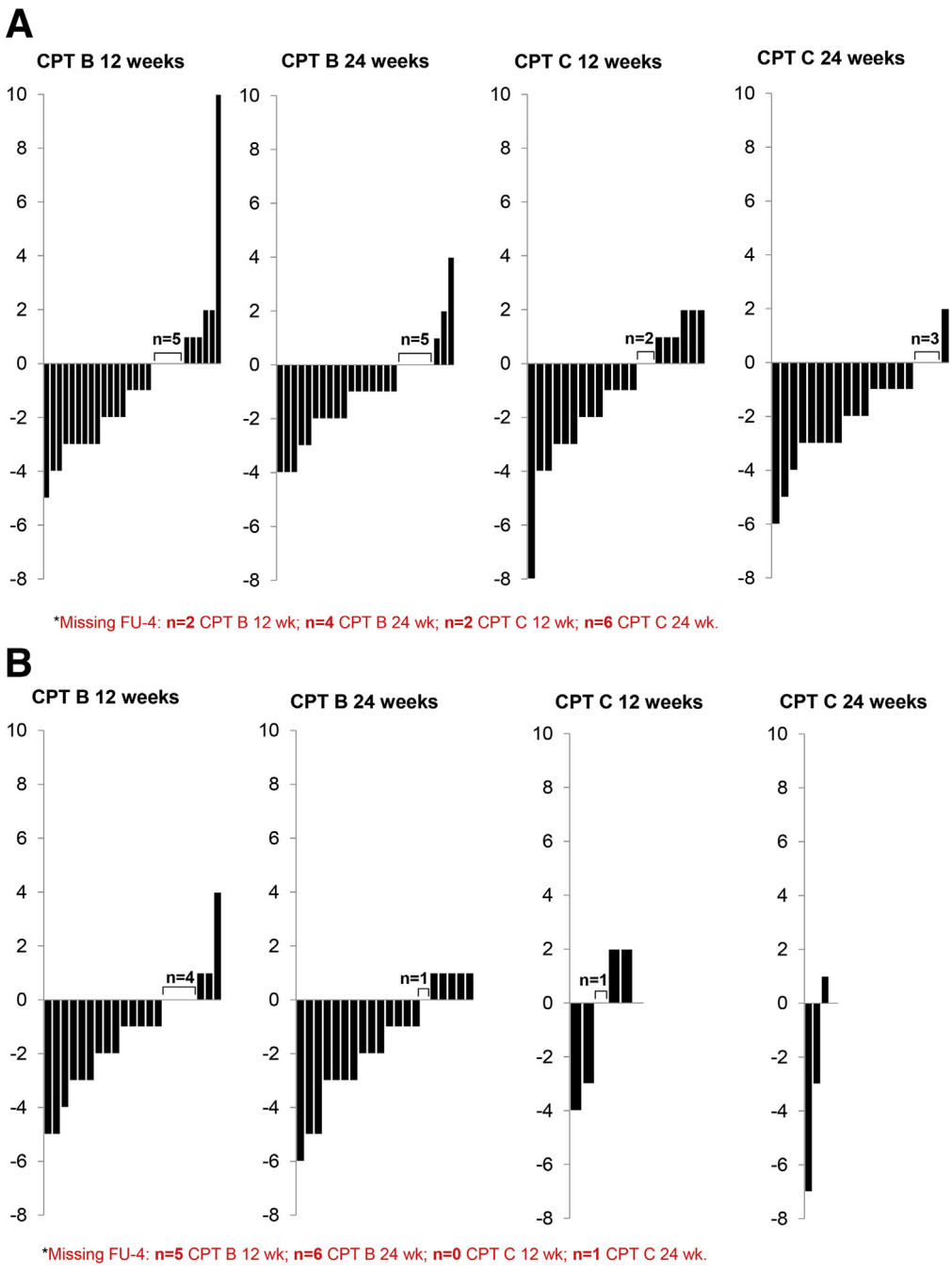

Figure 2. Change from baseline to post-treatment week 4 in MELD scores in patients with Child–Pugh B and C disease. The figure shows the change from baseline in MELD scores in patients in groups 1, 2, 5, and 6. MELD is a scoring system for assessing the severity of chronic liver disease and was designed to measure the urgency of the need for liver transplantation. The scores were calculated using the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time. The resulting scores range from 6 (the least ill patients) to 40+ (gravely ill patients). The 3-month mortality rate was 71% for patients with a score of 40 or higher, 53% for patients with a score of 30–39, 20% for patients with a score of 20–29, 6% for patients with a score of 10–19, and 2% for patients with a score of 9 or less.[26] Each *black bar* represents an individual patient. Missing patient data for the post-treatment week 4 visit are indicated in the figure.

patients with Child–Pugh class B and C disease who have achieved sustained virologic response is needed to determine possible long-term benefits, such as decreased demand for liver transplantation, reduced liver-related mortality, and hepatocellular carcinoma, as well as reversibility of clinical liver failure.

Our study included a small number of patients with FCH, an uncommon complication of liver transplantation characterized by highly aggressive progression of cholestasis and fibrosis. Until recently, there was no effective treatment for this frequently fatal condition. A number of recent case reports have shown that FCH can be treated successfully with direct-acting antiviral therapy.[16–19] Our results—all 6 patients with FCH treated with ledipasvir-sofosbuvir plus ribavirin achieved sustained virologic response—provide further encouraging evidence that FCH now may be a manageable complication of liver transplantation.

Among patients in groups 3 and 4, which represented a broad spectrum of patients post-transplant, from mild histologic disease to compensated cirrhosis, rates of sustained virologic response ranged from 96% to 98%. These rates are generally in keeping with those observed in the ION-1 and ION-2 trials, in which patients who had not undergone liver transplantation received ledipasvir-sofosbuvir for

Table 3. Rates of Serious Adverse Events and Adverse Events Leading to Study Drug Discontinuation

	Cohort A: pretransplantation				Cohort B: post-transplantation									
	CTP B		CTP C		No cirrhosis		CTP A		CTP B		CTP C		FCH	
Characteristic	12 wk (n = 30)	24 wk (n = 29)	12 wk (n = 23)	24 wk (n = 26)	12 wk (n = 55)	24 wk (n = 56)	12 wk (n = 26)	24 wk (n = 25)	12 wk (n = 26)	24 wk (n = 26)	12 wk (n = 5)	24 wk (n = 4)	12 wk (n = 4)	24 wk (n = 2)
Any adverse event, n (%)	29 (97)	28 (97)	23 (100)	26 (100)	55 (100)	55 (98)	25 (96)	24 (96)	25 (96)	26 (100)	5 (100)	4 (100)	4 (100)	2 (100)
Serious adverse event, n (%)	3 (10)	10 (34)	6 (26)	11 (42)	6 (11)	12 (21)	3 (12)	4 (16)	5 (19)	11 (42)	1 (20)	3 (75)	1 (25)	1 (50)
Discontinuation of LDV-SOF owing to, n (%)	0	2 (7)	1 (4)	2 (8)	0	2 (4)	1 (4)	0	2 (8)	3 (12)	0	0	0	0
Sepsis	0	2 (7)	0	0	0	0	0	0	0	0	0	0	0	0
Gastric hemorrhage	0	1 (3)	0	0	0	0	0	0	1 (4)	0	0	0	0	0
Acute renal failure	0	0	0	1 (4)	0	0	0	0	0	1 (4)	0	0	0	0
ALT level increased	0	0	0	0	0	1 (2)	0	0	0	0	0	0	0	0
AST level increased	0	0	0	0	0	1 (2)	0	0	0	0	0	0	0	0
Aortic dissection	0	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0
Chest pain	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0	0
Convulsion	0	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0	0
Dyspnea	0	0	0	0	0	1 (2)	1 (4)	0	0	0	0	0	0	0
Infection	0	0	1 (4)	0	0	0	0	0	0	0	0	0	0	0
Hepatic encephalopathy	0	0	0	1 (4)	0	0	0	0	0	0	0	0	0	0
Hepatic hydrothorax	0	0	1 (4)	0	0	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	1 (4)	0	0	0	0	0	0	0	0	0	0
Peritoneal hemorrhage	0	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0
Shock	0	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0	1 (4)	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDV-SOF, ledipasvir-sofosbuvir.

12 or 24 weeks with and without ribavirin.[20,21] The CORAL-1, a study that evaluated the combination of ombitasvir-paritaprevir/ritonavir-dasabuvir plus ribavirin for 24 weeks in patients with mild histologic recurrent HCV provided comparable efficacy for liver transplant recipients (fibrosis stages, 0–2).[22] However, the efficacy of this combination in patients with more severe liver disease is unknown because CORAL-1 did not include patients with hepatic decompensation or more advanced stages of recurrence (fibrosis stages 3 and 4).

An important attribute of ledipasvir-sofosbuvir is the lack of clinically relevant drug–drug interactions with CYP3A4 substrates such as calcineurin and mammalian target of rapamycin inhibitors. Although sofosbuvir and ledipasvir do not have significant direct effects on the metabolism of immunosuppressive agents,[23] HCV infection itself is known to affect dosing requirements of calcineurin inhibitors. In addition, eradication of HCV is likely to reverse, at least in part, the inhibitory effects of HCV proteins on adaptive immunity. For these reasons, we recommend close monitoring of immunosuppression trough levels during and after treatment of HCV infection.

This study was designed to evaluate 2 durations of ledipasvir-sofosbuvir plus ribavirin. Because patients in all treatment arms received the same combination, the importance of ribavirin in the regimen cannot be determined. Although ribavirin dosing was reduced in many patients with decompensated disease, there are not adequate data to determine whether relapse was associated with decreased ribavirin exposure. Patients with decompensated liver disease experience high frequencies of ribavirin hemotoxicity. For this reason, we used lower initial daily dosing in patients with Child–Pugh class C cirrhosis. Whether higher doses of ribavirin would be associated with enhanced SVR rates in participants with Child–Pugh class C cirrhosis would be an interesting subject of future studies.

The benefits of treating patients before the onset of decompensation have been shown clearly, with several-fold decreases in the risk of death, need for liver transplantation, and development of hepatocellular carcinoma.[24,25] Whether similar benefits in outcomes will accrue to patients with Child–Pugh class B and C cirrhosis who are cured of HCV infection remains to be seen. The optimal timing of treatment in patients with Child–Pugh class B and C cirrhosis among patients considering liver transplantation requires further investigation. Current treatment decisions should be made in collaboration with the transplant center caring for the patient. In the post-transplant setting our results again suggest that treating before the development of decompensation results in a numerically higher SVR and patients again will have to be followed up to determine the potential for long-term benefits on graft survival and post-transplantation mortality.

In conclusion, our findings show that ledipasvir-sofosbuvir plus ribavirin for 12 weeks is an effective treatment for a group of patients currently without effective treatment options—patients with advanced liver disease, including patients with decompensated liver function before and after liver transplantation. Extending treatment to 24 weeks did not appear to be associated with improved outcomes.

SOLAR-1 Study Team Members

The SOLAR-1 study team members included the following: Princy Kumar, Eugene Schiff, Nezam Afdhal, Robert S. Brown, Michael Fried, Kris Kowdley, Norah Terrault, Michael Charlton, Paul Kwo, Steve Flamm, John Lake, Greg Everson, Mark Sulkowski, Michael Curry, Rajender Reddy, Lewis Teperman, Hugo Vargas, Surakit Pungpapong, Andrew Muir, Atif Zaman, Kimberly Brown, Charles Landis, Alexander Kuo, Robert Fontana, Jacqueline O'Leary, Richard Gilroy, Obaid Shaikh, Kevin Korenblat, Richard Stravitz, Kymberly Watt, Narayanan Menon, James Bredfeldt, and Carlos Romero-Marrero.

Supplementary Material

Note: 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.2015.05.010.

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Conflicts of interest
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