

Daclatasvir With Sofosbuvir and Ribavirin for Hepatitis C Virus Infection With Advanced Cirrhosis or Post-Liver Transplantation Recurrence

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Chronic hepatitis C virus (HCV) infection with advanced cirrhosis or post-liver transplantation recurrence represents a high unmet medical need with no approved therapies effective across all HCV genotypes. The open-label ALLY-1 study assessed the safety and efficacy of a 60-mg once-daily dosage of daclatasvir (pan-genotypic NS5A inhibitor) in combination with sofosbuvir at 400 mg once daily (NS5B inhibitor) and ribavirin at 600 mg/day for 12 weeks with a 24-week follow-up in two cohorts of patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or post-transplantation recurrence. Patients with on-treatment transplantation were eligible to receive 12 additional weeks of treatment immediately after transplantation. The primary efficacy measure was sustained virologic response at posttreatment week 12 (SVR12) in patients with a genotype 1 infection in each cohort. Sixty patients with advanced cirrhosis and 53 with post-transplantation recurrence were enrolled; HCV genotypes 1 (76%), 2, 3, 4, and 6 were represented. Child-Pugh classifications in the advanced cirrhosis cohort were 20% A, 53% B, and 27% C. In patients with cirrhosis, 82% (95% confidence interval [CI], 67.9%-92.0%) with genotype 1 infection achieved SVR12, whereas the corresponding rates in those with genotypes 2, 3, and 4 were 80%, 83%, and 100%, respectively; SVR12 rates were higher in patients with Child-Pugh class A or B, 93%, versus class C, 56%. In transplant recipients, SVR12 was achieved by 95% (95% CI, 83.5%-99.4%) and 91% of patients with genotype 1 and 3 infection, respectively. Three patients received peritransplantation treatment with minimal dose interruption and achieved SVR12. There were no treatment-related serious adverse events. *Conclusion:* The pan-genotypic combination of daclatasvir, sofosbuvir, and ribavirin was safe and well tolerated. High SVR rates across multiple HCV genotypes were achieved by patients with post-liver transplantation recurrence or advanced cirrhosis. (HEPATOLOGY 2016;63:1493-1505)

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase/platelet ratio index; HCV, hepatitis C virus; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SVR, sustained virologic response; SVR12, SVR at 12 weeks posttreatment.

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Chronic infection with hepatitis C virus (HCV) affects 130–170 million people globally, contributing to an estimated 350,000 deaths each year.^(1,2) Although the incidence of HCV infections peaked in the 1980s, the burden of HCV-associated liver disease continues to rise due to disease progression among individuals with long-standing infections;⁽³⁾ HCV infection is the most common indication for liver transplantation in the United States.⁽⁴⁾ In addition, reinfection of the grafted liver is nearly universal in patients who are viremic at transplantation, conferring increased risk of accelerated disease progression and graft loss.⁽⁵⁾

Interferon-free therapies have markedly improved outcomes for HCV-infected patients. Multiple all-oral regimens with improved tolerability have achieved rates of sustained virologic response (SVR) exceeding 90%.^(6–8) However, data are limited regarding the treatment of patients with cirrhosis, particularly decompensated cirrhosis, or with post-liver transplantation HCV recurrence.^(9–11)

The pan-genotypic combination of daclatasvir and sofosbuvir, with or without ribavirin, has achieved high SVR rates in phase 2 and phase 3 studies.^(6,12) Daclatasvir is an inhibitor of the HCV NS5A replication complex; sofosbuvir is a nucleotide inhibitor of the HCV NS5B polymerase.^(13,14) Both have favorable safety profiles and are dosed once daily, with few clinically significant drug-drug interactions, including a lack of interactions with cyclosporine or tacroli-

mus.^(15,16) Together, these results support the present evaluation of daclatasvir with sofosbuvir and ribavirin in patients with chronic HCV infection and advanced cirrhosis, or with HCV recurrence after liver transplantation.

Methods

STUDY DESIGN

This prospective, phase 3, open-label study (ALLY-1 study; ClinicalTrials.gov #NCT02032875) included two parallel cohorts: (1) patients with HCV-associated cirrhosis and a potential need for future liver transplantation and (2) patients with HCV recurrence after liver transplantation. Patients received 12 weeks of treatment with daclatasvir at 60 mg once daily, sofosbuvir at 400 mg once daily, and ribavirin at 600 mg/day, with the potential for adjustment to 1000 mg/day based on hemoglobin levels and creatinine clearance (see Supporting Information for ribavirin dosing guidelines). Patients with cirrhosis who had treatment interrupted by liver transplantation could receive treatment extension for an additional 12 weeks beginning immediately after transplantation. Patients were followed for 24 weeks after treatment.

PATIENTS

Eligible patients were treatment-naïve or treatment-experienced adults infected with HCV genotype 1, 2,

(now Merck), and Sundise. He consults and advises Eisai, GlaxoSmithKline, HepQuant, Immuron, Salix, HepaLife, Herbalife, and SciGen and has received grants from Genfit, Ikaria, Mochida, Pfizer, and Zymogenetics. Charles Landis has received research grants from Bristol-Myers Squibb, Gilead, AbbVie, and Salix. Robert J. Fontana has received research grants from Bristol-Myers Squibb, Gilead, Janssen, and Vertex. Stephanie Noviello consults for Schering-Plough. She is an employee and shareholder of Bristol-Myers Squibb and Merck. She also owns stock in Johnson and Johnson. Rong Yang, Fiona McPhee, Eric A. Hughes, and Eugene S. Swenson are employees and shareholders of Bristol-Myers Squibb.

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3, 4, 5, or 6 with serum HCV RNA levels at least 10,000 IU/mL. Patients with hepatocellular carcinoma were eligible if they met Milan criteria for liver transplantation, based on required screening within 6 months before treatment.⁽¹⁷⁾ In the advanced cirrhosis cohort, there were no restrictions based on Child-Pugh score; allowed Model for End-Stage Liver Disease (MELD) scores were ≥ 8 and ≤ 40 . Patients in the posttransplantation cohort must have received a liver transplantation at least 3 months prior to screening without clinical or pathologic evidence of moderate or severe rejection. Treatment with cyclosporine, tacrolimus, sirolimus, everolimus, corticosteroids, or mycophenolate mofetil was permitted (see Supporting Information for complete enrollment criteria).

STUDY OVERSIGHT

The study was conducted in accordance with Good Clinical Practice guidelines and the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board or independent ethics committee at each site. Written informed consent was obtained from all patients. No liver transplantation recipients received donor organs from executed prisoners or other institutionalized individuals. Bristol-Myers Squibb (the sponsor) designed the study, conducted it with the principal investigators, collected and analyzed the data, and monitored study conduct. Daclatasvir was supplied by the sponsor; sofosbuvir was purchased commercially. The authors prepared the manuscript with assistance from a medical writer paid by the sponsor. The academic authors vouch for the completeness and accuracy of the data and analyses, and for the fidelity of the study to the protocol.

EFFICACY AND SAFETY MONITORING

Serum HCV RNA measurements, clinical laboratory tests, and physical examinations were performed at screening, baseline, treatment weeks 1, 2, 4, 6, 8, and 12, and posttreatment weeks 4, 8, 12, and 24. HCV RNA was assessed centrally using the COBAS TaqMan HCV test version 2.0 (Roche Molecular Systems), with a lower limit of quantitation of 25 IU/mL and a limit of detection of approximately 20 IU/mL. Adverse events were recorded throughout the study.

Virologic failure included on-treatment breakthrough (confirmed HCV RNA increase from a nadir of at least $1 \log_{10}$ IU/mL, or to 25 IU/mL or higher if

previously below this level), HCV RNA detectable at end of treatment, or posttreatment relapse (confirmed posttreatment HCV RNA increase to 25 IU/mL or higher when HCV RNA was undetectable at end of treatment). The HCV NS5A region was analyzed by population-based sequencing for all available samples at baseline and at virologic failure if HCV RNA was at least 1000 IU/mL.⁽¹²⁾ NS5B sequencing of each evaluable virologic failure and matched baseline samples was performed, and for each failure, comparator baseline samples from two patients who achieved SVR at 12 weeks posttreatment (SVR12) were also analyzed.

ENDPOINTS

The primary efficacy endpoint in each cohort was HCV RNA below 25 IU/mL at posttreatment week 12 (SVR12) among genotype 1-infected patients. Secondary efficacy endpoints included SVR12 rates among non-genotype 1-infected patients, virologic response during treatment, and virologic response by *IL28B* genotype (rs1297860). Safety endpoints included death, serious adverse events, discontinuation due to adverse events, and grade 3 or 4 adverse events and laboratory abnormalities.

STATISTICAL ANALYSIS

The primary statistical objective was to determine whether SVR12 rates among genotype 1-infected patients in the advanced cirrhosis and posttransplantation cohorts were higher than historical thresholds of 41.6% and 30.0%, respectively. The historical thresholds for the advanced cirrhosis cohort were composite SVR rates incorporating treatment outcomes for peginterferon with ribavirin and either sofosbuvir or simeprevir (see Supporting Information). The historical threshold for the posttransplantation cohort incorporated experience with peginterferon and ribavirin.^(18,19) Comparisons with historical thresholds used the lower bounds of the two-sided 95% confidence interval (CI) of SVR12 rates. For a cirrhosis cohort with 48 patients, a minimum 58% SVR12 rate (28/48; 95% CI, 43.2%-72.4%) was needed for the lower 95% CI bound to exceed 41.6% and conclude the SVR12 rate was higher than the historical threshold. Correspondingly, for a posttransplantation cohort with 40 patients, a minimum 48% SVR12 rate (19/40; 95% CI, 31.5%-63.9%) was needed for the lower 95% CI bound to exceed 30%. Assuming an 85% SVR12 rate in each population, these sample sizes would provide more than 90%

TABLE 1. Demographics and Baseline Disease Characteristics

	Advanced Cirrhosis Cohort (n = 60)	Posttransplantation Cohort (n = 53)
Age, years, median (range)	58 (19-75)	59 (22-82)
Sex, n (%)		
Female	22 (37)	15 (28)
Male	38 (63)	38 (72)
Race, n (%)		
White	57 (95)	51 (96)
Black/African American	3 (5)	1 (2)
Asian	0 (0)	1 (2)
Ethnicity, n (%)		
Hispanic/Latino	25 (42)	13 (25)
Non-Hispanic/Latino	35 (58)	40 (75)
Body mass index, n (%)		
<25 kg/m ²	13 (22)	10 (19)
25 to <30 kg/m ²	27 (45)	27 (51)
≥30 kg/m ²	20 (33)	16 (30)
Hemoglobin, g/dL, median (range)	12.80 (8.7-16.3)	13.40 (7.9-16.6)
Creatinine, mg/dL, median (range)	0.84 (0.51-1.81)	1.18 (0.63-2.23)
HCV genotype, n (%)		
1	45 (75)	41 (77)
1a	34 (57)	31 (58)
1b	11 (18)	10 (19)
2	5 (8)	0
3	6 (10)	11 (21)
4	4 (7)	0
6	0	1 (2)
HCV RNA		
log ₁₀ IU/mL, mean (SD)	6.01 (0.62)	6.61 (0.71)
≥8 × 10 ⁵ IU/mL, n (%)	33 (55)	47 (89)
<i>IL28B</i> (rs1297860) genotype, n (%)		
CC	13 (22)	13 (25)
CT	33 (55)	31 (58)
TT	14 (23)	9 (17)
Child-Pugh class, n (%)		
A	12 (20)	ND
B	32 (53)	ND
C	16 (27)	ND
Estimated METAVIR fibrosis score, n (%)*		
F0	NA	6 (11)
F1	NA	10 (19)
F2	NA	7 (13)
F3	NA	13 (25)
F4	NA	16 (30)
Not reported	NA	1 (2)
MELD score, median (range)	13 (8-27)	NA
Immunosuppressive agents, n (%)		
Tacrolimus	NA	44 (83)
Cyclosporine	NA	6 (11)
Sirolimus	NA	3 (6)
Mycophenolic acid	NA	10 (19)
Prior treatment response, n (%)		
Naïve	24 (40)	22 (42)
Experienced	36 (60)	31 (58)
Null response	10 (17)	5 (9)
Partial response	2 (3)	2 (4)
Relapse	7 (12)	10 (19)
Other treatment failures [†]	17 (28)	14 (26)

*Estimated METAVIR scores were derived from FibroTest scores (F0, 0-0.27; F1, >0.27-0.48; F2, >0.48-0.58; F3, >0.58-0.74; F4, >0.74-1.00).

[†]Includes indeterminate, intolerance, virologic breakthrough, and HCV RNA never undetectable.

Abbreviations: HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NA, not applicable; ND, not determined; SD, standard deviation.

TABLE 2. Baseline Characteristics by Child-Pugh Class: Advanced Cirrhosis Cohort

Parameter	Class A (n = 12)	Class B (n = 32)	Class C (n = 16)
Ascites, n (%)			
Absent	12 (100)	11 (34)	0
Present	0	21 (66)	16 (100)
Encephalopathy, n (%)			
Absent	10 (83)	13 (41)	0
Present	2 (17)	19 (59)	16 (100)
HCV genotype, n (%)			
1a	8 (67)	17 (53)	9 (56)
1b	3 (25)	7 (22)	1 (6)
2	1 (8)	2 (6)	2 (13)
3	0	3 (9)	3 (19)
4	0	3 (9)	1 (6)
MELD score, n (%)			
<10	7 (58)	7 (22)	0
10-15	5 (42)	20 (63)	3 (19)
16-20	0	5 (16)	9 (56)
21-25	0	0	3 (18)
>25	0	0	1 (6)
Albumin, g/dL, median (range)	3.65 (3.0-4.3)	3.15 (2.6-4.4)	2.50 (2.0-3.4)
INR, median (range)	1.20 (1.06-1.42)	1.37 (1.02-1.86)	1.71 (1.21-3.88)
Total bilirubin, mg/dL, median (range)	0.90 (0.4-1.7)	1.55 (0.6-4.4)	3.00 (1.1-6.4)
Platelet count, $\times 10^9$ cells/L, median (range)	94 (41-179)	86 (35-182)	72 (35-147)
Alpha fetoprotein, ng/mL, median (range)	13.00 (3.4-49.6)	13.25 (1.8-86.2)	7.70 (1.8-148.7)

Abbreviations: HCV, hepatitis C virus; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease.

power to show superiority over historical thresholds at a two-sided α of 0.05 for each cohort. Analyses of efficacy and safety endpoints included all patients who received at least one dose of study therapy.

RESULTS

PATIENTS

Sixty patients with HCV cirrhosis (Child-Pugh class A, B, or C) and 53 patients with post-liver transplantation recurrence of HCV were enrolled and treated at five centers in the United States between March 2014 and November 2014 (Table 1). In the advanced cirrhosis cohort, 80% of patients had Child-Pugh class B or C liver disease and 10% had hepatocellular carcinoma at screening (Table 2). MELD scores ranged from 8 to 27. Cirrhosis was confirmed by liver biopsy (10 patients), FibroScan >14.6 kPa (30 patients), FibroTest ≥ 0.75 , and aspartate aminotransferase/platelet ratio index (APRI) >2 (19 patients) or indeterminate (one patient with Child-Pugh class C disease). In the posttransplantation cohort, liver transplantation occurred 4 months to >13 years prior to enrollment; 55% of patients had F3 or F4 fibrosis by FibroTest, but none had cholestatic recurrence. In the advanced cirrhosis and posttransplantation cohorts, 60% and

58% of patients, respectively, had received HCV therapy previously, including interferon or peginterferon with ribavirin (57 of 67 experienced patients), peginterferon/ribavirin with telaprevir or boceprevir (9 of 67 experienced patients), or ribavirin monotherapy (1 of 67 experienced patients).

Fifty-six of 60 patients (93%) in the advanced cirrhosis cohort completed 12 weeks of therapy per protocol (Supporting Fig. 1). The remaining four patients, all with hepatocellular carcinoma, underwent liver transplantation after 1-71 days of treatment. Three of these patients received 12 weeks of posttransplantation treatment extension beginning 1-3 days posttransplantation and one, treated for 23 days before transplantation, did not receive treatment extension. Fifty-two of 53 patients (98%) in the posttransplantation cohort completed 12 weeks of therapy; one patient discontinued all therapy after 31 days due to headache. Overall, 107 of 110 patients (97%), excluding the three patients who received posttransplantation treatment extension, were at least 95% adherent to both dose and duration of daclatasvir and sofosbuvir therapy. The median dosage of ribavirin in the advanced cirrhosis cohort was 454 mg/day; after adjusting for the full intended duration of 84 days, Child-Pugh class A patients received a median dosage of 471 mg/day, class B patients received a median dosage of 445 mg/day, and Child-Pugh class C patients received a median dosage of

TABLE 3. SVR12 by Baseline Disease Characteristics

	Advanced Cirrhosis Cohort		Posttransplantation Cohort	
	% (n/N)	95% CI	% (n/N)	95% CI
All patients	83 (50/60)*,†	71.5%-91.7%	94 (50/53)	84.3%-98.8%
Child-Pugh class				
A	92 (11/12)	—	—	—
B	94 (30/32)	—	—	—
C	56 (9/16)	—	—	—
Genotype 1	82 (37/45)‡	68%-92%	95 (39/41)‡	84%-99%
Genotype 1a	76 (26/34)	—	97 (30/31)	—
Genotype 1b	100 (11/11)	—	90 (9/10)	—
Child-Pugh class				
A	91 (10/11)	—	—	—
B	92 (22/24)	—	—	—
C	50 (5/10)	—	—	—
Genotype 2	80 (4/5)	—	—	—
Genotype 3	83 (5/6)*	—	91 (10/11)	—
Genotype 4	100 (4/4)†	—	—	—
Genotype 6	—	—	100 (1/1)	—

*Includes one patient (genotype 3) who had SVR12 documented after database lock.

†Includes one patient (genotype 4) who discontinued after 3 weeks for liver transplantation and achieved SVR12 off-study.

‡Primary endpoints.

Abbreviations: CI, confidence interval; SVR12, sustained virologic response at 12 weeks posttreatment.

398 mg/day. In the posttransplantation cohort, the median dosage of ribavirin was 480 mg/day.

VIROLOGIC RESPONSE

In the overall study population, 50 of 60 patients (83%; 95% CI, 71.5%-91.7%) in the advanced cirrhosis cohort and 50 of 53 patients (94%; 95% CI, 84.3%-98.8%) in the posttransplantation cohort achieved SVR12. SVR12 in patients with genotype 1 infection, the primary study endpoint, was achieved by 37 of 45 patients (82%; 95% CI, 67.9%-92.0%) in the advanced cirrhosis cohort and by 39 of 41 patients (95%; 95% CI, 83.5%-99.4%) in the posttransplantation cohort (Table 3). All four patients in the advanced cirrhosis cohort who underwent liver transplantation achieved SVR12. One of these patients (genotype 1a) was treated for only one day before receiving a transplant from an HCV genotype 1a-infected donor, and then received an additional 12 weeks of therapy beginning immediately posttransplantation.

HCV RNA levels decreased rapidly after initiation of treatment in all patients. At 4 weeks, HCV RNA was below the quantitation limit (25 IU/mL) in 57 of 60 (95%) and 50 of 53 (94%) patients in the advanced cirrhosis and posttransplantation cohorts, respectively, and was undetectable in 32 of 60 (53%) and 30 of 53 (57%) patients. HCV RNA was undetectable at week 4 in fewer patients with Child-Pugh class C disease (5/15, 33%) than in those with class B (19/31,

61%) or class A (8/12, 67%) (Supporting Fig. 2). Of those who did not achieve SVR12, HCV RNA remained detectable at week 4 in eight of 10 patients in the advanced cirrhosis cohort and in two of three patients in the posttransplantation cohort. However, HCV RNA was undetectable by treatment week 8 or earlier in all 12 patients who relapsed during follow-up.

Twenty-six of 34 (76%) patients in the advanced cirrhosis cohort with genotype 1a and 11 of 11 (100%) patients with genotype 1b achieved SVR12. Of eight genotype 1a nonresponders, one was Child-Pugh class A, two were class B, and five were class C. In the posttransplantation cohort, 30 of 31 (97%) patients with genotype 1a and nine of 10 (90%) with genotype 1b achieved SVR12 (Table 2).

Overall, 15 of the 17 patients with genotype 3 infection achieved SVR12. All six patients with genotype 3 infection in the advanced cirrhosis cohort had Child-Pugh class B or C disease; five of six (83%) achieved SVR12 and one patient (class C) relapsed. Ten of 11 patients (91%) with genotype 3 infection in the posttransplantation cohort achieved SVR12 and one patient relapsed.

In both cohorts, SVR12 response rates were broadly similar across subgroups based on demographic characteristics (Fig. 1). Among patients in the advanced cirrhosis cohort, SVR12 was achieved by a higher proportion with Child-Pugh class A (11 of 12, 92%) or class B disease (30 of 32, 94%) compared with

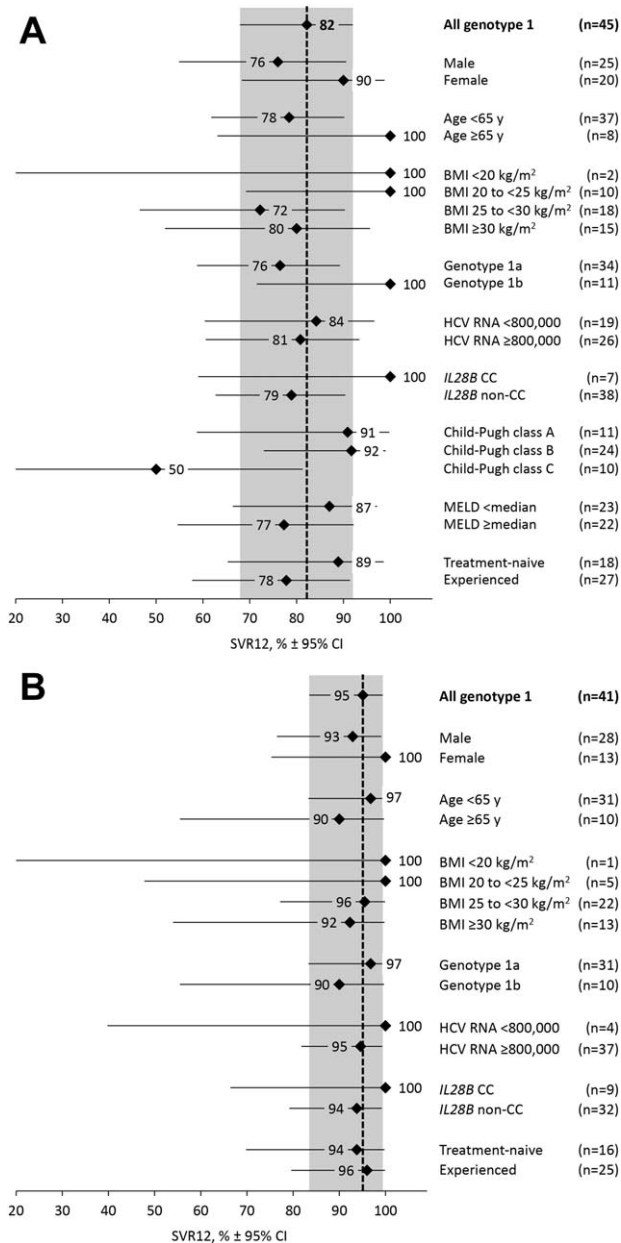


FIG. 1. SVR12 in subgroups with genotype 1 infection. SVR12 rates are shown for patients with genotype 1 infection in the advanced cirrhosis cohort (A) and the posttransplantation cohort (B). The shaded area indicates the 95% CI for the overall SVR12 rate among patients with genotype 1 infection in each cohort. BMI, body mass index.

class C (9 of 16, 56%) (Table 2). Each component of the Child-Pugh score reflecting more advanced disease at baseline (ascites, encephalopathy, albumin, total bilirubin, and international normalized ratio [INR]) was associated with reduced SVR12 rates (Supporting Table 2). Fifty-six percent of patients with albumin

below 2.8 g/dL achieved SVR12, compared with 95% of those with albumin ≥2.8 g/dL. All four patients with baseline MELD scores >20 achieved SVR12. Two of these four patients received the standard 12 weeks of treatment, and two had treatment interrupted for liver transplantation, of which one received a further 12 weeks of treatment posttransplantation. Impaired renal function did not adversely affect efficacy outcomes; across both cohorts, all 11 patients with creatinine clearance between 30 and 50 mL/min/1.73 m² at baseline achieved SVR12.

Nine patients in the advanced cirrhosis cohort discontinued ribavirin before completing 12 weeks of treatment; seven of these patients achieved SVR12. The effect of ribavirin dose reduction on SVR could not be evaluated due to limited patient numbers and the non-standard dosing guidelines and frequent changes (both decrease and increase) in dose during the treatment period. In the posttransplantation cohort, five patients discontinued ribavirin due to anemia or other adverse events; four of these five patients achieved SVR12.

Results of a population pharmacokinetic analysis indicated substantial overlap in average concentrations of daclatasvir, particularly in the more clinically relevant unbound fraction, between SVR12 responders and nonresponders, and between patients with Child-Pugh class A, B, and C disease (Supporting Fig. 3).

CHANGES IN LIVER DISEASE PARAMETERS

In the advanced cirrhosis cohort, therapy was associated with a modest tendency toward improvement in clinical and biochemical indicators of liver disease between baseline and posttreatment weeks 4 through 12. Between baseline and last available follow-up, Child-Pugh scores improved in 60% of patients overall, remained unchanged in 25%, and worsened in 15% (Fig. 2). Improvement in Child-Pugh score was most evident in patients with class B or C disease. Among 30 evaluable patients with Child-Pugh class B disease at baseline, 15 had improved to class A by the last posttreatment visit, and six of the 13 evaluable patients with Child-Pugh class C disease improved to class B (Supporting Table 6). MELD scores improved in 47% of patients overall, remained unchanged in 18%, and worsened in 35% (Fig. 2). Improvements in Child-Pugh class and MELD scores were generally attributable to modest improvement in liver synthetic function (Table 4). FibroTest scores, APRI, albumin, alanine

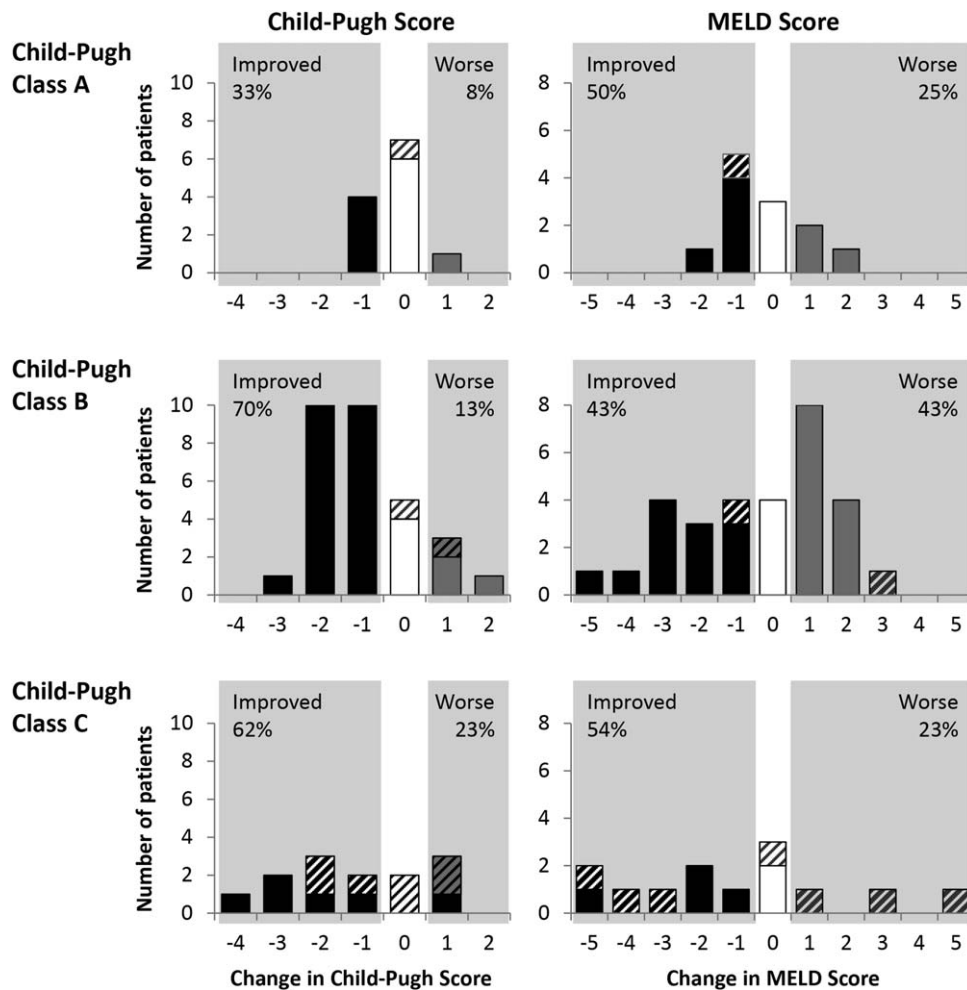


FIG. 2. Changes in Child-Pugh and MELD scores in the advanced cirrhosis cohort, baseline to last posttreatment visit. Changes in Child-Pugh and MELD scores according to baseline Child-Pugh class and treatment response are shown. Solid bars indicate patients who achieved SVR12; striped bars indicate patients with virologic failure. Four patients who underwent liver transplantation before completing 12 weeks of therapy were excluded from this analysis. One Child-Pugh class C patient was excluded due to normalization of INR after discontinuing warfarin during the study period. Follow-up data are from posttreatment week 12 or posttreatment week 8 if posttreatment week 12 data were unavailable.

aminotransferase (ALT), and direct bilirubin levels in patients with advanced cirrhosis all showed incremental improvements (Table 4). Mean platelet count, total bilirubin, serum creatinine, and creatinine clearance showed little change; mean INR improved slightly in patients with Child-Pugh class C disease and was stable in patients with class A or B disease.

VIROLOGIC FAILURE AND RESISTANCE ANALYSES

All 13 patients who did not achieve SVR12 experienced virologic failure. Nine patients in the

advanced cirrhosis cohort relapsed posttreatment, and one had detectable HCV RNA at the end of treatment. Three patients (genotypes 1a, 1b, and 3) in the posttransplantation cohort relapsed. All 12 patients with relapse are being retreated with daclatasvir, sofosbuvir, and ribavirin for 24 weeks.

NS5A resistance-associated polymorphisms at positions 28, 30, 31, or 93 were detected at baseline in 22 of the 112 patients with available data; 18 (82%) patients achieved SVR12, compared with 81 of 90 (90%) patients without these polymorphisms. NS5A resistance variants were detected at failure in all 13 patients with virologic failure; two of 13 had the same

TABLE 4. Liver Disease Parameters in Patients With Advanced Cirrhosis

Parameter	Child-Pugh Class A	Child-Pugh Class B	Child-Pugh Class C
MELD score			
Baseline	9.0 (1.13)	12.7 (2.94)	16.8 (3.76)
Δ Baseline to PT12	-0.3 (-1.1, 0.5)	-0.3 (-1.1, 0.5)	-0.9 (-2.8, 1.0)
FibroTest score			
Baseline	0.796 (0.10)	0.829 (0.15)	0.838 (0.09)
Δ Baseline to PT12	-0.110 (-0.2, 0.0)	-0.046 (-0.1, 0.0)	-0.067 (-0.1, 0.0)
APRI			
Baseline	2.26 (1.207)	4.06 (2.698)	3.84 (1.455)
Δ Baseline to PT12	-1.44 (-2.2, -0.7)	-2.84 (-3.9, -1.8)	-2.04 (-2.8, -1.3)
INR			
Baseline	1.21 (0.12)	1.38 (0.20)	1.81 (0.67)
Δ Baseline to PT12	-0.019 (-0.1, 0.0)	0.005 (-0.1, 0.1)	-0.142 (-0.6, 0.3)
Albumin, g/dL			
Baseline	3.64 (0.35)	3.18 (0.46)	2.53 (0.42)
Δ Baseline to PT12	0.44 (0.2, 0.7)	0.38 (0.2, 0.5)	0.24 (-0.2, 0.7)
ALT, U/L			
Baseline	66.1 (42.10)	75.8 (41.44)	69.5 (33.41)
Δ Baseline to PT4	-38.9 (-68.2, -9.6)	-50.3 (-65.5, -35.1)	-38.3 (-52.9, -23.7)
Direct bilirubin, mg/dL			
Baseline	0.41 (0.178)	0.77 (0.410)	1.13 (0.541)
Δ Baseline to PT4	-0.18 (-0.3, -0.1)	-0.28 (-0.4, -0.2)	-0.28 (-0.5, -0.1)
Total bilirubin, mg/dL			
Baseline	0.89 (0.37)	1.73 (0.98)	2.60 (1.07)
Δ Baseline to PT12	-0.02 (-0.2, 0.2)	-0.18 (-0.4, 0.1)	0.11 (-0.5, 0.8)
Platelet count, $\times 10^9$ cells/L			
Baseline	102.1 (39.7)	94.9 (38.23)	73.8 (32.53)
Δ Baseline to PT4	6.3 (-8.2, 20.7)	-8.0 (-17.8, 1.8)	-1.7 (-11.1, 7.8)
Creatinine, mg/dL			
Baseline	0.818 (0.168)	0.98 (0.327)	0.909 (0.289)
Δ Baseline to PT12	0.018 (0.0, 0.0)	-0.002 (-0.1, 0.1)	-0.069, -0.2, 0.1)
Creatinine clearance, mL/min/1.73 m ²			
Baseline	97.8 (33.44)	101.0 (38.66)	117.6 (47.91)
Δ Baseline to PT4	-9.0 (-14.9, -3.1)	0.6 (-5.0, 6.2)	-1.5 (-11.9, 8.8)

Baseline data are presented as the mean (standard deviation). Δ Baseline to PT12 or PT4 data are presented as the mean change from baseline to posttreatment week 12 or week 4 (95% CI), respectively. Four patients who underwent liver transplantation before completing 12 weeks of therapy were excluded from this analysis. One patient with Child-Pugh class C was excluded because of normalization of INR after discontinuing warfarin during the study period.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase/platelet ratio index; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; PT12, posttreatment week 12; PT4, posttreatment week 4.

NS5A variants detected at baseline and failure (Supporting Table 3). No NS5B-S282 variants were detected at baseline or failure.

SAFETY

There were no treatment-related serious adverse events and no deaths on treatment (Table 5). One patient in the advanced cirrhosis cohort (Child-Pugh class A) died due to sepsis after achieving SVR12. Treatment-related grade 3 or 4 adverse events were experienced by two patients in the advanced cirrhosis cohort (anemia, noncardiac chest pain) and by two in the posttransplantation cohort (arthralgia, headache). One patient in the advanced cirrhosis cohort with genotype 4 infection discontinued all study medications at the time of liver transplantation on day 23 and

achieved SVR12 without additional treatment after transplantation. One patient in the posttransplantation cohort with genotype 3 infection discontinued all study medications after 31 days due to headache and achieved SVR12. Fourteen patients (12%) discontinued ribavirin due to anemia or other adverse events (one of these occurred in a patient during treatment extension posttransplantation); 11 of 14 patients achieved SVR12. Only one patient in the posttransplantation cohort required dosage adjustment of immunosuppressive medications (tacrolimus decreased from 3.5 to 3.0 mg/day on day 58), and there were no events of graft rejection.

Two patients in the advanced cirrhosis cohort who initiated HCV treatment immediately posttransplantation had serum ALT levels more than 10 times the upper limit of normal immediately after transplantation.

TABLE 5. On-Treatment Safety

Event	Advanced Cirrhosis Cohort (n = 60)	Posttransplantation Cohort (n = 53)
Death	0	0
Serious adverse events*	10 (17)	5 (9)
Grade 3-4 adverse events†	11 (18)	4 (8)
Discontinuation of all study medications due to adverse events	1 (2)‡	1 (2)§
Discontinuation of ribavirin due to adverse events	10 (17)	4 (8)
Adverse events (any grade) on treatment in ≥10% of patients in either cohort		
Headache	9 (15)	19 (36)
Fatigue	11 (18)	15 (28)
Anemia	12 (20)	10 (19)
Diarrhea	5 (8)	10 (19)
Nausea	10 (17)	3 (6)
Arthralgia	1 (2)	7 (13)
Treatment-emergent grade 3-4 laboratory abnormalities		
Hemoglobin <9 g/dL	5 (8)	2 (4)
Leukocyte count <1500/mm ³	0	2 (4)
Lymphocyte count <500/mm ³	6 (10)	3 (6)
Platelet count <50,000/mm ³	4 (7)	0
INR >2 × ULN	1 (2)	0
Alkaline phosphatase >5 × ULN	0	1 (2)
ALT >5 × ULN	2 (3)	0
AST >5 × ULN	3 (5)	0
Total bilirubin >2.5 × ULN	9 (15)	2 (4)
Albumin <2 g/dL	1 (2)	0
Lipase >3 × ULN	3 (5)	2 (4)
Creatinine >1.8 × ULN	2 (3)	2 (4)

All data are presented as n (%).

*All adverse events were considered unrelated to the study medications, including abdominal pain, hematemesis with hepatocellular carcinoma, intraabdominal fluid collection, hepatocellular carcinoma (two patients), breast cancer, cellulitis, *Clostridium difficile* infection, hepatic encephalopathy, encephalopathy with ascites and hemorrhoidal hemorrhage, cirrhosis/liver transplantation, hyponatremia, polyarthritis, and acute renal failure.

†Four events (anemia, noncardiac chest pain, arthralgia, and headache) were considered possibly related to study medication. Other events considered unrelated to study medication included polyarthritis, hepatocellular carcinoma (three patients), cellulitis, *Clostridium difficile* infection, encephalopathy, hepatic encephalopathy, azotemia, acute renal failure, ascites, cirrhosis, and hyponatremia.

‡All treatment was discontinued for hepatocellular carcinoma (considered unrelated to study medication) at the time of liver transplantation; the patient achieved SVR12.

§Due to headache after 4 weeks of treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal.

In one of these patients, the concurrent elevated bilirubin had already decreased from pretransplant levels and continued to normalize after transplantation. In the other patient, concurrent bilirubin elevation was attributed to duct size mismatch at the surgical anastomosis and resolved following biliary stent placement. Neither case was considered to reflect drug-induced hepatotoxicity, and both patients continued treatment.

Discussion

Optimizing HCV treatment outcomes for patients with advanced liver disease or posttransplantation recurrence remains an important objective because of the reduced therapeutic responses often observed in these groups and the potentially life-threatening conse-

quences of treatment failure. In this study, 12 weeks of treatment with the pan-genotypic combination of daclatasvir with sofosbuvir and ribavirin achieved SVR12 rates of 83% and 94% in the advanced cirrhosis and posttransplantation cohorts, respectively.

The regimen was effective across all five HCV genotypes enrolled, consistent with the expected pan-genotypic activity of daclatasvir and sofosbuvir. Other oral regimens have thus far been evaluated primarily against HCV genotypes 1 and 4 in transplant recipients or in those with advanced cirrhosis.^(11,20,21) In the cirrhosis cohort, 76% of patients with genotype 1a infection achieved SVR12, compared with 100% of patients with genotype 1b. However, patients were not stratified based on both genotype 1 subtype and Child-Pugh score; notably, five of the eight nonresponding genotype 1a patients had Child-Pugh class C disease.

In the posttransplantation cohort, SVR12 rates were high in patients with genotypes 1a (97%) and 1b (90%). Notably, in this study, five of six patients with genotype 3 infection in the advanced cirrhosis cohort achieved SVR12. By comparison, in a previous study, 63% of genotype 3-infected patients with compensated cirrhosis achieved SVR12 after 12 weeks of treatment with daclatasvir and sofosbuvir alone,⁽⁶⁾ suggesting that ribavirin increases the efficacy of this regimen for genotype 3-infected patients with advanced liver disease. Outcomes for patients with genotypes 2, 4, or 6 were comparable with those for genotypes 1 and 3; however, the data are limited.

This is the first report of peritransplantation treatment with this regimen, with treatment given both before and immediately after liver transplantation with minimal interruption. Four patients, all with hepatocellular carcinoma, underwent transplantation during dosing; three of these patients received treatment extension for 12 weeks posttransplantation, whereas one did not resume HCV therapy. All four patients achieved SVR12, including one patient who received a liver from a genotype 1a-infected donor. Although preliminary, these results are consistent with a case report of peritransplantation treatment with sofosbuvir and ribavirin and suggest that this strategy can potentially prevent posttransplantation recurrence and achieve SVR when therapy prior to transplantation is insufficient.^(22,23) Pending confirmation in additional patients, these results may point the way to an important new approach to treatment of patients awaiting liver transplantation. The current approved regimen for patients with hepatocellular carcinoma awaiting liver transplantation is up to 48 weeks of sofosbuvir and ribavirin, but that has yielded relatively low SVR rates (64%) posttransplantation, and has not been studied in all genotypes.⁽²⁴⁾

Responses were generally comparable regardless of prior treatment experience, baseline viral load, and demographic characteristics. However, a higher proportion of patients in the advanced cirrhosis cohort with Child-Pugh class A or B disease achieved SVR12 (93%) compared with patients with Child-Pugh class C (56%). Multiple factors may contribute to reduced response in patients with the most advanced disease. The SVR12 rate was lower in patients with baseline NS5A polymorphisms (77%) than in those without NS5A polymorphisms (91%), although this modest difference suggests a contributory rather than definitive effect on the risk of failure. Second, relationships of similar magnitude between SVR12 and multiple clinical and biochemical indicators of hepatic function were

observed; in particular, SVR rates were lower in patients with albumin below 2.8 g/dL. Improving response in patients with the most advanced disease requires further study; potentially, extending treatment beyond 12 weeks may be beneficial and worthy of evaluation in a larger cohort of patients with Child-Pugh class C disease.

After initiation of treatment, most patients in the advanced cirrhosis cohort showed stabilization or improvement in Child-Pugh and MELD scores and in multiple other indicators of liver disease. Changes were generally modest during the relatively short follow-up, and the magnitude of change varied for different parameters. Ongoing long-term follow-up will assess the rate and extent of improvement in liver disease associated with successful HCV therapy. These data are relevant to the question of optimal timing for treating Child-Pugh class C patients awaiting liver transplantation. Some transplantation groups have been hesitant to initiate treatment before transplantation because of concern that reduction of MELD scores may reduce the priority for receiving a liver and prolong the risk of experiencing life-threatening hepatic events. Although data from this study suggest that SVR12 rates may be higher after transplantation, a recent study suggests that suppression of HCV RNA before transplantation improves survival.⁽²⁴⁾ Further studies are needed to determine the optimal timing of treating patients listed for transplantation.

Fifty of 53 patients in the posttransplantation cohort achieved SVR12, consistent with the positive results of several exploratory studies with this regimen.^(10,25,26) Baseline demographic and disease characteristics had no impact on SVR12, although patients in this cohort generally had well-compensated liver function. The study regimen was compatible with multiple immunosuppressive regimens without dose adjustments, and there were no events of graft rejection. In contrast, regimens containing the NS3 protease inhibitors simeprevir or paritaprevir can have significant pharmacokinetic interactions with calcineurin inhibitors.^(9,11,27) The optimal timing and duration of HCV treatment after transplantation remain to be determined.

A recent study evaluated the combination of sofosbuvir and velpatasvir (NS5A inhibitor), with or without ribavirin for 12 weeks or without ribavirin for 24 weeks in Child-Pugh class B patients.⁽²⁸⁾ In this study, patients with genotype 3 infection treated without ribavirin for 12 or 24 weeks had a suboptimal 50% SVR rate. The addition of ribavirin to the 12-week regimen improved the SVR rate to 85%, suggesting that

addition of ribavirin to the 12-week regimen was more effective than extension of ribavirin-free treatment to 24 weeks in genotype 3-infected patients with advanced cirrhosis. Several other interferon-free oral regimens have been evaluated in patients with chronic HCV infection and advanced cirrhosis or posttransplantation recurrence.^(11,13,20,21,29) Previously studied oral regimens were generally restricted to patients infected with HCV genotype 1, or 1 and 4, and those containing NS3 protease inhibitors are subject to drug-drug interactions that require dosage adjustment of immunosuppressive regimens in liver transplant recipients, and often require 24 weeks of treatment.

Adverse events during treatment were consistent with the underlying disease; no treatment-specific safety signals were apparent, and none of the 15 serious adverse events was considered to be related to study therapy. Overall, treatment-related safety findings were similar to those observed in patients with less advanced disease.^(6,12)

In conclusion, 12 weeks of oral treatment with the combination of daclatasvir with sofosbuvir and ribavirin achieved high SVR rates across multiple HCV genotypes in high-risk patients with posttransplantation recurrence or Child-Pugh class A or B cirrhosis. Further treatment optimization in patients with Child-Pugh class C disease is required. This pan-genotypic combination is not restricted to specific HCV genotypes and has a favorable drug-drug interaction profile, suggesting greater utility in a broader spectrum of patients with advanced cirrhosis or posttransplantation recurrence. The regimen was safe and well tolerated, without treatment-limiting pharmacokinetic interactions or toxicities.

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Supporting Information

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