Original Investigation

Fixed-Dose Combination Therapy With Daclatasvir, Asunaprevir, and Beclabuvir for Noncirrhotic Patients With HCV Genotype 1 Infection

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IMPORTANCE The antiviral activity of all-oral, ribavirin-free, direct-acting antiviral regimens requires evaluation in patients with chronic hepatitis C virus (HCV) infection.

OBJECTIVE To determine the rates of sustained virologic response (SVR) in patients receiving the 3-drug combination of daclatasvir (a pan-genotypic NS5A inhibitor), asunaprevir (an NS3 protease inhibitor), and beclabuvir (a nonnucleoside NS5B inhibitor).

DESIGN, SETTING, AND PARTICIPANTS This was an open-label, single-group, uncontrolled international study (UNITY-1) conducted at 66 sites in the United States, Canada, France, and Australia between December 2013 and August 2014. Patients without cirrhosis who were either treatment-naive (n = 312) or treatment-experienced (n = 103) and had chronic HCV genotype 1 infection were included.

INTERVENTIONS Patients received a twice-daily fixed-dose combination of daclatasvir, 30 mg; asunaprevir, 200 mg; and beclabuvir, 75 mg.

MAIN OUTCOMES AND MEASURES The primary study outcome was SVR12 (HCV-RNA <25 IU/mL at posttreatment week 12) in patients naive to treatment. A key secondary outcome was SVR12 in the treatment-experienced cohort.

RESULTS Baseline characteristics were comparable between the treatment-naive and treatment-experienced cohorts. Patients were 58% male, 26% had *IL28B* (rs12979860) CC genotype, 73% were infected with genotype 1a, and 27% were infected with genotype 1b. Overall, SVR12 was observed in 379 of 415 patients (91.3%; 95% CI, 88.6%-94.0%): 287 of 312 treatment-naive patients (92.0%; 95% CI, 89.0%-95.0%) and 92 of 103 treatment-experienced patients (89.3%; 95% CI, 83.4%-95.3%). Virologic failure occurred in 34 patients (8%) overall. One patient died at posttreatment week 3; this was not considered related to study medication. There were 7 serious adverse events, all considered unrelated to study treatment, and 3 adverse events (<1%) leading to treatment discontinuation, including 2 grade 4 alanine aminotransferase elevations. The most common adverse events (in ≥10% of patients) were headache, fatigue, diarrhea, and nausea.

CONCLUSIONS AND RELEVANCE In this open-label, nonrandomized, uncontrolled study, a high rate of SVR12 was achieved in treatment-naive and treatment-experienced noncirrhotic patients with chronic HCV genotype 1 infection who received 12 weeks of treatment with the oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir.

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Current estimates indicate that 130 million to 150 million people worldwide are chronically infected with hepatitis C virus (HCV), resulting in up to 350 000 deaths per annum due primarily to cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[1,2] Of the 7 HCV genotypes identified, genotype 1 is the most prevalent worldwide, accounting for approximately 60% of infections.[3] Treatment options for HCV genotype 1 are evolving rapidly from interferon-based regimens to all-oral, direct-acting antiviral (DAA)–only regimens.

Daclatasvir is a potent, pan-genotypic inhibitor of the HCV NS5A protein that has demonstrated activity against HCV genotypes 1 through 6 in vitro.[4] Asunaprevir is an NS3 protease inhibitor with activity against genotypes 1 and 4.[5] Beclabuvir (BMS-791325) is a nonnucleoside NS5B thumb-1 polymerase inhibitor with activity against genotypes 1 and 4. All-oral therapy with daclatasvir and asunaprevir for 24 weeks achieved a sustained virologic response at posttreatment week 12 (SVR12) in 90% of treatment-naive patients infected with genotype 1b.[6] In phase 2b studies, 92% of treatment-naive patients infected with genotype 1 (1a and 1b) and 100% of treatment-naive patients infected with genotype 4 achieved SVR12 with the all-oral, ribavirin-free combination of daclatasvir, asunaprevir, and beclabuvir for 12 weeks.[7,8] Here we report the findings of the multinational UNITY-1 study evaluating the all-oral, fixed-dose combination of daclatasvir, asunaprevir, and beclabuvir (DCV-TRIO regimen) among both treatment-naive and treatment-experienced patients with HCV genotype 1 infection who did not have cirrhosis (see the trial protocol in Supplement 1).

Methods

Patients were enrolled between December 2013 and February 2014 at 66 sites in the United States, Canada, France, and Australia, with patients followed up through August 2014. Patients received a twice-daily, fixed-dose combination of daclatasvir, 30 mg; asunaprevir, 200 mg; and beclabuvir, 75 mg, for 12 weeks and were subsequently followed up for 24 weeks after treatment (posttreatment-week-24 evaluations are currently ongoing). Treatment was discontinued in cases of virologic breakthrough, defined as a confirmed increase in HCV-RNA of 1 $\log_{10}$ IU/mL or greater from nadir or confirmed increase in HCV-RNA to greater than or equal to the assay lower limit of quantitation (LLOQ; 25 IU/mL) after a previous decline to less than the LLOQ.

Eligible patients did not have cirrhosis, were treatment-naive or treatment-experienced, had chronic HCV genotype 1 infection, were 18 years or older, and had HCV-RNA greater than 10 000 IU/mL. Treatment-naive patients had no prior exposure to any interferon formulation, ribavirin, or DAA. Treatment-experienced patients had received prior interferon-alfa therapy, with or without ribavirin; previous exposure to host-targeted and DAA agents of a mechanistic class other than NS5A, NS3 protease, or nonnucleoside NS5B (thumb-1 domain) polymerase inhibitors was permitted. The absence of cirrhosis was established by 1 of 3 criteria: a liver biopsy within 3 years of screening demonstrating a Metavir fibrosis score of F0 to F3, a FibroScan value of 9.6 kPa or less within 1 year of screen-

ing, or a FibroTest score of 0.48 or less and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) less than 1. If no biopsy or FibroScan result was available, the FibroTest/APRI results could be used only if patients met the criteria for exclusion of cirrhosis with both assays.

Patients were considered ineligible if they were co-infected with human immunodeficiency virus or hepatitis B virus, had alanine aminotransferase (ALT) levels 5× upper limit of normal or higher, or had any evidence of hepatic decompensation. Patient race was self-described as white, black/African American, Asian, American Indian/Alaska native, or other to provide the basis for assessing the effect of race on virologic response. The protocol was approved by the institutional review board or independent ethics committee at each site, and all patients provided written informed consent.

Assessments and End Points

Hepatitis C virus RNA was quantified at a central laboratory using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL; limit of detection, ≈10 IU/mL). Genotype and subtype were determined by the Abbott HCV Genotype II assay. In cases where genotype 1 was confirmed but subtype could not be determined, the VERSANT HCV genotype 2.0 line probe assay (LiPA) was used to confirm subtype. IL28B genotype (rs12979860 single-nucleotide polymorphism), which is associated with a patient's response to antiviral therapy, was determined using the Applied Biosystems TaqMan assay. Resistance testing was performed by population-based sequencing (sensitivity, ≈25%) of NS3, NS5A, and NS5B at baseline and on samples with HCV-RNA of 1000 IU/mL or greater from patients with virologic failure, defined as virologic breakthrough, detectable HCV-RNA at end of treatment, or relapse (undetectable HCV-RNA at end of treatment followed by confirmed detectable HCV-RNA >LLOQ during follow-up). Additional assessments included the incidence of adverse events (AEs) and abnormalities in clinical laboratory parameters, vital signs, and physical examinations.

Virologic response was defined as an HCV-RNA value less than LLOQ (<25 IU/mL) on treatment and during follow-up. The primary end point was SVR12 (HCV-RNA <25 IU/mL, detectable or undetectable) among treatment-naive patients. A key secondary end point was SVR12 in treatment-experienced patients. Other secondary end points included the proportion of patients with HCV-RNA less than LLOQ and the proportion with undetectable HCV-RNA at treatment weeks 1, 2, 4, 6, 8, and 12 and posttreatment weeks 4, 8, and 12. Additional on-treatment end points included the frequency of serious AEs and discontinuations due to AEs.

Statistical Analyses

Analyses of SVR12 rates were based on an all-treated analysis that included all patients who received at least 1 dose of study medication (see the statistical analysis plan in Supplement 2). To determine whether the primary end point of SVR12 in treatment-naive patients was significantly higher than the historical threshold rate of 79%, a 2-sided 95% confidence interval approach was used. If the lower bound of the 95% CI for the primary end point exceeded 79%, it was concluded that the primary end point was met and that the SVR12 rate in treatment-

naive patients was significantly higher than the historical threshold. The historical threshold rate was derived from SVR rates in treatment-naive, noncirrhotic patients treated with sofosbuvir plus peginterferon/ribavirin (eMethods in Supplement 3). Similarly, for the key secondary end point of SVR12 in treatment-experienced patients, it was concluded that the SVR12 rate in this patient population was significantly higher than the historical control if the lower bound of the 95% CI exceeded 48%. For the treatment-experienced population, the historical control rate was derived from a composite of SVR rates observed with simeprevir plus peginterferon/ribavirin in noncirrhotic, previously treated patients. All statistical analyses were performed using SAS version 9.02 (SAS Institute).

A target sample size of 300 treatment-naive patients was selected based on the anticipated minimum observed SVR12 rate of 84% (252/300; 95% CI, 79.9%-88.1%) for the lower bound to exceed 79% and conclude that the DCV-TRIO regimen is significantly higher than the historical control threshold. This sample size provided 95% confidence that the observed SVR12 rate can be estimated to within 4.1% of the estimates when the observed SVR12 is 84% or greater. The target sample size of 100 treatment-experienced patients was based on the anticipated minimum observed SVR12 rate of 58% (58/100; 95% CI, 48.3%-67.7%) for the lower bound to exceed 48% and conclude that the DCV-TRIO regimen is significantly higher than the historical threshold. This sample size provided 95% confidence that the observed SVR12 rate can be estimated to within 9.7% of the estimates when the observed SVR12 is 58% or greater.

Results

A total of 415 patients were enrolled and treated: 312 in the treatment-naive cohort and 103 in the treatment-experienced cohort. Fifty-seven patients were enrolled but not treated; reasons for not treating included no longer meeting study criteria (52 patients, primarily due to laboratory exclusions or comorbid medical conditions, including cirrhosis), patient withdrawal of consent (3 patients), loss to follow-up (1 patient), and an unreported reason (1 patient). Among treatment-naive patients, there were 7 treatment discontinuations (2.2%); 6 patients (1.9%) discontinued treatment before week 8 because of virologic breakthrough and 1 patient discontinued at week 6 for pregnancy (this patient achieved SVR12). Among treatment-experienced patients, 4 (3.9%) discontinued treatment: 1 patient experienced virologic breakthrough and discontinued before week 10, and 3 patients discontinued because of AEs. All patients who discontinued treatment remained in the study to the end of follow-up. Based on pill counts, patient diaries, and completed study visits, more than 90% of patients in the study were 95% adherent for both treatment dose and study duration.

Patient demographics and baseline disease characteristics are summarized in **Table 1**. The study population was mostly male (58%) and white (87%), had genotype 1a (73%), and had a non–CC *IL28B* genotype (74%). The proportion of patients with baseline HCV-RNA of 800 000 IU/mL or greater and a non–CC *IL28B* genotype was higher among treatment-experienced pa-

tients than among treatment-naive patients. Among treatment-experienced patients, 39 patients (38%) had experienced a previous posttreatment relapse with interferon-based therapy and 25 (24%) had a previous null response (Table 1).

Virologic Response

High rates of on-treatment (week 4 and week 12/end of treatment) virologic response were observed in both treatment-naive and treatment-experienced patients (**Table 2** and the eTable in Supplement 3). Overall, an SVR12 was achieved by 379 of 415 patients (91.3%; 95% CI, 88.6%-94.0%) of this population infected with HCV genotype 1. The SVR12 rate was significantly higher than the historical control in both treatment-naive and treatment-experienced patients (the lower bounds of the 95% CI exceeded the threshold rates: 89% vs 79% for treatment-naive patients and 83% vs 48% for treatment-experienced patients); thus, the primary objective of the study was met. Compared with patients infected with genotype 1a, patients with genotype 1b infection achieved higher SVR12 rates (Table 2). Rates of SVR12 were comparable across subpopulations based on baseline characteristics, including sex, age, HCV-RNA level, and *IL28B* genotype (**Figure**).

Virologic Failure

Virologic failure occurred in 34 patients (8%). A further 2 patients were considered nonresponders because of missing data (1 death at posttreatment week 4 and 1 loss to follow-up after posttreatment week 4). Reasons that patients did not achieve SVR12 were similar in the treatment-naive and treatment-experienced populations (Table 2). Posttreatment relapse was the most frequent reason for failure (15 patients [5%] in the treatment-naive cohort and 6 patients [6%] in the treatment-experienced cohort). Virologic breakthrough occurred in 8 patients (2%) overall.

Among patients with genotype 1a infection, NS5A resistance-associated variants (RAVs) emerged in 30 of 31 patients with available baseline and failure sequences, with the NS5A-Q30 RAV observed most frequently at failure (20 patients). NS3 RAVs emerged at failure in 29 of 31 patients with available sequences; the NS3-R155 RAV was observed most frequently (26 patients). NS5B RAVs emerged at failure in 12 of 31 patients with available sequences; the NS5B-P495 RAV was observed most frequently (11 patients). Analysis of multiple RAVs was possible in 32 patients who had all 3 sequences (NS5A, NS3, and NS5B) available at virologic failure. Eleven patients had RAVs to all 3 drugs: virologic breakthrough was the most common cause of treatment failure (5 virologic breakthrough, 4 detectable HCV-RNA at the end of treatment, 2 relapse). Nineteen patients had RAVs to 2 drugs (all NS5A and NS3 RAVs); the most common cause of treatment failure was relapse (1 virologic breakthrough, 1 detectable HCV-RNA at end of treatment, 17 relapse).

Two patients with genotype 1b infection experienced virologic failure. One patient had been classified as genotype 1b at screening by the Abbott assay. In this patient, sequencing at virologic breakthrough showed HCV genotype 2b sequence but not genotype 1b. Treatment-emergent NS5A RAVs were detected in this genotype 2b–infected patient, but there

Table 1. Baseline Demographic and Disease Characteristics

	Treatment-Naive Patients (n = 312)	Treatment-Experienced Patients (n = 103)	Total (N = 415)
Age, median (range), y	53.5 (19-77)	57.0 (22-69)	55.0 (19-77)
Male sex, No. (%)	175 (56.1)	64 (62.1)	239 (57.6)
Race, No. (%)			
White	270 (86.5)	91 (88.3)	361 (87.0)
Black/African American	34 (10.9)	7 (6.8)	41 (9.9)
Asian	6 (1.9)	2 (1.9)	8 (1.9)
Other	2 (0.6)	3 (2.9)	5 (1.2)
HCV-RNA, No. (%)			
<800 000 IU/mL	68 (21.8)	10 (9.7)	78 (18.8)
≥800 000 IU/mL	244 (78.2)	93 (90.3)	337 (81.2)
HCV genotype 1 subtype, No. (%)			
1a	229 (73.4)	75 (72.8)	304 (73.3)
1b	83 (26.6)	28 (27.2)	111 (26.7)
IL28B genotype, No. (%)			
CC	90 (28.8)	16 (15.5)	106 (25.5)
CT	174 (55.8)	73 (70.9)	247 (59.5)
TT	47 (15.1)	14 (13.6)	61 (14.7)
Not reported	1 (0.3)	0	1 (0.2)
Prior interferon-based treatment, No. (%)		93 (90.3)	93 (22.4)
Posttreatment relapse		39 (37.9)	39 (9.4)
Null response		25 (24.3)	25 (6.0)
Partial response		12 (11.7)	12 (2.9)
Interferon intolerant		7 (6.8)	7 (1.7)
Indeterminate[a]		10 (9.7)	10 (2.4)
Other prior anti-HCV treatment, No. (%)		10 (9.7)[b]	10 (2.4)

Abbreviation: HCV, hepatitis C virus.

[a] Prior treatment response missing or could not be categorized.

[b] Other treatments included balapiravir, IDX184, mericitabine, and amantadine in combination with peginterferon.

Table 2. Virologic Response

	Treatment-Naive Patients (n = 312)[a]	Treatment-Experienced Patients (n = 103)[a]	Total (N = 415)[a]
SVR12, No./Total No. (%) [95% CI]	287 (92.0) [89.0-95.0]	92 (89.3) [83.4-95.3]	379 (91.3) [88.6-94.0]
Genotype 1a	206/229 (90.0) [86.1-93.8]	64/75 (85.3) [77.3-93.3]	270/304 (88.8) [85.3-92.4]
Genotype 1b	81/83 (97.6) [91.6-99.7][b]	28/28 (100.0) [87.7-100][b]	109/111 (98.2) [93.6-99.8][b]
Undetectable HCV-RNA, No. (%) [95% CI]			
Week 4	248 (79.5) [75.0-84.0]	71 (68.9) [60.0-77.9]	319 (76.9) [72.8-80.9]
Week 12/end of treatment	301 (96.5) [93.8-98.2][b]	98 (95.1) [89.0-98.4][b]	399 (96.1) [93.8-97.8][b]
Nonresponse (non-SVR12), No. (%)			
All	25 (8.0)	11 (10.7)	36 (8.7)
On-treatment failures, No. (%)			
Virologic breakthrough	6 (1.9)	2 (1.9)	8 (1.9)
Other[c]	3 (1.0)	2 (1.9)	5 (1.2)
Posttreatment failures, No./Total No. (%)[d]			
Posttreatment relapse	15/301 (5.0)	6/98 (6.1)	21/399 (5.3)
Other posttreatment nonresponse	1/301 (<1)[e]	1/98 (<1)[f]	2/399 (<1)

Abbreviations: HCV, hepatitis C virus; SVR12, sustained virologic response at posttreatment week 12.

[a] Column heading values apply to all entries unless denominator provided.

[b] Exact binomial confidence interval.

[c] Other on-treatment failures included nonresponders with missing or detectable HCV-RNA at end of treatment.

[d] Posttreatment failure rates based on patients with undetectable HCV-RNA at end of treatment.
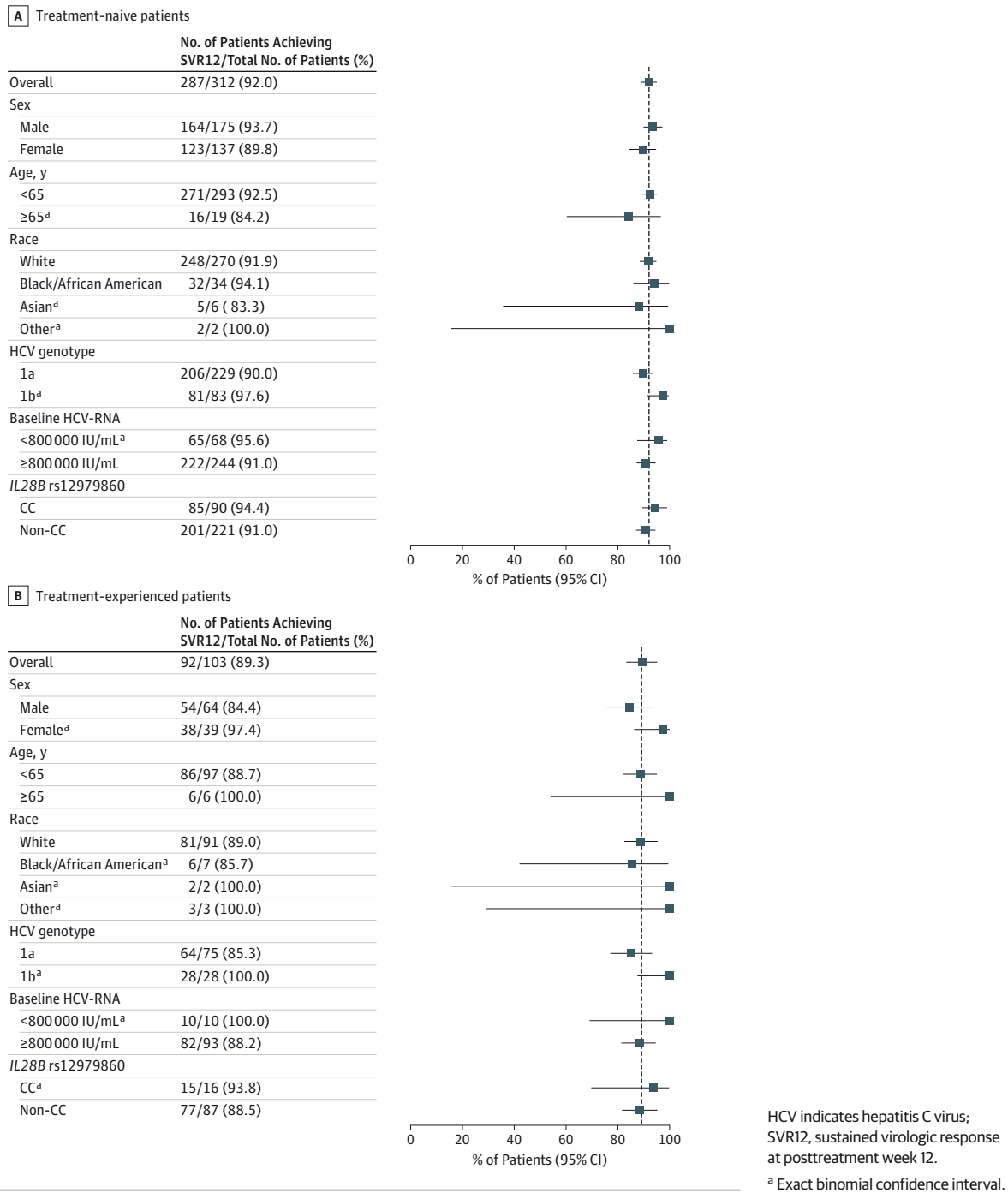
[e] Patient was lost to follow-up at posttreatment week 4.

[f] Patient died before posttreatment week 4.

were no treatment-emergent RAVs in NS3 or NS5B. The second patient infected with genotype 1b whose treatment failed had been classified as genotype 1 without subtype by the Abbott assay during screening and was genotype 1b by LiPA.

Amplification of NS5A and NS3 regions from samples at baseline and at failure was not possible with genotype 1b- or genotype 1a–specific primers used for genotypic analysis; amplification of these regions using alternative primers confirmed that

Figure. Sustained Virologic Response Rates at Posttreatment Week 12 by Baseline Subgroups in Treatment-Naive and Treatment-Experienced Patients

A Treatment-naive patients

	No. of Patients Achieving SVR12/Total No. of Patients (%)
Overall	287/312 (92.0)
Sex	
Male	164/175 (93.7)
Female	123/137 (89.8)
Age, y	
<65	271/293 (92.5)
≥65[a]	16/19 (84.2)
Race	
White	248/270 (91.9)
Black/African American	32/34 (94.1)
Asian[a]	5/6 (83.3)
Other[a]	2/2 (100.0)
HCV genotype	
1a	206/229 (90.0)
1b[a]	81/83 (97.6)
Baseline HCV-RNA	
<800 000 IU/mL[a]	65/68 (95.6)
≥800 000 IU/mL	222/244 (91.0)
IL28B rs12979860	
CC	85/90 (94.4)
Non-CC	201/221 (91.0)

B Treatment-experienced patients

	No. of Patients Achieving SVR12/Total No. of Patients (%)
Overall	92/103 (89.3)
Sex	
Male	54/64 (84.4)
Female[a]	38/39 (97.4)
Age, y	
<65	86/97 (88.7)
≥65	6/6 (100.0)
Race	
White	81/91 (89.0)
Black/African American[a]	6/7 (85.7)
Asian[a]	2/2 (100.0)
Other[a]	3/3 (100.0)
HCV genotype	
1a	64/75 (85.3)
1b[a]	28/28 (100.0)
Baseline HCV-RNA	
<800 000 IU/mL[a]	10/10 (100.0)
≥800 000 IU/mL	82/93 (88.2)
IL28B rs12979860	
CC[a]	15/16 (93.8)
Non-CC	77/87 (88.5)

HCV indicates hepatitis C virus; SVR12, sustained virologic response at posttreatment week 12.

[a] Exact binomial confidence interval.

the sequence was non–genotype 1a and non–genotype 1b. This patient was of African descent with an HCV genotype sequence approximately 96% homologous to that of a previously reported GT1 sequence yet to be designated a subtype.[9]

Baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93 (positions previously associated with resistance to daclatasvir) were detected in genotype 1a samples from 34 of 302 patients (11%) and in genotype 1b samples from 17 of 106

patients (16%) with available data. All 17 patients with genotype 1b infection achieved SVR12 (Table 3). Among the 34 patients with genotype 1a infection and baseline NS5A RAVs, 25 (74%) achieved SVR12. Of the 9 patients who did not achieve SVR12, 1 had undetectable HCV-RNA before being lost to follow-up at posttreatment week 4, and of the remaining 8 patients, 4 had baseline NS5A polymorphisms that conferred 1000-fold or greater reduction in susceptibility to daclatasvir

Table 3. Sustained Virologic Response Rates at Posttreatment Week 12 by Baseline NS5A Polymorphisms

NS5A Polymorphism[a]	No./Total No. (%)[b]		
	Treatment-Naive Patients (n = 312)	Treatment-Experienced Patients (n = 103)	Total (N = 415)
Genotype 1a			
M28: L/I/T/V	12/17 (71)	8/9 (89)	20/26 (77)
Q30: H/R	0/5	1/1 (100)	1/6 (17)
L31: M	2/2 (100)	2/2 (100)	4/4 (100)
Y93: C/H	1/2 (50)	0	1/2 (50)
M28, Q30, L31, or Y93[c]	15/23 (65)	10/11 (91)	25/34 (74)
Genotype 1b			
L28: M/V	1/1 (100)	1/1 (100)	2/2 (100)
R30: Q	3/3 (100)	1/1 (100)	4/4 (100)
L31: I/M	3/3 (100)	1/1 (100)	4/4 (100)
Y93: H	6/6 (100)	3/3 (100)	9/9 (100)
L28, R30, L31, or Y93[c]	12/12 (100)	5/5 (100)	17/17 (100)

Abbreviations: C, cysteine; H, histidine; I, isoleucine; L, leucine; M, methionine; Q, glutamine; R, arginine; SVR12, sustained virologic response at posttreatment week 12; T, threonine; V, valine; Y, tyrosine.

[a] Reference wild-type amino acid (for genotype 1a, H77 strain; for genotype 1b, Con1 strain), NS5A amino acid number: polymorphism. Multiple polymorphisms identified at an amino acid number are separated by a slash.

[b] Number of patients achieving SVR12/total number of patients with baseline polymorphism (%).

[c] Includes patients with ≥1 NS5A resistance-associated variants at baseline.

(2 with Q30H, 1 with M28T-Q30R, and 1 with Q30H-Y93H). There was no association between baseline polymorphisms in NS3 or NS5B and SVR12; the frequency of NS3-Q80K and NS5B-A421V variants at baseline (36% and 22%, respectively) was comparable in those who achieved or failed to achieve SVR12 (39% and 23%, respectively).

AEs and Laboratory Abnormalities

Serious AEs occurred in 7 patients, all of which were considered unrelated to study treatment. One patient died at posttreatment week 3 due to a heroin overdose, which was not considered related to study medication by the investigator. The most common AEs observed during treatment (≥10% of patients) were headache, fatigue, diarrhea, and nausea (Table 4). Adverse events leading to the discontinuation of treatment occurred in 3 patients (<1%): insomnia (reported as an AE at week 2, but treatment was not discontinued until week 10), elevated ALT (grade 4 at week 6 [579 U/L]; ALT levels returned to near baseline after 4 weeks; total bilirubin, international normalized ratio [INR], and albumin were within normal ranges), and elevated ALT/AST (grade 4 ALT [862 U/L] and grade 2 total bilirubin [2.3 mg/dL] at week 11; ALT and bilirubin levels normalized after 3 weeks and 9 days, respectively; INR and albumin remained normal). All these AEs were considered related to study treatment and all 3 patients achieved SVR12. Grade 1 through 4 on-treatment ALT elevations were observed in 38 patients overall, with grade 3 or 4 elevations in 19 patients (4.6%). The majority of grade 3 or 4 ALT elevations (14/19) occurred at treatment week 12 and all resolved during follow-up. Two patients with grade 3 ALT elevation (peak ALT occurring at day 57 and 73, respectively) continued treatment without interruption and resolved during follow-up. One patient experienced a grade 3 ALT elevation in the context of mild rhabdomyolysis at day 48 caused by an ankle injury (peak ALT = 184 U/L, AST = 405 U/L, creatine phosphokinase = 4550 U/L); HCV treatment continued without interruption but was subsequently discontinued because of viral breakthrough at day 57. Grade 1 or 2 on-treatment bilirubin elevations were reported in 10 patients (2.4%), but none were associated with ALT greater than 2× baseline and 5× upper limit of normal.

Discussion

This study evaluated 12 weeks of treatment with a fixed-dose combination of daclatasvir, asunaprevir, and beclabuvir in patients infected with HCV genotype 1 without cirrhosis. Sustained virologic response at posttreatment week 12 was achieved by 92% of treatment-naive patients and 89% of patients previously treated for HCV infection, with low rates of serious AEs and treatment discontinuations. Thus, this study demonstrates that 12 weeks of therapy with the DCV-TRIO regimen without ribavirin was associated with high rates of SVR12 in patients with HCV genotype 1 infection.

The SVR12 rates observed in this study are comparable with results observed with other phase 3 studies of all-oral, DAA-only regimens in patients with HCV genotype 1 infection. Treatment with a fixed-dose combination of sofosbuvir plus ledipasvir for 12 weeks resulted in SVR12 rates of 95% to 99% and 94% in treatment-naive and treatment-experienced patients, respectively.[10-12] Similarly, a regimen of ABT-450/ritonavir, ombitasvir, dasabuvir, and ribavirin for 12 weeks provided SVR12 rates of 96% in both treatment-naive and treatment-experienced patients.[13,14] The SVR12 rates in this study are also similar to those observed among treatment-naive patients with genotype 1 infection in phase 2 studies of this regimen[7,15]; however, the data presented here include treatment-experienced patients and only the beclabuvir, 75-mg, dose component of the DCV-TRIO fixed-dose combination. Furthermore, SVR12 rates in this study were consistently high across baseline subgroups of patients, including sex, age, HCV-RNA level, and IL28B genotype, suggesting that this regimen has the potential to be broadly effective across genotype 1 patient populations. Rates of SVR12 among patients infected with genotype 1b were higher compared with patients infected with genotype 1a in both the treatment-naive cohort (98% vs 90%, respectively) and treatment-experienced cohort (100% vs 85%, respectively). Lower SVR rates with genotype 1a compared with genotype 1b were also observed with a 12-week regimen of paritaprevir/ritonavir, ombitasvir, and dasabuvir and further affected by ribavirin inclu-

Table 4. Summary of On-Treatment Adverse Events and Grade 3/4 Laboratory Abnormalities

	No. of Patients (%) (N = 415)
Serious AEs[a]	7 (1.7)
AEs leading to discontinuation[b]	3 (0.7)
AEs (any grade) in ≥10% of patients	
Headache	107 (25.8)
Fatigue	69 (16.6)
Diarrhea	58 (14.0)
Nausea	56 (13.5)
Grade 3/4 laboratory abnormalities	
Hemoglobin <9.0 g/dL	0
Platelets <50 × 10^9/L	0
Leukocytes <1.5 × 10^9/L	0
Lymphocytes <0.5 × 10^9/L	1 (0.2)
Neutrophils <0.75 × 10^9/L	2 (0.5)
Alanine aminotransferase >5× ULN	19 (4.6)
Aspartate aminotransferase >5× ULN	9 (2.2)
Bilirubin, total >2.5× ULN	0
Lipase, total >3.0× ULN	16 (3.9)[c]

Abbreviations: AEs, adverse events; SVR12, sustained virologic response at posttreatment week 12; ULN, upper limit of normal.

[a] All serious AEs were judged by the investigator as not related to study drug.

[b] All 3 patients discontinued because of related AEs, and all 3 achieved SVR12.

[c] None of the grade 3/4 total lipase elevations were associated with pancreatitis.

sion in the regimen: SVR rates for genotype 1b were 99.5% with ribavirin and 99.0% without ribavirin, and among those with genotype 1a, SVR rates were 97% and 90%, respectively.[16] The addition of ribavirin to the DCV-TRIO regimen was not evaluated in this study but may increase rates of SVR12 in patients infected with HCV genotype 1a. DCV-TRIO plus ribavirin was evaluated in patients with compensated cirrhosis and demonstrated high SVR12 rates of 98% and 93% in treatment-naive and treatment-experienced patients, respectively (UNITY-2[17]).

Baseline NS5A polymorphisms associated with resistance to daclatasvir were observed infrequently in this study (12.5% of patients). All genotype 1b-infected patients with baseline NS5A polymorphisms achieved SVR12, and of the 34 genotype 1a patients with baseline polymorphisms, 25 achieved SVR12, demonstrating that these polymorphisms were not fully predictive of treatment failure in genotype 1a–infected patients. Emergent RAVs detected in patients experiencing virologic failure were similar to those observed previously with DCV-TRIO.[15] Resistance-associated variants at amino acid positions NS5A-Q30, NS3-R155K, and NS5B-P495 were observed most frequently at viral breakthrough; NS5B variants were generally not observed in patients experiencing relapse.

The limitations of this study include an open-label study design with no active comparator; at the time of study initiation, the only active comparator would have been an interferon-containing regimen. Patients with cirrhosis, who represent a population with a current unmet need that is predicted to increase significantly as the HCV-infected patient population increases in age, were also excluded from this study. Furthermore, this study enrolled a low number of patients of black race; while this may make extrapolation of these results to the wider population of black patients with HCV more difficult, high SVR12 rates (93%; 38/41) were observed among black patients receiving DCV-TRIO in this study.

Consistent with other all-oral, DAA-only regimens, DCV-TRIO was associated with low frequencies of serious AEs and discontinuations due to AEs. The most common grade 3/4 laboratory abnormality occurring in the study was ALT elevation, occurring in 4.6% of patients. No concomitant grade 3/4 total bilirubin elevations were observed, and all ALT elevations were reversible, consistent with previous studies evaluating asunaprevir-containing regimens.[6,18-21] No grade 3/4 anemia was observed with the ribavirin-free DCV-TRIO regimen.

Conclusions

In this open-label, nonrandomized, uncontrolled study, a high rate of SVR12 was achieved in treatment-naive and treatment-experienced noncirrhotic patients with chronic HCV genotype 1 infection who received 12 weeks of treatment with the oral fixed-dose regimen of daclatasvir, asunaprevir, and beclabuvir.

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