ORIGINAL ARTICLE

Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1

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ABSTRACT

BACKGROUND

The combination of daclatasvir, a hepatitis C virus (HCV) NS5A inhibitor, and the NS5B inhibitor sofosbuvir has shown efficacy in patients with HCV monoinfection. Data are lacking on the efficacy and safety of this combination in patients coinfected with human immunodeficiency virus type 1 (HIV-1).

METHODS

This was an open-label study involving 151 patients who had not received HCV treatment and 52 previously treated patients, all of whom were coinfected with HIV-1. Previously untreated patients were randomly assigned in a 2:1 ratio to receive either 12 weeks or 8 weeks of daclatasvir at a standard dose of 60 mg daily (with dose adjustment for concomitant antiretroviral medications) plus 400 mg of sofosbuvir daily. Previously treated patients were assigned to undergo 12 weeks of therapy at the same doses. The primary end point was a sustained virologic response at week 12 after the end of therapy among previously untreated patients with HCV genotype 1 who were treated for 12 weeks.

RESULTS

Patients had HCV genotypes 1 through 4 (83% with genotype 1), and 14% had compensated cirrhosis; 98% were receiving antiretroviral therapy. Among patients with genotype 1, a sustained virologic response was reported in 96.4% (95% confidence interval [CI], 89.8 to 99.2) who were treated for 12 weeks and in 75.6% (95% CI, 59.7 to 87.6) who were treated for 8 weeks among previously untreated patients and in 97.7% (95% CI, 88.0 to 99.9) who were treated for 12 weeks among previously treated patients. Rates of sustained virologic response across all genotypes were 97.0% (95% CI, 91.6 to 99.4), 76.0% (95% CI, 61.8 to 86.9), and 98.1% (95% CI, 89.7 to 100), respectively. The most common adverse events were fatigue, nausea, and headache. There were no study-drug discontinuations because of adverse events. HIV-1 suppression was not compromised.

CONCLUSIONS

Among previously untreated HIV–HCV coinfected patients receiving daclatasvir plus sofosbuvir for HCV infection, the rate of sustained virologic response across all genotypes was 97.0% after 12 weeks of treatment and 76.0% after 8 weeks. (Funded by Bristol-Myers Squibb; ALLY-2 ClinicalTrials.gov number, NCT02032888.)

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Liver disease is a leading cause of death among patients with human immunodeficiency virus type 1 (HIV-1) infection.[1] Coinfection with HIV-1 and hepatitis C virus (HCV) appears to accelerate the course of HCV-associated liver disease[2-5] and is widespread, particularly among injection-drug users.[6] The effect of HIV-1 coinfection on the course of HCV disease is reduced but not eliminated by antiretroviral therapy.[7,8]

Adoption of interferon-based HCV treatments has been low among HIV–HCV coinfected patients[9,10] owing to a high adverse-event burden.[11] Furthermore, the rate of sustained virologic response to interferon–ribavirin is lower among patients with HIV–HCV coinfection than among those with HCV monoinfection.[12-14] Response rates similar to those in patients with HCV monoinfection were observed among patients receiving peginterferon–ribavirin plus the first-generation HCV protease inhibitors telaprevir or boceprevir,[15,16] but these regimens were associated with increased rates of adverse events and pharmacokinetic interactions with concomitant antiretroviral drugs.[17,18]

The development of interferon-free, oral regimens of direct-acting antiviral agents represents an important opportunity for improved HCV treatment in patients with HIV–HCV coinfection. Such regimens have shown superior efficacy and an improved side-effect profile with shorter treatment durations than those with interferon-based therapy.[19-25]

Daclatasvir inhibits HCV nonstructural protein 5A (NS5A) and sofosbuvir inhibits the HCV RNA polymerase (nonstructural protein 5B [NS5B]), two proteins that play key roles in the replication of HCV RNA.[26,27] The two drugs are administered orally once daily and in combination have pangenotypic anti-HCV activity. The combination of daclatasvir and sofosbuvir has been associated with high rates of sustained virologic response and a favorable side-effect profile when administered for 12 weeks or 24 weeks, with or without ribavirin, to patients monoinfected with HCV genotype 1, 2, or 3.[28] Furthermore, clinical data for sofosbuvir plus ledipasvir, another NS5A inhibitor, in patients with genotype 1 monoinfection and without cirrhosis suggested that previously untreated patients receiving 8 weeks of treatment would have a rate of sustained virologic response similar to that of patients receiving 12 weeks of treatment.[29]

Daclatasvir and sofosbuvir have limited pharmacokinetic interactions with antiretroviral drugs,[30,31] and dose adjustments for daclatasvir in patients receiving moderate antiretroviral inducers or strong inhibitors of cytochrome P-450 3A4 are straightforward. Thus, this combination may be valuable for treating patients with HIV–HCV coinfection. In the ALLY-2 trial, we evaluated daclatasvir plus sofosbuvir for 12 weeks or 8 weeks in HIV–HCV coinfected patients without previous HCV treatment and for 12 weeks in previously treated patients.

METHODS

PATIENTS

Eligible patients were HIV-1–infected adults who were coinfected with HCV, with a screening level of HCV RNA of at least 10,000 IU per milliliter. The enrollment of patients with HCV genotypes other than type 1 was limited to 20%. Previous treatment for HCV was permitted. (Details regarding inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients receiving antiretroviral therapy were required to have fewer than 50 copies of HIV-1 RNA per milliliter at screening and below 200 copies per milliliter for at least 8 weeks, plus a CD4+ count of at least 100 cells per microliter. Patients were permitted to receive the following antiretroviral agents: darunavir–ritonavir, atazanavir–ritonavir, lopinavir–ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc, tenofovir, emtricitabine, abacavir, lamivudine, and zidovudine (Table S1 in the Supplementary Appendix). Patients who were not receiving an antiretroviral regimen were required to have a screening CD4+ count of at least 350 cells per microliter. Patients who had been previously treated for HCV could have received any anti-HCV agents except NS5A inhibitors.

Patients with compensated cirrhosis were eligible at a maximum enrollment of 50% of the study population. Cirrhosis was determined according to a testing hierarchy as follows: results on liver biopsy showing cirrhosis any time before or during screening, then a liver-stiffness measurement of more than 14.6 kPa on transient elastography (FibroScan, on a scale from 2.5 kPa to 75 kPa, with higher scores indicating more severe fibrosis) within 1 year before baseline, then

a screening FibroTest (FibroSURE) fibrosis score of at least 0.75 (on a scale of 0 to 1, with higher scores indicating a greater severity of fibrosis), with an aspartate aminotransferase-to-platelet ratio index of more than 2.

STUDY OVERSIGHT

The study was conducted in accordance with Good Clinical Practice guidelines and was approved by the institutional review board or independent ethics committee at each site. Bristol-Myers Squibb, the study sponsor, designed and monitored the study, conducted it with the principal investigators, and collected and analyzed the data. Study drugs were both sponsor-supplied (daclatasvir) and purchased (sofosbuvir). The manuscript was prepared by the authors with assistance from a medical writer paid by the sponsor. The academic authors vouch for the completeness and accuracy of the data presented and for the fidelity of the study to the protocol, which is available at NEJM.org.

STUDY DESIGN

In this open-label study, patients who had not received previous HCV treatment were randomly assigned in a 2:1 ratio to receive either 12 weeks or 8 weeks of daclatasvir (at a standard dose of 60 mg) plus sofosbuvir (400 mg), both once daily. Previously treated patients received the same regimen for 12 weeks. On the basis of pharmacokinetic data with antiretroviral inducers and inhibitors of cytochrome P-450 3A4,[31] the standard 60-mg dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted protease inhibitors and to 90 mg in those receiving efavirenz or nevirapine. Patients were followed for 24 weeks after the end of treatment.

Randomization was stratified according to cirrhosis status and HCV genotype. Patients with genotype 1 were further stratified according to subtype.

EFFICACY AND SAFETY MONITORING

Serum levels of HCV RNA and HIV-1 RNA and CD4+ cells were centrally assessed at screening, at baseline, and at weeks 1, 2, 4, 6, 8, and 12 (in 12-week groups). At the end of the study period, the same levels were assessed at weeks 4, 12, and 24, except for the CD4+ count, which was measured at post-treatment week 4 only. HCV RNA was measured with the use of the COBAS TaqMan HCV test, version 2.0 (Roche Molecular Systems).

Virologic response was defined as undetectable HCV RNA (<20 IU per milliliter) during the study period and as unquantifiable HCV RNA post-treatment (<25 IU per milliliter).

Clinical laboratory tests and physical examinations were performed at screening, at baseline, and during scheduled visits. Adverse events and laboratory abnormalities were recorded throughout and graded according to the criteria of the Division of AIDS of the National Institute of Allergy and Infectious Diseases (see the Supplementary Appendix).

VIROLOGIC BREAKTHROUGH, RELAPSE, AND RESISTANCE MONITORING

HCV virologic failure was defined as confirmed breakthrough (an increase from unquantifiable to quantifiable HCV RNA or to at least 1 $\log_{10}$ above nadir) during the study period or post-treatment relapse (the presence of quantifiable HCV RNA after an end-of-treatment response) or as the presence of quantifiable HCV RNA that is not otherwise defined as breakthrough or relapse. HIV-1 virologic failure was defined as a confirmed or last available measurement of at least 400 copies of HIV-1 RNA per milliliter.

We assessed the HCV NS5A region at baseline in all patients by means of population-based sequencing of plasma samples (sensitivity, approximately 20%) and samples that were obtained at or around the time of virologic failure when the HCV RNA level was at least 1000 IU per milliliter. Population-based sequencing of HCV NS5B was performed in each sample obtained from patients with virologic failure that could be evaluated (plus a matched baseline sample) and in comparator baseline samples obtained from two patients who had a sustained virologic response.

STUDY END POINTS

The primary efficacy end point was a sustained virologic response (HCV RNA, <25 IU per milliliter) at post-treatment week 12 among previously untreated patients with genotype 1 infection treated for 12 weeks. Key secondary efficacy end points were rates of sustained virologic response at post-treatment week 12 among previously untreated patients with genotype 1 infection who were treated for 8 weeks and corresponding rates among previously treated patients who were treat-

ed for 12 weeks. Other secondary end points included a sustained virologic response regardless of genotype, virologic response throughout the study, and safety.

SUBGROUP ANALYSES

We derived sustained virologic response rates at post-treatment week 12 (with 95% confidence intervals) for multiple categories in prespecified analyses for each of the three study groups. We also performed post hoc analyses to assess rates of sustained virologic response, including rates for patients with baseline HCV RNA levels above or below 2 million IU per milliliter and for prespecified and post hoc categories in combined data from the two 12-week study groups. The reporting of both the prespecified and post hoc subgroup analyses are descriptive, without statistical comparison. Full details with respect to these analyses are reported in Table S6 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary statistical objective was to determine whether the rate of sustained virologic response at post-treatment week 12 among previously untreated patients with HCV genotype 1 was higher after 12 weeks of daclatasvir plus sofosbuvir than the historical response rate of 29% in similar patients after 48 weeks of treatment with peginterferon–ribavirin.[13] Key secondary objectives were to determine whether the response rate for genotype 1 was above 29% in previously untreated patients after 8 weeks of treatment and above an estimated historical threshold of 5% in previously treated patients. Missing response data at post-treatment week 12 were inferred from the next available HCV RNA measurement with the use of a next-value-carried-backward approach.

For results obtained from 80 previously untreated patients with genotype 1 who received 12 weeks of treatment, 40 previously untreated patients who received 8 weeks of treatment, and 40 previously treated patients who received 12 weeks of treatment, minimum observed response rates of 40%, 45%, and 15%, respectively, would provide lower boundaries for the 95% confidence interval (CI) exceeding 29% (95% CI, 29.2 to 51.6), 29% (95% CI, 29.3 to 61.5), and 5% (95% CI, 5.7 to 29.8), respectively. On the assumption that the observed response rate would be 85% in each group, we calculated that these sample sizes would provide a power of more than 90% to show response rates higher than the relevant thresholds at a two-sided alpha level of 0.05.

RESULTS

STUDY PATIENTS

From February 10, 2014, to April 28, 2014, a total of 238 patients were screened and 203 enrolled at 37 centers in the United States. A majority of the patients were male (87%) and infected with HCV genotype 1 (83%); 34% were black. Twenty-nine patients (14%) had cirrhosis, and 92 of 200 (46%) with baseline FibroTest data had a fibrosis score of 0.59 or more, which corresponds to an estimated Metavir fibrosis stage of at least F3. A total of 199 patients (98%) were receiving antiretroviral therapy, and 149 (73%) had an *IL28B* non-CC genotype at the RS1297860 single-nucleotide polymorphism locus, which indicates an increased risk of a lack of response to interferon-based therapies. Fifty-three patients had received previous HCV treatment (including 1 patient who was erroneously assigned to the previously untreated 12-week group and was included in the analysis as randomized). Among the previously treated patients, 50 (94%) had received interferons (22% with HCV protease inhibitors) and 3 (6%) had had an HCV relapse after treatment with sofosbuvir plus ribavirin. Nearly half (47%) of all previously treated patients had either no response or a partial virologic response to previous therapy (Table 1, and Tables S2, S3, and S4 in the Supplementary Appendix).

Ninety-eight percent of the patients completed the treatment period. There were two study-drug discontinuations because of nonadherence and two because of incarceration (Fig. 1).

VIROLOGIC RESPONSE

The decline in HCV RNA levels during the study period was rapid, and 92 to 98% of patients had an HCV RNA level of less than 25 IU per milliliter by week 4 of treatment (Table S5 and Fig. S1 in the Supplementary Appendix). For patients with genotype 1 infection, the rate of a sustained virologic response at post-treatment week 12 was 96.4% (95% CI, 89.8 to 99.2) among previously untreated patients who received 12 weeks of treatment (primary end point), 75.6% (95% CI, 59.7 to 87.6) among previously untreated patients who received 8 weeks of treatment, and 97.7% (95% CI,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Previously Untreated		Previously Treated
	12-Wk Group (N=101)	8-Wk Group (N=50)	12-Wk Group (N=52)
Median age (range) — yr	52 (24–71)	51 (28–75)	57 (43–66)
Male sex — no. (%)	92 (91)	42 (84)	43 (83)
Race — no. (%)†			
White	66 (65)	28 (56)	31 (60)
Black	30 (30)	19 (38)	20 (38)
Asian or other	5 (5)	3 (6)	1 (2)
HCV genotype — no. (%)			
1	83 (82)	41 (82)	44 (85)
1a	71 (70)	35 (70)	33 (63)
1b	12 (12)	6 (12)	11 (21)
2	11 (11)	6 (12)	2 (4)
3	6 (6)	3 (6)	4 (8)
4	1 (1)	0	2 (4)
Median HCV RNA (range) — $\log_{10}$ IU/ml	6.7 (3.3–7.6)	6.4 (4.2–7.5)	6.7 (3.9–7.9)
Cirrhosis — no. (%)‡	9 (9)	5 (10)	15 (29)
Previous HCV treatment — no. (%)			
Interferon alone	0	0	1 (2)
Interferon or peginterferon plus ribavirin	1 (1)§	0	37 (71)
Peginterferon plus ribavirin plus NS3 protease inhibitor	0	0	11 (21)
Sofosbuvir plus ribavirin	0	0	3 (6)
HIV-1 RNA <50 copies/ml — no./total no. (%)¶	94/100 (94)	45/48 (94)	47/49 (96)
Median CD4+ count (range) — cells/mm^3	520 (122–1147)	575 (157–1430)	636 (262–1470)
HIV-1 treatment — no./total no. (%)‖	100/101 (99)	48/50 (96)	51/52 (98)
Darunavir–ritonavir	19/100 (19)	21/48 (44)	11/51 (22)
Atazanavir–ritonavir	19/100 (19)	5/48 (10)	12/51 (24)
Lopinavir–ritonavir	9/100 (9)	3/48 (6)	0
Efavirenz	18/100 (18)	8/48 (17)	8/51 (16)
Nevirapine	5/100 (5)	1/48 (2)	3/51 (6)
Rilpivirine	5/100 (5)	1/48 (2)	1/51 (2)
Raltegravir	22/100 (22)	8/48 (17)	10/51 (20)
Dolutegravir	3/100 (3)	1/48 (2)	4/51 (8)
Nucleosides only	0	0	2/51 (4)

* The previously untreated patients underwent randomization, but the previously treated patients did not. Among the significant between-group differences at baseline, previously treated patients were older (P=0.004), had a higher rate of cirrhosis (P=0.004), and had a higher median CD4+ count (P=0.03), and previously untreated patients who received 8 weeks of treatment were more likely to receive darunavir–ritonavir (P=0.006). HCV denotes hepatitis C virus, and HIV human immunodeficiency virus.

† Race was self-reported. Other races include American Indian, Alaskan or Hawaiian native, other Pacific Islander, or other not listed.

‡ The cirrhosis status was determined by means of biopsy in 13 of 29 patients (45%), FibroScan analysis in 7 of 29 patients (24%), or FibroTest analysis plus the aspartate aminotransferase-to-platelet ratio index in 9 of 29 patients (31%).

§ One previously treated patient was randomly assigned in error to the 12-week group for previously untreated patients and was included in the primary analysis of that group.

¶ Included in this category are patients who were receiving antiretroviral therapy and had available HIV-1 RNA data at baseline.

‖ Nucleoside analogues that were included in the regimens are not listed. Patients receiving more than one class of antiretroviral agent other than nucleoside analogues are listed according to the following hierarchy: protease inhibitor, nonnucleoside reverse-transcriptase inhibitor, and integrase inhibitor.

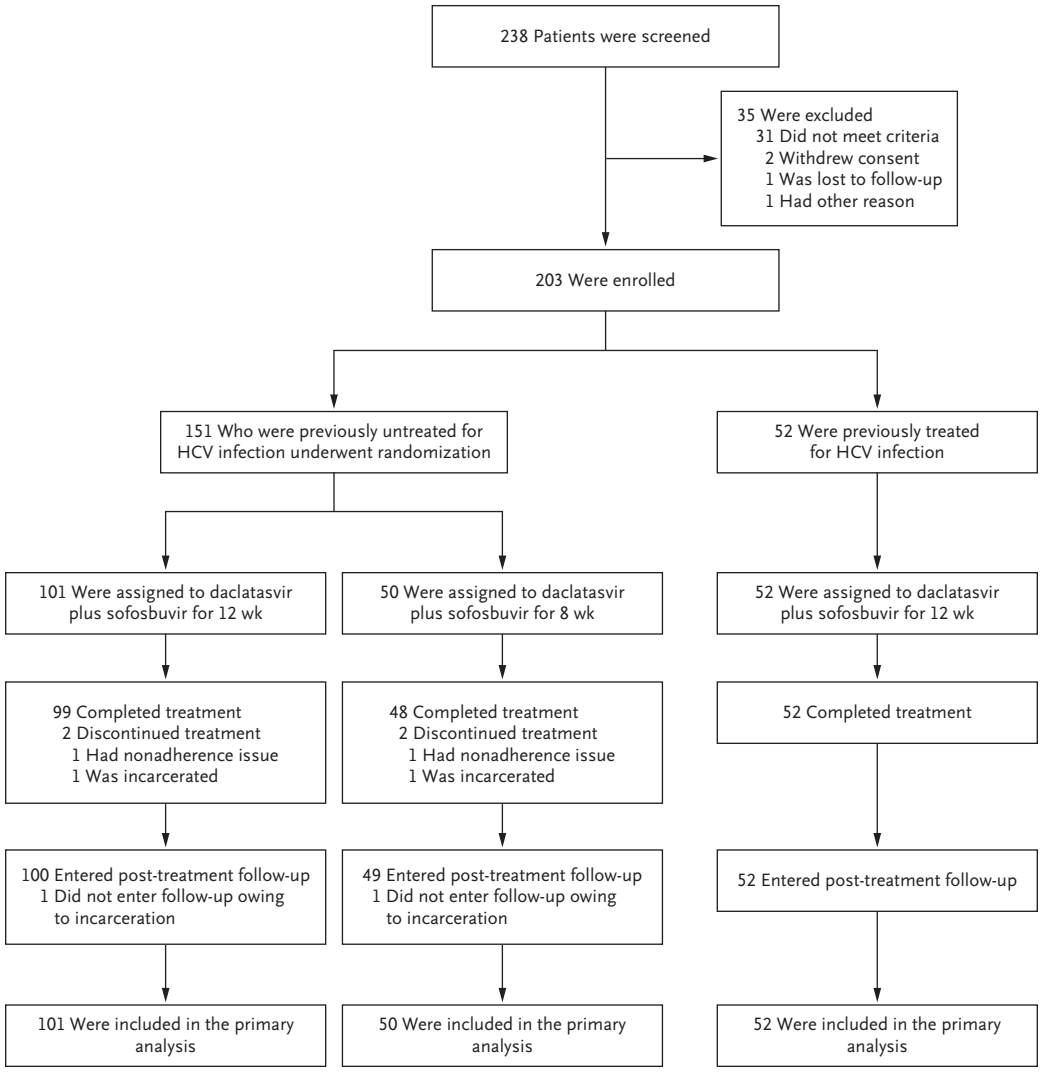

Figure 1. Enrollment and Follow-up.

One patient who had received previous treatment was randomly assigned to the previously untreated group in error and received 12 weeks of treatment.

88.0 to 99.9%) among previously treated patients who received 12 weeks of treatment. Among all patients, response rates were 97.0%, 76.0%, and 98.1%, respectively (Fig. 2).

For patients with genotypes 2, 3, and 4, a sustained virologic response was reported in all 26 patients (100%) in the two 12-week groups and in 7 of 9 patients (78%) in the 8-week group. The rates of sustained virologic response at post-treatment week 24 in the intention-to-treat population were 92% in the two 12-week groups and 72% in the 8-week group, with missing data counted as treatment failures. Differences between rates at post-treatment week 12 and those at week 24 were primarily due to missing data. The concordance between the two post-treatment periods was 98 to 99% in patients for whom data were available at the two time points. Two probable reinfections after post-treatment week 12 were identified (Table S12 in the Supplementary Appendix).

Rates of sustained virologic response in the

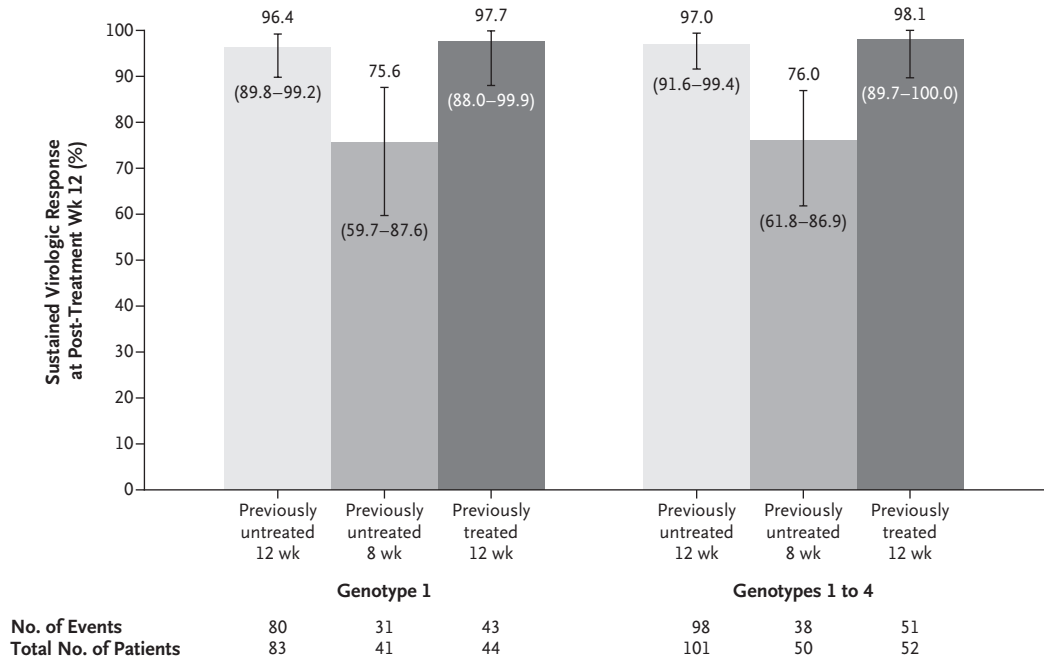

Figure 2. Primary and Secondary Efficacy End Points.

The primary end point was the rate of sustained virologic response at post-treatment week 12 among previously untreated patients with genotype 1 infection who received 12 weeks of treatment. Key secondary efficacy end points were rates of sustained virologic response at post-treatment week 12 among previously untreated patients with genotype 1 infection who received 8 weeks of treatment and corresponding rates among previously treated patients who received 12 weeks of treatment. The values shown in parentheses and the I bars represent 95% confidence intervals.

two 12-week groups were similar regardless of baseline subgroup (Table S6 in the Supplementary Appendix). The results of analyses according to study group are provided in Figures S2A, S2B, and S2C in the Supplementary Appendix; the results of a post hoc analysis of combined data from the two 12-week study groups are provided in Figure S2D. The rate of sustained virologic response after 8 weeks of treatment was lower overall and across subgroups, with the exception of patients with a baseline HCV RNA level of less than 2 million IU per milliliter (18 of 18 patients [100%]), as compared with patients with a level of 2 million IU per milliliter or more (20 of 32 patients [62%]).

Although the number of patients with cirrhosis was small, their rates of sustained virologic response were similar to those among patients without cirrhosis: 22 of 24 patients with cirrhosis (92%) versus 122 of 124 patients without cirrhosis (98%) in the combined 12-week groups.

VIROLOGIC BREAKTHROUGH, RELAPSE, AND RESISTANCE

There were no patients with HCV virologic breakthrough during the treatment period. Of the 16 patients who did not have a sustained virologic response at post-treatment week 12, 12 had a relapse (1 in each 12-week treatment group and 10 in the 8-week group) (Table S7 in the Supplementary Appendix). Of the 12 patients who had a relapse, 9 were receiving concomitant darunavir–ritonavir. All 4 patients with cirrhosis who had a relapse had HCV genotype 1a. One previously untreated patient who received 12 weeks of treatment discontinued treatment after week 1 with detectable HCV RNA and was considered to have virologic failure. Of the 3 patients with nonvirologic failure, 2 were lost to follow-up, and 1 died during week 4 of post-treatment follow-up.

At baseline, NS5A sequences were available for 198 patients, and NS5B sequences were available for 39 patients, including 12 patients with

virologic failure who could be evaluated. Polymorphisms at positions associated with resistance to daclatasvir (NS5A amino acids 28, 30, 31, or 93) were observed in baseline NS5A sequences in 33 patients (17%). One baseline NS5B sequence obtained in a previously untreated patient showed substitutions at amino acids previously observed in patients in whom sofosbuvir therapy had failed (C316H and V321I).[32,33]

Of the 12 patients who had a relapse through post-treatment week 12, only 3 were found to have daclatasvir-resistance polymorphisms at baseline. These patients included 2 in the 8-week group — 1 with genotype 2 who had the NS5A-L31M, NS5B-C316H, and NS5B-V321I variants at baseline and at the time of therapy failure and 1 with genotype 3 who had the NS5A-A30S variant at baseline and at the time of therapy failure (with unavailable data on NS5B variants at the time of therapy failure) — and 1 previously untreated patient with genotype 1a who was treated for 12 weeks and who had cirrhosis and a high baseline HCV RNA level (>10 million IU per milliliter) and carried the NS5A-Y93N variant at baseline and at the time of therapy failure and the NS5B-L159F variant at the time of therapy failure (Fig. S3 in the Supplementary Appendix).

Of the remaining 9 patients who had a relapse, 2 with genotype 1a had treatment-emergent NS5A-Q30 substitutions: 1 previously treated patient with cirrhosis and a high baseline HCV RNA level (>10 million IU per milliliter) and a Q30R substitution who was treated for 12 weeks and 1 patient with a Q30E substitution who was treated for 8 weeks. Variants associated with resistance to daclatasvir or sofosbuvir were not detected in the remaining 6 patients in the 8-week group. One previously untreated patient with genotype 1a who was treated for 12 weeks and who did not have a sustained virologic response owing to study-drug nonadherence had a treatment-emergent Q30R substitution.

Two patients had HIV-1 virologic failure: 1 with unconfirmed failure who discontinued the study at week 6 because of incarceration and 1 with confirmed failure (at the last [week 12] on-treatment visit and follow-up post-treatment week 4 visit) who subsequently was found to have a sustained HCV virologic response and undetectable HIV-1 RNA without antiretroviral adjustment at post-treatment week 12.

SAFETY

The most common adverse events were fatigue, nausea, and headache (Table 2, and Tables S8, S9, and S10 in the Supplementary Appendix). No patient discontinued treatment because of adverse events. Serious adverse events during treatment included priapism in a patient receiving medication for erectile dysfunction, presyncope plus chest pain, drug abuse plus pulmonary embolism, and syncope plus hypertensive crisis. No serious event was assessed as being related to a study drug by investigators. There were two deaths during post-treatment follow-up: a 52-year-old man who was treated for 8 weeks and who had a cardiac arrest by post-treatment week 4 and a 53-year-old man who was treated for 12 weeks and who died of cardiomyopathy of undetermined cause and multiorgan failure by post-treatment week 24.

The most common grade 3 or 4 laboratory abnormalities were elevations in the total bilirubin level among patients receiving atazanavir–ritonavir and transient elevations in lipase without associated pancreatitis (Table 2, and Table S11 in the Supplementary Appendix).

Mean CD4+ counts remained unchanged during treatment (Fig. S4 in the Supplementary Appendix). Among patients receiving antiretroviral therapy for whom HIV-1 RNA data were available, 189 of 199 (95%) had fewer than 50 copies per milliliter at the end of treatment. Of the 10 who had 50 copies per milliliter or more, 7 had fewer than 50 copies per milliliter on repeat testing without a change in antiretroviral therapy, 1 had 59 copies per milliliter, and 2 were lost to follow-up before repeat testing.

DISCUSSION

Among HIV–HCV coinfected patients who received 12 weeks of daclatasvir plus sofosbuvir, 97% had a sustained virologic response, regardless of whether they had received previous HCV treatment or a concomitant antiretroviral regimen, without disruption of HIV-1 virologic control. Rates of sustained virologic response after 12 weeks of treatment were high across all groups, including black patients and those with cirrhosis. The range of HIV-1 regimens in this study was broad and encompassed most of the therapies recommended by the Department of Health and Human Services guidelines,[18] and there were

Table 2. Adverse Events during the Treatment Period.*

Adverse Event	Previously Untreated		Previously Treated	All Patients (N=203)
	12-Wk Group (N=101)	8-Wk Group (N=50)	12-Wk Group (N=52)	
	number of patients (percent)			
Any adverse event	74 (73)	29 (58)	37 (71)	140 (69)
Serious adverse event†	1 (1)	0	3 (6)	4 (2)
Death‡	1 (1)	1 (2)	0	2 (1)
Grade 3 or 4 adverse event	2 (2)	2 (4)	4 (8)	8 (4)
Discontinuation because of adverse event	0	0	0	0
Common adverse events during study period§				
Fatigue	19 (19)	5 (10)	10 (19)	34 (17)
Nausea	14 (14)	4 (8)	8 (15)	26 (13)
Headache	12 (12)	3 (6)	8 (15)	23 (11)
Diarrhea	11 (11)	1 (2)	3 (6)	15 (7)
Vomiting	6 (6)	1 (2)	3 (6)	10 (5)
Rash	6 (6)	0	3 (6)	9 (4)
Insomnia	5 (5)	0	3 (6)	8 (4)
Abdominal pain	5 (5)	1 (2)	1 (2)	7 (3)
Cough	3 (3)	3 (6)	1 (2)	7 (3)
Dizziness	1 (1)	2 (4)	3 (6)	6 (3)
Constipation	3 (3)	0	3 (6)	6 (3)
Treatment-related grade 3 or 4 laboratory abnormality				
International normalized ratio ≥2.1×ULN¶	1 (1)	0	1 (2)	2 (1)
Aspartate aminotransferase ≥5.1×ULN‖	0	1 (2)	0	1 (<1)
Total bilirubin ≥2.6×ULN**	5 (5)	1 (2)	2 (4)	8 (4)
Lipase ≥3.1×ULN††	5 (5)	1 (2)	1 (2)	7 (3)

* ULN denotes upper limit of the normal range.
† Of the four patients with serious adverse events, three in the previously treated group had two events each: one with chest pain and presyncope, one with pulmonary embolism and drug abuse, and one with a hypertensive crisis and syncope. One patient in the previously untreated group had priapism that was deemed to be unrelated to the study treatment.
‡ The two deaths were reported in a 53-year-old man in the previously untreated 12-week group with cardiomyopathy and multiorgan failure at post-treatment week 24 and in a 52-year-old man in the 8-week group with cardiac arrest at post-treatment week 4.
§ Adverse events were included in this category if they were reported in at least 5% of the patients in any study group.
¶ Included in this category are one patient in the previously untreated 12-week group who had a history of aortic-valve replacement and was receiving anticoagulation therapy (with a grade 2 international normalized ratio at baseline and a grade 3 elevation at week 8); and one patient in the previously treated 12-week group who had an isolated grade 3 elevation at week 6 that was within normal limits on repeat testing at week 8.
‖ This event was an isolated asymptomatic level of 209 U per liter at the end of treatment (week 8), which was reduced to grade 1 (51 U per liter) 2 weeks later and returned to normal (18 U per liter) at post-treatment week 4.
** All the patients in this category were receiving concomitant atazanavir–ritonavir.
†† All the patients in this category had transient hyperlipasemia without reported pancreatitis.

no modifications in HIV-1 therapy that were associated with the receipt of daclatasvir or sofosbuvir during treatment. The rates of sustained virologic response in the 12-week groups were consistent with the high rates observed in trials of other combinations of direct-acting HCV antiviral agents in patients coinfected with HIV-1 and HCV genotype 1[34-36] and similar to those for all-oral regimens in patients with HCV monoinfection.[19-25] There were no study discontinuations because of adverse events and few serious adverse events.

On-treatment HCV RNA responses were similar in the 8-week group and the 12-week groups. However, HCV relapse was more common after 8 weeks of treatment than after 12 weeks. This finding was unexpected, since previous data from the ION-3 study of sofosbuvir plus ledipasvir in patients with HCV genotype 1 monoinfection showed similar rates of sustained virologic response after either 8 or 12 weeks of treatment.[29] The findings of this study suggest that 12 weeks of therapy should be considered for most patients with HIV-HCV coinfection.

Patients in this trial differed from those in the ION-3 study in that the focus here was on patients with HIV–HCV coinfection and the study included patients with cirrhosis and genotypes other than genotype 1. It is possible that HIV-1 coinfection adversely influences HCV eradication when treatment is truncated, though further data are needed. It is also notable that 9 of the 12 patients with HCV relapse (7 of 10 in the 8-week group) received concurrent darunavir–ritonavir and daclatasvir at a dose of 30 mg daily. The 30-mg dose of daclatasvir for patients receiving darunavir–ritonavir or lopinavir–ritonavir was selected through an extrapolation of data showing a doubling in daclatasvir systemic exposure when the drug was administered with atazanavir–ritonavir.[31] More recent data regarding observed drug interactions[37] showed that darunavir–ritonavir and lopinavir–ritonavir had a reduced effect on daclatasvir exposure that would not require dose adjustment, thereby suggesting that the most effective dose for daclatasvir is 60 mg daily with concomitant administration of darunavir–ritonavir or lopinavir–ritonavir. The dose of daclatasvir was not a strong predictor of response in the 12-week groups, since a sustained virologic response at post-treatment week 12 was reported in 28 of 30 patients (93%) taking 30 mg of daclatasvir concomitantly with darunavir–ritonavir in the 12-week groups and in all patients receiving lopinavir–ritonavir in the three groups, including 9 patients in the 12-week groups and 3 in the 8-week group.

As was observed in the ION-3 study, among patients who had a high baseline HCV RNA level, relapse rates were higher after 8 weeks of treatment than after 12 weeks, although the threshold for an increased rate of relapse in our study (2 million IU per milliliter) was lower than that in the ION-3 study (6 million IU per milliliter).[33]

Baseline NS5A resistance-associated polymorphisms did not have a significant effect on response in our study. In the three study groups, a sustained virologic response did not occur in only 1 of 8 patients with Y93 variants, in 1 of 8 with amino acid 31 variants, and in 2 of 13 with amino acid 30 variants (including 1 patient who died after having a sustained virologic response at post-treatment week 4).

A sustained virologic response was reported in 22 of 24 patients with cirrhosis (92%) after 12 weeks of treatment. Patients with HCV genotype 3 monoinfection with cirrhosis who were receiving daclatasvir plus sofosbuvir had a lower rate of sustained virologic response than did those without cirrhosis in a previous study.[38] Thus, one limitation of our study is that the numbers of patients with cirrhosis or HCV genotypes other than genotype 1 were too small to assess the interaction between cirrhosis and genotype 3 or provide definitive data on response rates among HIV–HCV coinfected patients with HCV genotype 2, 3, or 4. Further data are needed in such patients.

In conclusion, daclatasvir plus sofosbuvir for 12 weeks resulted in a high rate of sustained virologic response in patients coinfected with HIV-1 and HCV genotypes 1 through 4, regardless of previous HCV treatment, the presence of cirrhosis, or demographic or disease characteristics. HIV-1 therapy with a broad range of antiretroviral drugs was not compromised. The lower efficacy observed after 8 weeks of treatment suggests that 12 weeks of therapy may be preferred for most patients with HIV–HCV coinfection.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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