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ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

In clinical trials, treatment with a combination of the nucleotide polymerase inhibitor sofosbuvir and the antiviral drug ribavirin was associated with high response rates among patients with hepatitis C virus (HCV) genotype 2 infection, with lower response rates among patients with HCV genotype 3 infection.

METHODS

We conducted a study involving patients with HCV genotype 2 or 3 infection, some of whom had undergone previous treatment with an interferon-based regimen. We randomly assigned 91 patients with HCV genotype 2 infection and 328 with HCV genotype 3 infection, in a 4:1 ratio, to receive sofosbuvir–ribavirin or placebo for 12 weeks. On the basis of emerging data from phase 3 trials indicating that patients with HCV genotype 3 infection had higher response rates when they were treated for 16 weeks, as compared with 12 weeks, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing. The primary end point was a sustained virologic response at 12 weeks after the end of therapy.

RESULTS

Of the 419 patients who were enrolled and treated, 21% had cirrhosis and 58% had received previous interferon-based treatment. The criterion for a sustained virologic response was met in 68 of 73 patients (93%; 95% confidence interval [CI], 85 to 98) with HCV genotype 2 infection who were treated for 12 weeks and in 213 of 250 patients (85%; 95% CI, 80 to 89) with HCV genotype 3 infection who were treated for 24 weeks. Among patients with HCV genotype 3 infection, response rates were 91% and 68% among those without and those with cirrhosis, respectively. The most common adverse events were headache, fatigue, and pruritus.

CONCLUSIONS

Therapy with sofosbuvir–ribavirin for 12 weeks in patients with HCV genotype 2 infection and for 24 weeks in patients with HCV genotype 3 infection resulted in high rates of sustained virologic response. (Funded by Gilead Sciences; VALENCE ClinicalTrials.gov number, NCT01682720.)

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Of the six main genotypes of the hepatitis C virus (HCV), genotypes 2 and 3 account for approximately 30% of chronic infections worldwide.[1] Although these two genotypes have historically been grouped together in treatment guidelines and clinical trials,[2,3] accumulating evidence suggests that there are important clinical differences between them.[1,4,5] HCV genotype 3 infection is associated with a higher incidence of hepatic steatosis, more rapid progression of fibrosis, and possibly a greater risk of hepatocellular carcinoma than is HCV genotype 2 infection.[6] Moreover, patients with HCV genotype 3 infection are less responsive to peginterferon-based treatment than are patients with HCV genotype 2 infection.[7-9] Until recently, peginterferon plus ribavirin administered for 24 weeks was the standard treatment for patients with either genotype 2 or genotype 3 infection.[2,3] However, the ongoing discovery and development of agents that directly target various stages of HCV replication are likely to provide HCV-infected patients with effective interferon-free therapy.[10-12]

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV NS5B polymerase that is effective against HCV genotypes 2 and 3 when it is administered in combination with ribavirin.[13,14] In phase 3 trials involving patients with HCV genotype 2 or 3 infection, therapy with sofosbuvir–ribavirin for 12 weeks resulted in rates of sustained virologic response of 67% among patients who had not undergone previous interferon-based therapy and 78% among patients for whom peginterferon therapy was not possible because of contraindications or in whom unacceptable side effects developed. Among patients who had undergone previous therapy, rates of sustained virologic response were 50% among those who received 12 weeks of sofosbuvir–ribavirin and 73% among those who received 16 weeks of the drug combination.[14] In all the phase 3 studies of sofosbuvir–ribavirin, higher rates of sustained virologic response were observed among patients with genotype 2 infection than among those with genotype 3 infection.

We conducted a study of sofosbuvir and ribavirin that included patients who had not received previous treatment and those who had undergone previous treatment. The purpose of our study was to assess the efficacy of 24 weeks of sofosbuvir–ribavirin therapy in patients with HCV genotype 3 infection and to confirm previous findings with respect to 12 weeks of therapy in patients with HCV genotype 2 infection.

Methods

Patients

We enrolled patients from September 2012 through January 2013 at 77 sites in Europe. Eligible patients were 18 years of age or older and had chronic infection with HCV genotype 2 or 3, with serum HCV RNA levels of 10,000 IU per milliliter or higher. Patients could participate in the study regardless of whether they had received previous therapy for HCV infection with an interferon-based regimen. Some of the study patients either had not had a sustained virologic response after at least 12 weeks of previous treatment with an interferon-based regimen or had discontinued interferon treatment after no more than 12 weeks of treatment because of severe adverse reactions, psychiatric disease requiring hospitalization, major disability, or other recognized side effects of interferon. According to prespecified criteria, approximately 20% of patients who were enrolled could have cirrhosis. All patients provided written informed consent. Full eligibility criteria, including details of the assessment for cirrhosis and reasons for ineligibility for interferon treatment are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design

The study was initially designed as a multicenter phase 3 trial. Patients were randomly assigned, in a 4:1 ratio, to receive either sofosbuvir–ribavirin or matching placebo. Randomization was stratified according to status with respect to previous therapy (no previous therapy or previous therapy) and the presence or absence of cirrhosis at the time of screening. Sofosbuvir (Gilead Sciences) was administered orally at a dose of 400 mg once daily. Ribavirin (Ribasphere, Kadmon) was administered orally twice daily, with doses determined according to body weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight of ≥75 kg).

The study design originally called for all patients to receive 12 weeks of treatment with sofosbuvir–ribavirin or matching placebo. However, after the initiation of the study, newly available results from the FUSION phase 3 study of sofosbuvir strongly suggested that patients with HCV genotype 3 infection could benefit from extending treatment beyond 12 weeks.[14] The study protocol was accordingly amended so that the study-group assignments were unblinded, the placebo group was terminated,

patients with HCV genotype 2 infection were treated as originally planned for 12 weeks, and the treatment of patients with HCV genotype 3 infection was extended to 24 weeks. Patients with HCV genotype 3 infection who had already completed 12 weeks of treatment before the amendment was approved were not given additional treatment. Patients in the discontinued placebo group were offered open-label treatment with sofosbuvir–ribavirin in another clinical trial (ClinicalTrials.gov number, NCT01625338), with a duration based on the HCV genotype.

The study was redefined as a descriptive study to characterize sustained response rates in patients with HCV genotype 2 infection who were treated for 12 weeks and in patients with HCV genotype 3 infection who were treated for 24 weeks, with no plans for hypothesis testing. Details regarding the assessments that were used in the study are provided in the Supplementary Appendix.

PRIMARY END POINT

The primary efficacy end point was a sustained virologic response at 12 weeks after the end of treatment. This response was defined as a level of HCV RNA below the lower limit of quantification (25 IU per milliliter).

STUDY OVERSIGHT

This study was approved by the institutional review board or independent ethics committee at each participating site and was conducted in compliance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study was designed and conducted according to protocol by the sponsor (Gilead) in collaboration with the principal investigators. The sponsor collected the data, monitored the conduct of the study, and performed the statistical analyses. An independent data and safety monitoring committee reviewed the progress of the study. The investigators, participating institutions, and sponsor agreed to maintain the confidentiality of the data. All the authors vouch for the completeness and accuracy of the data and data analyses and for the fidelity of this report to the study protocol, which is available at NEJM.org. The manuscript was prepared by Gilead Sciences and the first author with input from all the authors.

STATISTICAL ANALYSIS

In the original analysis plan, we determined that a sample size of 320 patients in the sofosbuvir–ribavirin group and 80 patients in the placebo group would provide a power of 99% to detect a difference between the two groups, assuming rates of sustained virologic response of 45% and 5%, respectively, on the basis of a two-sided continuity-corrected chi-square test at a significance level of 0.05. As a result of the study amendment and unblinding of the study-group assignments, all the patients in the placebo group were discontinued from the study, and the primary objective was changed to provide descriptive estimates of efficacy within each active-treatment group, with no comparison with placebo and no hypothesis testing. We calculated the proportion of patients who had a sustained virologic response along with exact two-sided 95% confidence intervals constructed with the use of the Clopper–Pearson method for each active-treatment group and for subgroups. In an exploratory analysis, we performed a multivariate logistic-regression analysis involving baseline demographic and clinical characteristics, using a stepwise procedure to identify independent predictors of a sustained virologic response.

RESULTS

PATIENTS

A total of 475 patients were screened for enrollment (Fig. S1 in the Supplementary Appendix). Of these patients, 421 underwent randomization and 419 began treatment.

The demographic and clinical characteristics of the patients at baseline are shown in Table 1. Overall, 40% were women, 21% had cirrhosis, and 58% had been previously treated for HCV infection, of whom 30% had had no response. The characteristics of the patients were generally balanced among the study groups, with expected differences between patients with HCV genotype 2 infection and those with HCV genotype 3 infection.

EFFICACY

Patients receiving sofosbuvir–ribavirin had substantial reductions in circulating HCV RNA levels during the first weeks of treatment (Table 2). By week 4 of treatment, 99% of the patients had an HCV RNA level of less than 25 IU per milliliter. No patients in the placebo group had an HCV RNA level of less than 25 IU per milliliter at any time point.

Among patients with HCV genotype 2 infection who received 12 weeks of sofosbuvir–ribavirin,

68 of 73 (93%; 95% confidence interval [CI], 85 to 98) had a sustained virologic response 12 weeks after the cessation of treatment (Table 2). All 68 patients also had a sustained virologic response 24 weeks after treatment. Among patients with HCV genotype 3 who received 24 weeks of sofosbuvir–ribavirin, 213 of 250 patients (85%; 95% CI, 80 to 89) had a sustained virologic response 12 weeks after the cessation of treatment. Of these 213 patients, 206 had a sustained virologic response 24 weeks after treatment, 2 had a virologic relapse, 4 were lost to follow-up after post-treatment week 12, and 1 had an invalid HCV RNA result because the visit occurred outside the window of 24 weeks after treatment.

Exploratory analyses revealed that among patients with HCV genotype 2 infection, the rates of response were consistently high across subgroups (Fig. 1, and Table S1 in the Supplementary Appendix). Rates of sustained virologic response among patients with HCV genotype 3 infection varied according to treatment history and status with respect to cirrhosis. Among patients who had not received previous treatment, the rates of sustained virologic response were 92% among those with cirrhosis and 95% among those without cirrhosis (Fig. S2 in the Supplementary Appendix). However, among previously treated patients with HCV genotype 3 infection, the rates of sustained virologic response were lower: 62% among those with cirrhosis and 87% among those without cirrhosis. Among patients with HCV genotype 3 infection, overall response rates were 68% among those

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Genotype 2 or 3	Genotype 2	Genotype 3	
	Placebo for 12 Wk (N=85)†	Sofosbuvir plus Ribavirin for 12 Wk (N=73)	Sofosbuvir plus Ribavirin for 12 Wk (N=11)	Sofosbuvir plus Ribavirin for 24 Wk (N=250)
Mean age (range) — yr‡	49 (19–72)	58 (28–74)	46 (30–59)	48 (19–69)
Mean body-mass index (range)§	26 (18–40)	26 (20–35)	28 (20–44)	25 (17–41)
Male sex — no. (%)	49 (58)	40 (55)	6 (55)	155 (62)
Race — no. (%)¶				
White	81 (95)	65 (89)	11 (100)	236 (94)
Black	1 (1)	5 (7)	0	0
Asian	3 (4)	1 (1)	0	9 (4)
Not reported	0	2 (3)	0	5 (2)
Ethnic group — no. (%)¶				
Hispanic or Latino	10 (12)	6 (8)	1 (9)	36 (14)
Not Hispanic or Latino	71 (84)	65 (89)	10 (91)	203 (81)
Not reported	4 (5)	2 (3)	0	11 (4)
HCV genotype‡				
2	18 (21)	73 (100)	0	0
3	67 (79)	0	11 (100)	250 (100)
HCV RNA — $\log_{10}$ IU/ml	6.5±0.7	6.5±0.7	6.2±0.8	6.3±0.7
HCV RNA ≥6 $\log_{10}$ IU/ml — no. (%)	64 (75)	57 (78)	7 (64)	178 (71)
IL28B genotype — no. (%)				
CC	22 (26)	24 (33)	4 (36)	86 (34)
CT	49 (58)	41 (56)	4 (36)	131 (52)
TT	14 (16)	8 (11)	3 (27)	33 (13)
Cirrhosis — no. (%)	17 (20)	11 (15)	2 (18)	60 (24)
Baseline alanine aminotransferase >1.5× ULN — no. (%)‡	53 (62)	34 (47)	7 (64)	186 (74)

Table 1. (Continued.)

Characteristic	Genotype 2 or 3	Genotype 2	Genotype 3	
	Placebo for 12 Wk (N=85)†	Sofosbuvir plus Ribavirin for 12 Wk (N=73)	Sofosbuvir plus Ribavirin for 12 Wk (N=11)	Sofosbuvir plus Ribavirin for 24 Wk (N=250)
Previous interferon-based treatment — no. (%)				
No previous treatment	35 (41)	32 (44)	2 (18)	105 (42)
Eligible	30 (35)	27 (37)	2 (18)	94 (38)
Ineligible‖	5 (6)	5 (7)	0	11 (4)
Previous treatment	50 (59)	41 (56)	9 (82)	145 (58)
Discontinued owing to side effects**	0	3 (4)	0	10 (4)
No response††	18 (21)	10 (14)	4 (36)	41 (16)
Relapse or breakthrough infection‡‡	32 (38)	28 (38)	5 (45)	94 (38)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline except as indicated. All P values were calculated with the use of the Kruskal–Wallis test for continuous variables and the Cochran–Mantel–Haenszel test for categorical variables. Percentages may not total 100 because of rounding. ULN denotes upper limit of the normal range.
† The mean duration of treatment in the placebo group before the discontinuation of the study group by the sponsor was 7 weeks.
‡ P<0.001 for the comparison among groups.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Race and ethnic group were self-reported.
‖ Ineligibility for interferon treatment was determined by the site investigator on the basis of whether the patients had contraindications to interferon therapy.
** Patients were considered to have unacceptable side effects with interferon if they completed 12 weeks or less of treatment (ending ≥3 months before screening) with interferon and discontinued treatment because of the development or substantial worsening of at least one of the following conditions: local or systemic adverse reaction, psychiatric disease necessitating hospitalization, schizophrenia, bipolar disorder, depression, schizoaffective disorder, suicidal ideation or attempt, substantial cognitive impairment, neuropathy, disabling flulike symptoms, gastrointestinal toxic effects (nausea, vomiting, or diarrhea), thrombocytopenia (platelet count, <25,000 per cubic millimeter), neutropenia (absolute neutrophil count, <500 per cubic millimeter), colitis, nonalcoholic pancreatitis, ophthalmologic disorders, or various autoimmune disorders.
†† Patients were considered to have no response if they did not have undetectable HCV RNA levels at any time during previous treatment.
‡‡ Breakthrough infection was defined as a finding of undetectable HCV RNA levels during treatment but detectable HCV RNA levels before the end of treatment. Relapse was defined as a finding of undetectable HCV RNA levels during treatment but detectable HCV RNA levels within 4 weeks after the discontinuation of treatment.

with cirrhosis and 91% among those without cirrhosis. In an exploratory multivariate regression analysis of patients with genotype 3 infection, four factors were independently associated with a sustained virologic response: a baseline HCV RNA level of less than 6 $\log_{10}$ IU per milliliter (odds ratio, 4.23; 95% CI, 1.21 to 14.81; P=0.02), female sex (odds ratio, 3.18; 95% CI, 1.22 to 8.31; P=0.02), absence of cirrhosis (odds ratio, 3.46; 95% CI, 1.60 to 7.48; P=0.002), and an age of less than 50 years (odds ratio, 2.82; 95% CI, 1.21 to 6.57; P=0.02) (Table S5 in the Supplementary Appendix).

Of the 334 patients receiving sofosbuvir–ribavirin, 1 had a virologic breakthrough during treatment. According to a subsequent pharmacokinetic analysis, this patient had undetectable drug levels during weeks 12 through 24 of treatment, suggesting nonadherence.

VIRAL RESISTANCE TESTING

The S282T variant is the only HCV mutation that has been found to reduce susceptibility to sofosbuvir in vitro. S282T variants were not detected at baseline in any patient, nor were they detected by means of deep sequencing at the time of virologic failure in the patients who did not have a sustained virologic response. Among the 41 patients with HCV genotype 3 infection who had virologic failure, the mutations that have been associated with sofosbuvir treatment — V321A and L159F — were detected in 2 and 6 patients, respectively. The V321A mutation was not observed at baseline in any patient, and L159F was not assessed at baseline in this study, since only short-fragment sequencing from NS5B positions 227–338 was performed. During in vitro testing, neither the V321A mutation nor the L159F mutation conferred resistance to sofosbuvir. The clin-

Table 2. Response during and after Treatment.*

Response	Genotype 2	Genotype 3	
	Sofosbuvir plus Ribavirin for 12 Wk (N=73)	Sofosbuvir plus Ribavirin for 12 Wk (N=11)	Sofosbuvir plus Ribavirin for 24 Wk (N=250)
HCV RNA <25 IU/ml during treatment period			
At 2 wk			
No. of patients	57	6	214
Percent (95% CI)	78 (67–87)	55 (23–83)	86 (81–90)
At 4 wk			
No. of patients	73	11	247
Percent (95% CI)	100 (95–100)	100 (72–100)	99 (96–99)
HCV RNA <25 IU/ml after end of treatment			
At 4 wk			
No. of patients	68	5	218
Percent (95% CI)	93 (85–98)	45 (17–77)	87 (82–91)
At 12 wk			
No. of patients	68	3	213
Percent (95% CI)	93 (85–98)	27 (6–61)	85 (80–89)
Virologic failure — no. (%)			
During treatment	0	0	1 (<1)†
Relapse			
In patients who completed treatment	5 (7)	5 (45)	33 (13)‡
In patients who did not complete treatment	0	1 (9)	1 (<1)
Lost to follow-up	0	2 (18)	2 (1)

* Data are not listed for the placebo group, in which no patients had an HCV RNA level of less than 25 IU per milliliter (the lower limit of quantification) at any time point.
† Pharmacokinetic analysis suggested that this patient was nonadherent to the dosing regimen.
‡ Two additional patients had a relapse after post-treatment week 12.

ical significance of these mutations that develop during treatment is not known.

ADVERSE EVENTS

Premature discontinuation of study treatment because of adverse events was uncommon in all the study groups. One patient in the placebo group discontinued therapy because of elevated alanine aminotransferase and aspartate aminotransferase levels, one patient with HCV genotype 3 infection receiving 12 weeks of treatment discontinued because of malaise and headache, and one patient with HCV genotype 3 receiving 24 weeks of treatment discontinued after attempting suicide. The most common adverse events are shown in Table 3. Most adverse events occurred with similar frequency in the 12-week and 24-week treatment groups. Diarrhea and irritability were observed more frequently in the 24-week group than in the 12-week group. No single grade 3 or 4 adverse event occurred in more than 1% of patients receiving sofosbuvir for 12 or 24 weeks. (A complete list of serious adverse events is provided in Table S6 in the Supplementary Appendix.)

Among patients receiving 12 weeks of treatment with sofosbuvir–ribavirin, grade 3 laboratory abnormalities were reported in 19% of the patients and grade 4 abnormalities in 1%; among those receiving 24 weeks of therapy, such abnormalities were reported in 17% and 1% of the patients, respectively. Reductions in hemoglobin levels were observed, a finding that was consistent with the expected hemolytic anemia associ-

ated with ribavirin treatment: 6% of patients in both the 12-week and 24-week groups had hemoglobin levels of less than 10 g per deciliter, and one patient in each group had a hemoglobin level of less than 8.5 g per deciliter. Reductions in the dose of ribavirin were performed according to the prescribing information and did not adversely influence the treatment outcome (Table S2 in the Supplementary Appendix). The mean reduction in hemoglobin level at the end of treatment was 2.3 g per deciliter in the 12-week group and 2.1 g per deciliter in the 24-week group. Transient increases in total serum bilirubin were observed to have a temporal association with reductions in hemoglobin associated with hemolysis.

DISCUSSION

This descriptive study of the oral regimen of sofosbuvir in combination with ribavirin, which was conducted at nearly 80 sites in Europe, confirmed findings from previous studies of sofosbuvir in similar populations in North America.[13,14] We found high rates of sustained virologic response among patients with HCV genotype 2 infection and among those with genotype 3 infection, with a longer treatment duration providing benefit in the latter group.

Among patients with HCV genotype 2 infection, high rates of response and low rates of relapse were observed in all subgroups, indicating the efficacy of 12 weeks of treatment in patients with this genotype. For patients infected with HCV genotype 3, extending sofosbuvir–ribavirin treatment to 24 weeks resulted in substantially higher rates of response and lower rates of relapse than previously reported with the same regimen for 12 weeks and 16 weeks, regardless of the status with respect to previous therapy and the presence or absence of cirrhosis.[12] Extending the duration of treatment from 12 weeks

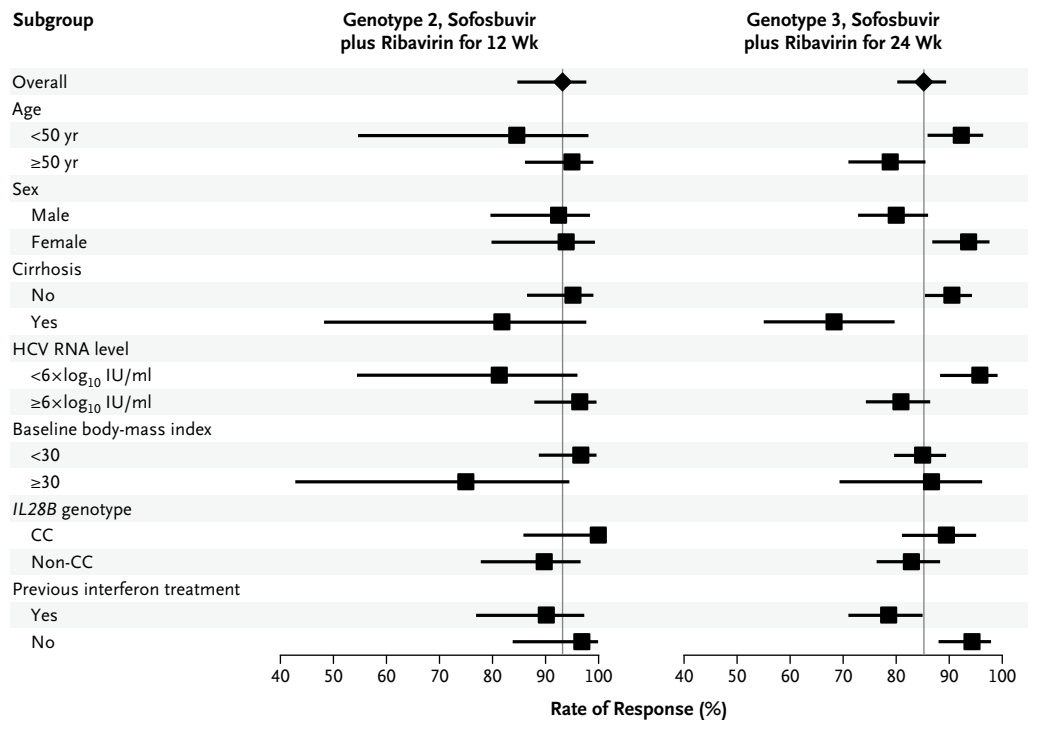

Figure 1. Subgroup Analyses of Sustained Virologic Response.

Shown are rates of sustained virologic response among 73 patients infected with hepatitis C virus (HCV) genotype 2 and 250 patients infected with HCV genotype 3. The position of the squares indicates the rate of virologic response 12 weeks after the end of treatment. The horizontal lines indicate 95% confidence intervals. The vertical lines and the diamonds represent the overall rates of sustained virologic response. Exact values for these and other subgroup results are provided in Table S1 in the Supplementary Appendix.

Table 3. Adverse Events, Discontinuations, and Hematologic Abnormalities.*

Event	Placebo (N=85)	Sofosbuvir plus Ribavirin for 12 Wk, Genotype 2 or 3 (N=84)	Sofosbuvir plus Ribavirin for 24 Wk, Genotype 3 (N=250)
		number of patients (percent)	
Any adverse event	60 (71)	72 (86)	229 (92)
Discontinuation of treatment owing to adverse event	1 (1)	1 (1)	1 (<1)
Serious adverse event†	2 (2)	0	10 (4)
Common adverse event‡			
Headache	23 (27)	24 (29)	74 (30)
Fatigue	16 (19)	19 (23)	75 (30)
Pruritus	8 (9)	20 (24)	67 (27)
Asthenia	4 (5)	21 (25)	53 (21)
Nausea	9 (11)	26 (31)	33 (13)
Insomnia	2 (2)	9 (11)	41 (16)
Nasopharyngitis	9 (11)	4 (5)	36 (14)
Dry skin	5 (6)	8 (10)	31 (12)
Dyspnea	1 (1)	12 (14)	27 (11)
Cough	4 (5)	8 (10)	27 (11)
Diarrhea	4 (5)	4 (5)	30 (12)
Arthralgia	6 (7)	3 (4)	25 (10)
Irritability	3 (4)	4 (5)	26 (10)
Hematologic event			
Decreased hemoglobin			
<10 g/dl	NA	5 (6)	15 (6)
<8.5 g/dl	NA	1 (1)	1 (<1)
Lymphocyte count 350 to <500/mm^3	0	1 (1)	5 (2)
Neutrophil count 500 to <750/mm^3	1 (1)	1 (1)	0
Platelet count 25,000 to <50,000/mm^3	0	0	3 (1)
White-cell count 1000 to 1500/mm^3	1 (1)	0	0

* The mean (±SD) durations of treatment were 7.0±3.0 weeks in the placebo group, 12.0±1.2 weeks in the group assigned to receive sofosbuvir plus ribavirin for 12 weeks, and 24.0±1.0 weeks in the group assigned to receive sofosbuvir plus ribavirin for 24 weeks. NA denotes not available.
† A complete list of serious adverse events is provided in Table S6 in the Supplementary Appendix.
‡ Common adverse events are those that occurred in at least 10% of patients in any study group.

to 24 weeks was not associated with increases in the severity or frequency of adverse events, nor in the rate of treatment discontinuation, which was approximately 1% in both the 12-week and 24-week groups. In addition, the absence of virologic breakthrough during treatment and the absence of resistance-associated variants in patients who had a virologic relapse confirm that the sofosbuvir–ribavirin regimen has a high barrier to resistance.

These findings provide further confirmation of important differences in response to treatment between HCV genotype 2 and genotype 3 and the need for a longer treatment duration with sofosbuvir–ribavirin in patients with HCV genotype 3 infection. The biologic bases and the host or viral factors that account for the differences in treatment responsiveness between the two genotypes are not well understood. Between-genotype differences in response were not evident during

treatment, since the kinetics of the viral decline during the first weeks of treatment were nearly identical in patients with genotype 2 infection and those with genotype 3 infection. However, in a multivariate regression analysis of results, we identified four possible predictors of a sustained virologic response among patients with genotype 3 infection: female sex, absence of cirrhosis, younger age, and a low viral load at baseline. These four factors have also been regarded as predictors of a response to interferon-based treatment.[15,16] It should be noted that the results of this multivariate analysis cannot be regarded as definitive without validation in another cohort.

Previously treated patients with HCV genotype 3 infection and cirrhosis had the lowest rate of sustained virologic response (62%, in 29 of 47 patients). The cause or causes for this finding are not known. Small differences among subgroups in the rate of viral decline during the first weeks of treatment were no longer evident by week 4 (Table S3 in the Supplementary Appendix).

Our study has several limitations. First, the original design of this study specified 12 weeks, rather than 24 weeks, of treatment for patients with genotype 3 infection and included comparisons with patients in the placebo group. The revised design resulted in a descriptive study, without any hypothesis testing or formal statistical comparisons. Second, given that few liver-biopsy specimens were available for the study population, questions regarding the extent of liver disease, including steatosis and its association with relapse among patients with genotype 3 infection, cannot be adequately addressed. Third, although response rates with 12 weeks of treatment were high among patients with HCV genotype 2 infection who had characteristics associated with a lower response, the small numbers preclude definitive conclusions regarding the possible benefits of a longer duration of therapy or the addition of peginterferon in harder-to-treat patients.

In conclusion, the oral sofosbuvir–ribavirin regimen resulted in high rates of sustained virologic response both in patients with HCV genotype 2 infection and in those with genotype 3 infection. This treatment offers an alternative to a peginterferon-based regimen and may make possible treatment of a substantial number of patients with HCV infection who are ineligible to receive interferon because of absolute or relative contraindications.

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

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