

ORIGINAL ARTICLE

Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

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ABSTRACT

BACKGROUND

In phase 2 trials, the nucleotide polymerase inhibitor sofosbuvir was effective in previously untreated patients with chronic hepatitis C virus (HCV) genotype 1, 2, or 3 infection.

METHODS

We conducted two phase 3 studies in previously untreated patients with HCV infection. In a single-group, open-label study, we administered a 12-week regimen of sofosbuvir plus peginterferon alfa-2a and ribavirin in 327 patients with HCV genotype 1, 4, 5, or 6 (of whom 98% had genotype 1 or 4). In a noninferiority trial, 499 patients with HCV genotype 2 or 3 infection were randomly assigned to receive sofosbuvir plus ribavirin for 12 weeks or peginterferon alfa-2a plus ribavirin for 24 weeks. In the two studies, the primary end point was a sustained virologic response at 12 weeks after the end of therapy.

RESULTS

In the single-group study, a sustained virologic response was reported in 90% of patients (95% confidence interval, 87 to 93). In the noninferiority trial, a sustained response was reported in 67% of patients in both the sofosbuvir–ribavirin group and the peginterferon–ribavirin group. Response rates in the sofosbuvir–ribavirin group were lower among patients with genotype 3 infection than among those with genotype 2 infection (56% vs. 97%). Adverse events (including fatigue, headache, nausea, and neutropenia) were less common with sofosbuvir than with peginterferon.

CONCLUSIONS

In a single-group study of sofosbuvir combined with peginterferon–ribavirin, patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks. In a noninferiority trial, patients with genotype 2 or 3 infection who received either sofosbuvir or peginterferon with ribavirin had nearly identical rates of response (67%). Adverse events were less frequent with sofosbuvir than with peginterferon. (Funded by Gilead Sciences; FISSION and NEUTRINO ClinicalTrials.gov numbers, NCT01497366 and NCT01641640, respectively.)

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*A complete list of investigators who participated in this trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 23, 2013, at NEJM.org.

N Engl J Med 2013.

DOI: 10.1056/NEJMoa1214853

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AS MANY AS 170 MILLION PERSONS ARE chronically infected with the hepatitis C virus (HCV) worldwide, and more than 350,000 die annually from liver disease caused by HCV.^{1,2} Estimates of the number of persons in the United States who have chronic HCV infection range from 2.7 million to 5.2 million.^{3,4} For previously untreated cases of HCV genotype 1 infection (representing more than 70% of all cases of chronic HCV infection in the United States), the current standard of care is 12 to 32 weeks of an oral protease inhibitor combined with 24 to 48 weeks of peginterferon alfa-2a plus ribavirin, with the duration of therapy guided by the on-treatment response and the stage of hepatic fibrosis.⁵⁻⁷ For patients infected with HCV genotype 2 or 3, no direct-acting antiviral drugs have been approved, and the recommended treatment is 24 weeks of peginterferon-ribavirin.⁸

Although 60 to 80% of previously untreated patients who undergo treatment with these regimens in clinical trials have had a sustained virologic response,^{6,7,9,10} a large number of patients go untreated owing to absolute and relative contraindications or unwillingness to receive interferon. Moreover, the protease inhibitor regimens have several disadvantages, including a low genetic barrier to the development of resistance, safety issues, potential for drug interactions, and complicated regimens with high pill burdens.^{11,12}

Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor with similar *in vitro* activity against all HCV genotypes.¹³ In phase 2 trials, a regimen of 400 mg of sofosbuvir plus peginterferon-ribavirin for 12 or 24 weeks resulted in rates of sustained virologic response of 87 to 92% in previously untreated patients with HCV genotype 1 infection.^{14,15} Patients with genotype 4 or 6 infection also had high rates of sustained virologic response with a 24-week regimen of sofosbuvir plus peginterferon-ribavirin.¹⁴ In another phase 2 trial, all 40 previously untreated patients with HCV genotype 2 or 3 infection had a sustained virologic response with 12 weeks of treatment with sofosbuvir plus ribavirin (with or without peginterferon).¹⁶ In clinical studies to date, no virologic breakthrough has been observed during therapy with sofosbuvir, which is consistent with the drug's mechanism of action and high genetic barrier to resistance. The resistance-associated HCV mutation S282T has not been detected in any

patient treated with sofosbuvir and ribavirin either during or after treatment. We therefore conducted two phase 3 studies to evaluate the efficacy and safety of 12 weeks of therapy with regimens containing sofosbuvir in patients who had not previously received treatment for HCV infection.

METHODS

PATIENTS AND STUDY DESIGNS

In two multicenter trials, we enrolled patients at least 18 years of age who had serum HCV RNA levels of 10,000 IU per milliliter or higher during screening and who had never received treatment for HCV infection. In the two studies, it was specified that approximately 20% of patients could have evidence of cirrhosis. Full eligibility criteria for the two trials, including details of the assessment for cirrhosis, are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The NEUTRINO trial was a single-group, open-label study of sofosbuvir plus peginterferon-ribavirin in 327 patients infected with HCV genotype 1, 4, 5, or 6. From June 2012 through August 2012, patients were enrolled at 56 sites in the United States. All patients received sofosbuvir, ribavirin, and peginterferon alfa-2a for 12 weeks. Sofosbuvir (Gilead Sciences) was administered orally at a dose of 400 mg once daily along with ribavirin (Ribasphere, Kadmon), which was administered orally as a divided dose 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). Peginterferon alfa-2a (Pegasys, Roche) was administered subcutaneously once weekly at a dose of 180 μg.

The FISSION trial was a randomized, open-label, active-control study of sofosbuvir plus ribavirin in patients with HCV genotype 2 or 3 infection; patients with the two genotypes were enrolled in an approximately 1:3 ratio, respectively. From December 2011 through May 2012, patients were enrolled at 97 sites in the United States, Australia, New Zealand, Italy, Sweden, and the Netherlands and were randomly assigned in a 1:1 ratio by means of a centralized system to receive either 12 weeks of sofosbuvir plus ribavirin or 24 weeks of peginterferon alfa-2a plus ribavirin. The doses of sofosbuvir and ribavirin were the same as those administered in the

NEUTRINO study. The dose of ribavirin for patients in the peginterferon–ribavirin group was 800 mg daily in two divided doses, in accordance with product labeling.¹⁷ Randomization was stratified according to HCV genotype (2 or 3), screening HCV RNA level ($<6 \log_{10}$ IU per milliliter or $\geq 6 \log_{10}$ IU per milliliter), and the presence or absence of cirrhosis.

STUDY ASSESSMENTS

Screening assessments included standard clinical laboratory testing, measurement of serum HCV RNA levels, and *IL28B* genotyping. (The presence of two CC alleles in *IL28B* is associated with an improved response to interferon-based HCV therapy.) HCV RNA levels were measured by means of the COBAS AmpliPrep/COBAS TaqMan HCV Test, version 2.0, for use with the High Pure system (Roche Molecular Systems), with a lower limit of quantification of 25 IU per milliliter. The HCV genotype and subtype were determined with the use of the Siemens Versant HCV Genotype 2.0 Assay. The *IL28B* genotype was determined by means of polymerase-chain-reaction amplification and sequencing of the rs12979860 single-nucleotide polymorphism.¹⁸

Assessments during treatment included standard laboratory tests, measurement of serum HCV RNA levels, measurement of vital signs, electrocardiography, and symptom-directed physical examinations. All adverse events were recorded and graded according to a standardized scale (see the NEUTRINO study protocol, available at NEJM.org).

Resistance testing was performed in patients receiving sofosbuvir who did not have a virologic response (virologic failure) (for details, see the Supplementary Appendix). We conducted analyses of nucleotide changes in the HCV NS5B gene (which can confer resistance to therapy) in samples collected at baseline and at the time of virologic failure. DDL Diagnostics Laboratory performed NS5B amplification and population sequencing, and WuXi AppTec performed deep-sequencing assays to characterize virologic resistance.

PRIMARY END POINT

In the two studies, the primary efficacy end point was a sustained virologic response, which was defined as an HCV RNA level below the lower limit of quantification, at 12 weeks after the end of treatment.

STUDY OVERSIGHT

Each study was approved by the institutional review boards or independent ethics committees at the participating sites and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Both studies were designed and conducted according to their protocols 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; all the authors had access to the data. An independent data and safety monitoring committee reviewed safety data from the two studies. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors assume responsibility for the integrity and completeness of the reported data and vouch for the fidelity of this report to the study protocols, available at NEJM.org. The manuscript was prepared by authors employed by Gilead, with input from all the authors and the assistance of a professional writer who was also employed by Gilead.

STATISTICAL ANALYSIS

In the NEUTRINO study, we determined that the enrollment of 300 patients with HCV genotype 1, 4, 5, or 6 infection would provide a power of 90% to show a rate of sustained virologic response with the sofosbuvir regimen that was higher than 60%, a calculated control rate based on previous efficacy after adjustment for the presence of cirrhosis and expected safety benefit (for details, see the Supplementary Appendix). The expectation of high response rates, improved safety, and shorter treatment duration led to the joint decision with regulatory authorities not to include a currently available protease-inhibitor regimen as an active control.

In the FISSION study, we determined that a sample of 250 patients with HCV genotype 2 or 3 in each study group would provide a power of more than 95% to establish the noninferiority of sofosbuvir and ribavirin, as compared with peginterferon and ribavirin. Noninferiority would be shown if the lower limit of the two-sided confidence interval for the difference was more than -15% .

We used two-sided testing at the 0.05 level in both studies. Multivariable logistic-regression

analyses characterizing the relationship between a sustained virologic response and various pre-specified demographic and baseline clinical characteristics were performed. A stepwise selection procedure was used to identify independent predictors of a sustained virologic response.

RESULTS

STUDY PATIENTS

In the NEUTRINO study, of the 456 patients with HCV genotype 1, 4, 5, or 6 who were initially screened, 328 were enrolled, and 327 began treatment (Fig. S1 in the Supplementary Appendix). Most of the patients who were included in the study had HCV genotype 1 (89%); 9% had genotype 4, and 2% had genotype 5 or 6 (Table 1), a distribution that is consistent with the prevalence of HCV genotypes in the United States. A total of 17% of patients were black, 71% had a non-CC IL28B genotype, and 17% had cirrhosis.

In the FISSION study, of the 666 patients with genotype 2 or 3 infection who were initially screened, 527 underwent randomization, and 499 began treatment (Fig. S2 in the Supplementary Appendix). The demographic and baseline clinical characteristics of the patients were balanced between the two study groups in the FISSION study (Table 1). A total of 20% of patients in the sofosbuvir group and 21% of those in the peginterferon group had cirrhosis.

EFFICACY

All patients receiving sofosbuvir in the two studies had rapid and substantial decreases in serum HCV RNA levels. There were no substantial differences in the magnitude of the decrease in HCV RNA levels during treatment on the basis of HCV genotype, race, IL28B genotype, or presence or absence of cirrhosis. By week 2 of treatment, 91% of patients with genotype 1, 4, 5, or 6 infection and 92% of those with genotype 2 or 3 infection in the sofosbuvir groups had a level of HCV RNA of less than 25 IU per milliliter. By week 4, the proportions of patients with this reduced level of HCV RNA were 99% and just under 100% (99.6%), respectively — rates that were maintained throughout the treatment period (Table 2). Response rates during the first weeks of treatment were lower among patients receiving peginterferon-ribavirin without sofosbuvir.

Among the 580 patients receiving sofosbuvir in the two studies, 1 patient in the FISSION study

had viral breakthrough during week 8 of treatment. Plasma levels of sofosbuvir in this patient were undetectable at that time, suggesting non-adherence.

NEUTRINO STUDY

A total of 295 of the 327 patients (90%; 95% confidence interval [CI], 87 to 93) with HCV genotype 1, 4, 5, or 6 had a sustained virologic response 12 weeks after treatment (Table 2). The two-sided one-sample exact test established the primary efficacy end point of the superiority of sofosbuvir plus peginterferon-ribavirin, as compared with an adjusted historical response rate of 60% ($P < 0.001$).

Patients' responses according to baseline characteristics are shown in Figure 1. Rates of sustained virologic response did not differ greatly according to the HCV genotype: 89% for patients with HCV genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% (27 of 28 patients) for those with HCV genotype 4. The single patient with genotype 5 and all six patients with genotype 6 in this trial had a sustained virologic response.

Multivariate logistic-regression modeling to investigate predefined covariate effects indicated that cirrhosis and a non-CC IL28B genotype were strongly associated with a reduced response (Table S5 in the Supplementary Appendix). The rate of sustained virologic response was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A sustained virologic response occurred in 93 of 95 patients (98%) with the CC genotype of IL28B, as compared with 202 of 232 patients (87%) with the non-CC IL28B genotype. Responses did not vary substantially according to race or ethnic group, with rates of sustained virologic response of 87% among black patients and 91% among Hispanic or Latino patients (Fig. 1).

FISSION STUDY

Sofosbuvir-ribavirin was shown to be noninferior to peginterferon-ribavirin with respect to the primary end point. At 12 weeks, the rates of sustained virologic response for patients receiving 12 weeks of sofosbuvir-ribavirin and those receiving 24 weeks of peginterferon-ribavirin were each 67% (Table 2). The absolute difference between the two groups after adjustment for stratification factors was 0.3 percentage points (95% CI, -7.5 to 8.0) in favor of sofosbuvir-ribavirin. In

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	NEUTRINO Study		FISSION Study	
	SOF+PEG+RBV for 12 Wk (N=327)		SOF+RBV for 12 Wk (N=256)	PEG+RBV for 24 Wk (N=243)
Mean age — yr (range)	52 (19–70)		48 (20–72)	48 (19–77)
Mean body-mass index (range)	29 (18–56)		28 (17–51)	28 (19–52)
Male sex — no. (%)	209 (64)		171 (67)	156 (64)
Race or ethnic group — no. (%)†				
White	257 (79)		223 (87)	212 (87)
Black	54 (17)		12 (5)	5 (2)
Asian	7 (2)		14 (5)	15 (6)
Other	9 (3)		7 (3)	11 (5)
Hispanic or Latino	46 (14)		41 (16)	31 (13)
HCV subtype — no. (%)				
1a	225 (69)‡		2 (1)§	0
1b	66 (20)		1 (<1)§	0
2	0		70 (27)	67 (28)
3	0		183 (71)	176 (72)
4	28 (9)		0	0
5	1 (<1)		0	0
6	6 (2)		0	0
Mean HCV RNA — log ₁₀ IU/ml	6.4±0.7		6.0±0.8	6.0±0.8
HCV RNA ≥800,000 IU/ml — no. (%)	267 (82)		145 (57)	157 (65)
IL28B genotype — no. (%)				
CC	95 (29)		108 (42)	106 (44)
CT	181 (55)		121 (47)	98 (40)
TT	51 (16)		25 (10)	38 (16)
Missing data	0		2 (1)	1 (<1)
Cirrhosis — no. (%)¶	54 (17)		50 (20)	50 (21)
Alanine aminotransferase >1.5×ULN — no. (%)	166 (51)		138 (54)	146 (60)

* Plus–minus values are means ±SD. There were no significant between-group differences in the FISSION study in the listed baseline characteristics. The NEUTRINO study was a single-group trial involving previously untreated patients with HCV genotype 1, 4, 5, or 6 infection. The FISSION study was a randomized trial involving previously untreated patients with HCV genotype 2 or 3 infection. PEG+RBV denotes peginterferon alfa-2a plus ribavirin, SOF+PEG+RBV sofosbuvir plus peginterferon alfa-2a and ribavirin, SOF+RBV sofosbuvir plus ribavirin, and ULN upper limit of the normal range.

† Race or ethnic group was self-reported. Patients could choose more than one category.

‡ One patient had mixed subtype 1a/1b infection.

§ The three patients who were found to have genotype 1 infection on deep-sequencing analysis after randomization were excluded from the efficacy analysis but were included in the safety analysis.

¶ Cirrhosis was defined as any one of the following: a liver-biopsy sample showing cirrhosis; transient elastography (FibroScan) showing cirrhosis or liver stiffness of more than 12.5 kPa; a serum FibroTest score of more than 0.75 (on a scale of 0 to 1) plus a ratio of aspartate aminotransferase to platelets of more than 2 during screening.

a supplemental analysis, we calculated that the one-sided P value associated with the formal test of noninferiority was P<0.001. There was a high concordance (>99%) between the rates of response at 12 and 24 weeks after treatment among

patients who received sofosbuvir–ribavirin; only 1 of 166 patients who could be evaluated had a virologic relapse after post-treatment week 12.

Rates of response in prespecified subgroups of patients are shown in Figure 1. Logistic-regres-

Table 2. Response during and after Treatment Period.

Response	NEUTRINO Study		FISSION Study	
	SOF+PEG+RBV for 12 Wk (N=327)	SOF+RBV for 12 Wk (N=253)	PEG+RBV for 24 Wk (N=243)	
HCV RNA <25 IU/ml — no./total no. (%)				
During treatment				
At 2 wk	299/327 (91)	231/251 (92)	76/241 (32)	
At 4 wk	321/325 (99)	249/250 (>99)	158/236 (67)	
At last observed measurement	326/327 (>99)	249/253 (98)	217/243 (89)	
After end of treatment				
At 4 wk	302/327 (92)	187/253 (74)	181/243 (74)	
At 12 wk	295/327 (90)	170/253 (67)	162/243 (67)	
Virologic breakthrough during treatment — no. (%)	0	1 (<1)	18 (7)	
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no./total no. (%)				
Patients who completed treatment	25/320 (8)	71/242 (29)	37/188 (20)	
Patients who did not complete treatment	3/6 (50)	3/7 (43)	9/29 (31)	

sion analysis showed that among patients receiving sofosbuvir, genotype 2 infection and an absence of cirrhosis were strongly associated with high rates of sustained virologic response (Table S8 in the Supplementary Appendix). A sustained virologic response occurred in 97% of patients with genotype 2 and in 56% of those with genotype 3 in the group receiving sofosbuvir–ribavirin, as compared with response rates of 78% and 63%, respectively, in the group receiving peginterferon–ribavirin. Among patients with cirrhosis at baseline, 47% of those receiving sofosbuvir–ribavirin had a sustained virologic response, as compared with 38% of those receiving peginterferon–ribavirin.

TESTING FOR VIRAL RESISTANCE

Among the 28 patients in the NEUTRINO study and the 74 patients in the FISSION study who received sofosbuvir and had a relapse after a virologic response at the end of treatment, deep-sequencing analysis of samples that were collected at the post-treatment visits when HCV RNA was detected showed no resistance-associated variants (see the Supplementary Appendix).

SAFETY

Treatment discontinuation because of adverse events was uncommon among patients receiving sofosbuvir regimens, with rates of 2% among pa-

tients receiving 12 weeks of sofosbuvir plus peginterferon–ribavirin and 1% among those receiving 12 weeks of sofosbuvir–ribavirin, as compared with 11% among patients receiving 24 weeks of peginterferon–ribavirin (Table 3). The rates of serious and severe adverse events were low in all the study groups (Tables S12 and S14 and Fig. S4 and S5 in the Supplementary Appendix).

In the FISSION trial, the incidence of adverse events associated with the various organ systems was consistently lower among patients receiving sofosbuvir–ribavirin than among those receiving peginterferon–ribavirin without sofosbuvir (Fig. S5 in the Supplementary Appendix). The most common adverse events in all study groups were fatigue, headache, nausea, and insomnia (Table 3). With the exception of dizziness and anemia, all events occurring in at least 10% of patients were more common among patients receiving peginterferon than among those receiving sofosbuvir. The influenza-like symptoms and fever that are characteristic of interferon treatment were reported in 16% and 18% of patients receiving peginterferon, respectively, but in only 3% of patients receiving sofosbuvir. Depression, another common side effect of interferon therapy, occurred in 14% of patients receiving peginterferon, as compared with 5% of patients receiving sofosbuvir (Table S10 in the Supplementary Appendix).

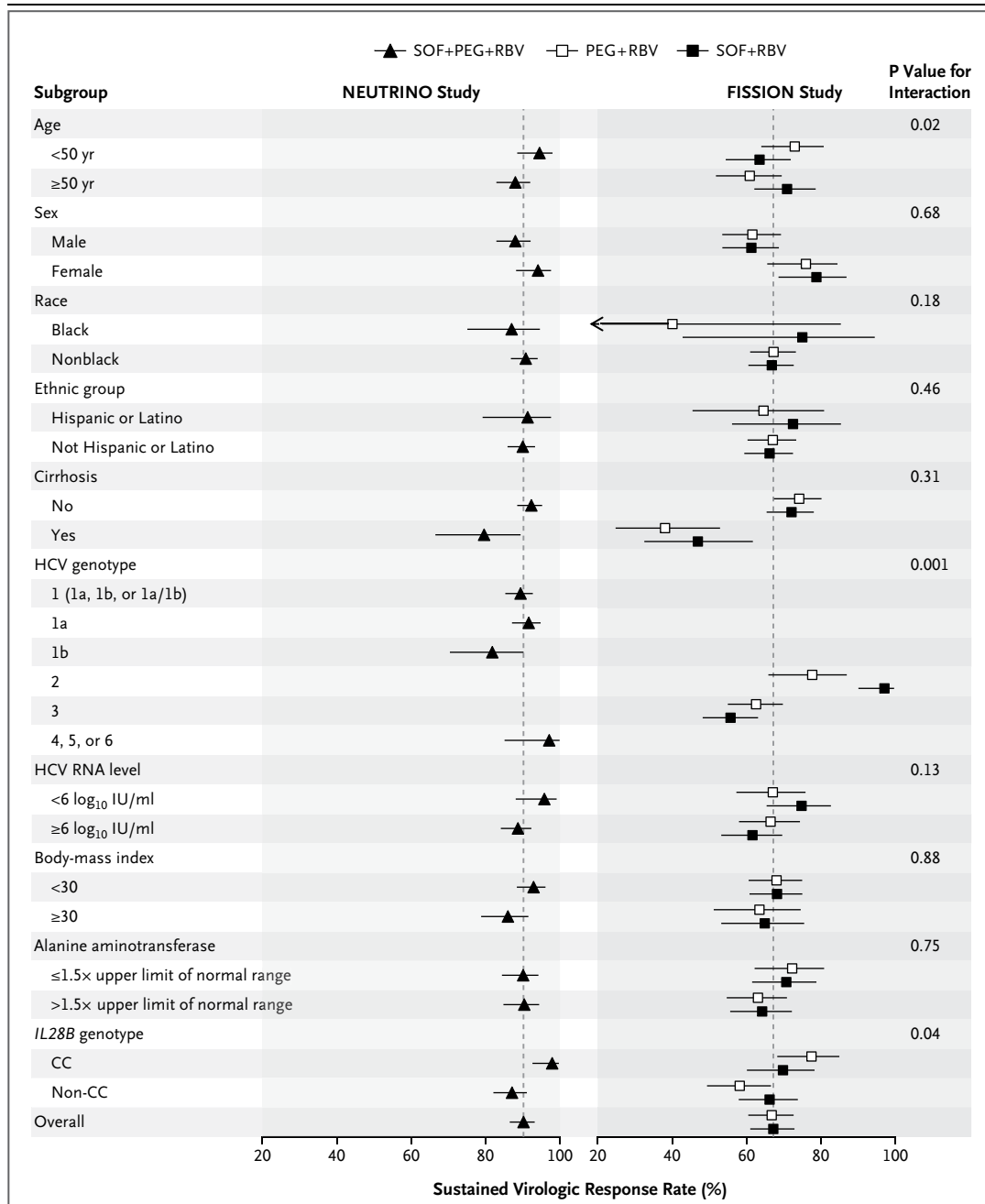


Figure 1. Rates of Sustained Virologic Response in the NEUTRINO and FISSION Studies, According to Subgroup and Baseline Factors.

The position of each triangle or square indicates the rate of sustained virologic response 12 weeks after the end of treatment, which consisted of sofosbuvir plus peginterferon alfa-2a and ribavirin (SOF+PEG+RBV) for all patients in the single-group NEUTRINO study and either peginterferon alfa-2a plus ribavirin (PEG+RBV) or sofosbuvir plus ribavirin (SOF+RBV) in the randomized FISSION study. The horizontal lines indicate 95% confidence intervals. The vertical dotted lines represent the overall rates of sustained virologic response for the sofosbuvir groups. Arrows indicate confidence intervals that exceed the x-axis scale. Race and ethnic group were self-reported. The body-mass index is the weight in kilograms divided by the square of the height in meters. Other analyses of responses according to subgroup are provided in Tables S3 through S8 and Figure S3 in the Supplementary Appendix.

Table 3. Adverse Events, Discontinuation of Treatment, and Hematologic Abnormalities.*

Event	NEUTRINO Study		FISSION Study	
	SOF+PEG+RBV for 12 Weeks (N=327)	SOF+RBV for 12 Wk (N=256)	PEG+RBV for 24 Wk (N=243)	
Mean duration of treatment — wk	12±1	12±2	21±6	
Discontinuation because of an adverse event — no. (%)	5 (2)	3 (1)	26 (11)	
Any serious adverse event during treatment — no. (%)	4 (1)	7 (3)	3 (1)	
Any adverse event during treatment — no. (%)	310 (95)	220 (86)	233 (96)	
Common adverse events — no. (%)†				
Fatigue	192 (59)	92 (36)	134 (55)	
Headache	118 (36)	64 (25)	108 (44)	
Nausea	112 (34)	46 (18)	70 (29)	
Insomnia	81 (25)	31 (12)	70 (29)	
Anemia	68 (21)	20 (8)	28 (12)	
Decreased appetite	58 (18)	17 (7)	44 (18)	
Influenza-like illness	51 (16)	7 (3)	44 (18)	
Chills	54 (17)	7 (3)	43 (18)	
Pyrexia	58 (18)	6 (2)	33 (14)	
Rash	59 (18)	23 (9)	43 (18)	
Diarrhea	38 (12)	23 (9)	42 (17)	
Pruritus	54 (17)	19 (7)	42 (17)	
Myalgia	45 (14)	21 (8)	40 (16)	
Irritability	42 (13)	25 (10)	40 (16)	
Neutropenia	54 (17)	0	30 (12)	
Hematologic event — no. (%)‡				
Decreased hemoglobin level				
<10 g/dl	74 (23)	23 (9)	35 (14)	
<8.5 g/dl	8 (2)	1 (<1)	4 (2)	
Decreased lymphocyte count				
350 to 500/mm ³	17 (5)	0	15 (6)	
<350/mm ³	0	0	12 (5)	
Decreased neutrophil count				
500 to 750/mm ³	49 (15)	0	30 (12)	
<500/mm ³	17 (5)	0	6 (2)	
Platelet count <50,000/mm ³	1 (<1)	0	18 (7)	
Decreased white-cell count				
1000 to 1500/mm ³	18 (6)	0	10 (4)	
<1000/mm ³	0	0	1 (<1)	

* Plus–minus values are means ±SD.

† The listed events were reported in at least 15% of patients in any study group in either study.

‡ Hematologic events were evaluated in 254 patients in the SOF+RBV group and 242 in the PEG+RBV group in the FISSION study.

Hematologic abnormalities were more common among patients in the peginterferon–ribavirin group than among those in the sofosbuvir–ribavirin group (Table 3). Among patients receiving sofosbuvir–ribavirin, 9% of patients had a hemoglobin level of less than 10 g per deciliter and under 1% of patients had a level of less than 8.5 g per deciliter, as compared with 14% and 2% of patients, respectively, who received peginterferon–ribavirin for 24 weeks. Likewise, among patients

receiving peginterferon–ribavirin, 12% of patients had a neutrophil count of 500 to 750 per cubic millimeter and 2% had a count of less than 500 per cubic millimeter, whereas no patients in the sofosbuvir–ribavirin had such reductions. Similarly, rates of decreased lymphocyte, platelet, and white-cell counts ranged from 1 to 7% among patients receiving peginterferon–ribavirin, whereas no patients receiving sofosbuvir–ribavirin had decreases in these measures (Table 3).

DISCUSSION

In our open-label, single-group study of sofosbuvir, peginterferon, and ribavirin in previously untreated patients with HCV infection, most of whom had genotype 1 or 4 infection, 90% of patients receiving treatment had a sustained virologic response at 12 weeks (the primary end point). In our open-label, randomized trial of previously untreated patients with genotype 2 or 3 infection, the rate of sustained virologic response at 12 weeks was the same among patients who were assigned to receive 12 weeks of sofosbuvir–ribavirin and those assigned to receive 24 weeks of peginterferon–ribavirin (67% in each group).

In the FISSION study, among patients receiving sofosbuvir–ribavirin, response rates were lower among patients with genotype 3 infection than among those with genotype 2 infection (56% vs. 97%) and were lower for patients with cirrhosis than for those without cirrhosis (47% vs. 72%). The 67% response rate we observed in this phase 3 trial was lower than the 100% rate observed in a smaller phase 2 trial involving patients with genotype 2 or 3 infection who received the same drug regimen. High rates of sustained virologic response were observed among patients who have historically been less likely to have a sustained response, including black patients and those with the unfavorable *IL28B* CT/TT genotypes.

In the NEUTRINO study, the 81% response rate for patients with genotype 1 infection who had cirrhosis was lower than that observed for patients without cirrhosis, but to our knowledge, it is still the highest rate that has been reported to date for this population.¹⁹ High rates of sustained virologic response were observed among patients with genotype 1a infection and those with genotype 1b infection. The study populations in these trials included substantial propor-

tions of patients with characteristics that have historically been associated with lower rates of response to treatment, including cirrhosis, a high baseline viral load, black race, and a non-CC *IL28B* genotype. Since virologic suppression was achieved by week 4 in almost all patients and was maintained until the end of treatment, response-guided treatment was not required.

In the randomized trial, sofosbuvir–ribavirin was associated with fewer adverse events than peginterferon–ribavirin. Influenza-like constitutional symptoms and neuropsychiatric events were less common among patients receiving sofosbuvir–ribavirin than among those receiving peginterferon–ribavirin. Although the rates of anemia among patients receiving sofosbuvir–ribavirin and those receiving peginterferon–ribavirin were similar, neutropenia and thrombocytopenia were not observed in the sofosbuvir–ribavirin group. Furthermore, patients with genotype 1, 4, 5, or 6 infection who received 12 weeks of sofosbuvir and ribavirin combined with peginterferon had a very low rate of treatment discontinuation (2%), as compared with historical rates among patients receiving interferon-containing regimens for a longer period.^{9,20} In the subgroup of patients with cirrhosis, 1 of 54 discontinued treatment. This observation is particularly important for patients with genotype 1 infection and cirrhosis, who often have unacceptable adverse events with the recommended regimen of 48 weeks of peginterferon–ribavirin in combination with first-generation oral protease inhibitors. Although no data from randomized comparisons are available, findings from our single-group study of sofosbuvir plus peginterferon–ribavirin suggest that adverse events associated with this regimen are similar to those associated with peginterferon–ribavirin alone.

We did not detect the S282T mutation (the only variant known to be associated with resistance to sofosbuvir) on deep-sequencing assays in any patient receiving sofosbuvir. The absence of detectable resistance to sofosbuvir is in sharp contrast to the rapid emergence of viral resistance that has been observed with other classes of direct-acting anti-HCV agents in patients who had virologic breakthrough during treatment or relapse after the completion of therapy.¹² For patients who did not have a sustained virologic response to sofosbuvir, the precise reasons for relapse despite the very high rates of viral sup-

pression early in the course of treatment with sofosbuvir remain unclear. However, the lack of documented resistance to sofosbuvir provides a rationale for studying retreatment with sofosbuvir-containing regimens in such patients in the future.

In the open-label, single-group study, 12 weeks of treatment with sofosbuvir plus peginterferon-ribavirin had high efficacy in previously untreated patients with genotype 1 or 4 infection, with apparent reductions in adverse events. In the randomized trial of previously untreated patients with genotype 2 or 3 infection, the efficacy of the all-oral regimen of sofosbuvir plus ribavirin was similar to that of peginterferon-ribavirin, but response rates among patients with genotype 3 infection were lower than the rates among those

with genotype 2 infection. It is possible that response rates in patients with genotype 3 infection can be improved by adding peginterferon to sofosbuvir and ribavirin or by extending the duration of treatment with sofosbuvir and ribavirin.

Supported by Gilead Sciences.

Presented in part at the Annual Meeting of the European Association for the Study of the Liver, Amsterdam, April 24–28, 2013.

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

We thank the patients and their families, as well as the following employees of Gilead Sciences: Juan Betular and Kitty Yale for study conduct, Hongmei Mo and Evgenia Svarovskaia for resistance analysis, Neby Bekele and Julie Ma for statistical analyses, Brian Kearney for study-team leadership, and David McNeil for medical writing support.

APPENDIX

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