Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options

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Abstract— Background: Patients chronically infected with hepatitis C virus (HCV) genotype 2 or 3 for whom treatment with peginterferon is not an option, or who have not had a response to prior interferon treatment, currently have no approved treatment options. In phase 2 trials, regimens including the oral nucleotide polymerase inhibitor sofosbuvir have shown efficacy in patients with HCV genotype 2 or 3 infection.

Methods: We conducted two randomized, phase 3 studies involving patients with chronic HCV genotype 2 or 3 infection. In one trial, patients for whom treatment with peginterferon was not an option received oral sofosbuvir and ribavirin (207 patients) or matching placebo (71) for 12 weeks. In a second trial, patients who had not had a response to prior interferon therapy received sofosbuvir and ribavirin for 12 weeks (103 patients) or 16 weeks (98). The primary end point was a sustained virologic response at 12 weeks after therapy.

Results: Among patients for whom treatment with peginterferon was not an option, the rate of a sustained virologic response was 78% (95% confidence interval [CI], 72 to 83) with sofosbuvir and ribavirin, as compared with 0% with placebo (P<0.001). Among previously treated patients, the rate of response was 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (difference, -23 percentage points; 95% CI, -35 to -11; P<0.001). In both studies, response rates were lower among patients with genotype 3 infection than among those with genotype 2 infection and, among patients with genotype 3 infection, lower among those with cirrhosis than among those without cirrhosis. The most common adverse events were headache, fatigue, nausea, and insomnia; the overall rate of discontinuation of sofosbuvir was low (1 to 2%).

Conclusions: In patients with HCV genotype 2 or 3 infection for whom treatment with peginterferon and ribavirin was not an option, 12 or 16 weeks of treatment with sofosbuvir and ribavirin was effective. Efficacy was increased among patients with HCV genotype 2 infection and those without cirrhosis. In previously treated patients with genotype 3 infection, 16 weeks of therapy was significantly more effective than 12 weeks. (Funded by Gilead Sciences; POSITRON and FUSION ClinicalTrials.gov numbers, NCT01542788 and NCT01604850, respectively.)

Index Terms— Sofosbuvir, Chronic HCV, Genotype 2 or 3, peginterferon, therpay, chronically infected

1 INTRODUCTION:

When studied in clinical trials the current standard patients with hepatitis C virus (HCV) -of-care therapy for, genotype 2 or 3 infection — pegylated interferon in combination with ribavirin for 24 weeks — resulted in a sustained virologic response in 70 to 85% of patients who had not received prior treatment and in 55 to 60% of those who had received treatment.1-4 However, a substantial proportion of patients with HCV infection remain untreated owing to absolute or relative contraindications to interferon therapy, such as hepatic decompensation, autoimmune disease, and psychiatric illness.5 In addition, interferon causes a range of constitutional symptoms or hematologic abnormalities that may require discontinuation of therapy in a considerable number of patients.6 Some patients decide against interferon therapy for a variety of reasons, including aversion to injections and anxiety about the adverse events associated with treatment.

Moreover, the 15 to 30% of patients with HCV genotype 2 or 3 infection who do not have a response to interferon therapy have no alternate therapeutic options. These populations — which by one estimate constitute the majority of patients infected with HCV5 — are in need of effective treatments.

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase with in vitro activity against all HCV genotypes.7 In phase 2 study of treatment for 12 weeks with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 infection, 10 of 10 previously untreated patients (100%) and 17 of 25 previously treated patients (68%) had a sustained virologic response.8,9 This oral regimen had an acceptable safety profile, with no premature discontinuations of sofosbuvir therapy owing to adverse events.9 In this article, we present the results of two phase 3 trials of treatment with sofosbuvir and ribavirin in patients with HCV genotype 2 or 3 infection for whom treatment with peginterferon was not an option and in those who did not have a response to prior interferon treatment. The primary objective of both studies was to evaluate the efficacy of sofosbuvir and ribavirin, as

measured by the proportion of patients with a sustained virologic response at 12 weeks after the end of treatment, and to evaluate the safety of this regimen.

2 METHODS

STUDY DESIGNS AND PATIENTS

We conducted two multicenter, randomized trials to assess the efficacy and safety of sofosbuvir
administered with ribavirin in patients chronically infected with HCV genotype 2 or 3. In both
studies, patients received sofosbuvir (Gilead Sciences) and ribavirin (Ribasphere, Kadmon) or
matching placebo. Sofosbuvir was administered orally at a dose of 400 mg once daily. Ribavirin
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 POSITRON trial was a blinded, placebocontrolled study that compared 12 weeks of treatment with sofosbuvir and ribavirin with matching placebo in patients who had previously
discontinued interferon therapy owing to unacceptable adverse events, who had a concurrent
medical condition precluding therapy with an interferon-containing regimen, or who had decided against treatment with an interferon-containing regimen (see the Supplementary Appendix, available with the full text of this article at NEJM.org, for further details). Prior treatment failure with an interferon-based regimen was not a reason for exclusion. Approximately 20% of patients enrolled could have evidence of compensated cirrhosis at screening. Patients were enrolled at 63 sites in the United States, Canada, Australia, and New Zealand from March 2012 through May 2012. Randomization was performed centrally in a 3:1 ratio with stratification according to the presence or absence of cirrhosis.

The FUSION study was a blinded, active-control study involving patients who had not had a response to prior treatment with an interferoncontaining regimen. Approximately 30% of the patients enrolled could have evidence of compensated cirrhosis at screening. Patients were enrolled at 67 sites in the United States, Canada, and New Zealand from May 2012 through July 2012. Patients were randomly assigned in a 1:1 ratio to one of two treatment groups: 12 weeks of sofosbuvir and ribavirin, followed by 4 weeks of matching placebo, or 16 weeks of sofosbuvir and ribavirin. Random ization was stratified according to the presence or absence of cirrhosis and HCV genotype 2 or 3 infection. Full eligibility criteria for both trials, including details of the assessment of cirrhosis, are provided in the Supplementary Appendix.

3 STUDY ASSESSMENTS

Screening assessments included measurement of the serum HCV RNA level and IL28B genotyping in addition to standard laboratory and clinical tests. The HCV RNA level was measured with the 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. HCV genotype and subtype were determined with the use of the Siemens Versant HCV Genotype 2.0 Assay. Status with respect to the gene encoding interleukin 28B [IL28B], an indicator of the response to HCV therapy, was determined by means of polymerase-chainreaction amplification and sequencing of the rs12979860 single-nucleotide polymorphism.10 Assessments during treatment included standard laboratory testing, measurement of serum HCV RNA level, assessment of vital signs, and symptom-directed physical examinations. All adverse events were recorded and graded according to a standardized scale.

Patients with virologic failure (see the Supplementary Appendix for the definition) underwent resistance testing. 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 (Rijswijk, the Netherlands) performed NS5B amplification and population sequencing, and WuXi Apptec (Shanghai, China) performed deep-sequencing assays to characterize virologic resistance.

4 STUDY OVERSIGHT

Both studies were approved by the institutional review board or independent ethics committee at each participating site and were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. They were

designed and conducted according to their respective protocols by the sponsor (Gilead Sciences) in collaboration with the principal investigators. The sponsor collected the data, monitored study conduct, and performed the statistical analyses. An independent data and safety monitoring committee reviewed the progress of both studies. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data.

All the authors had access to the data, 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 the sponsor and a professional writer, who is an employee of the sponsor, with input from all the authors. The decision to submit the manuscript for publication was made by all the authors.

5 Statistical Analysis

For the POSITRON study, we calculated that a sample of 180 patients in the sofosbuvir group and 60 in the placebo group would provide 99% power to detect a between-group difference in the rate of a sustained virologic response of 40% with the use of a two-sided continuity-corrected chi-square test at a significance level of 0.05. For the FUSION study, we calculated that a sample of 100 patients in each group would provide more than 97% power to detect an improvement of at least 20% in the rate of a sustained virologic response, as compared with a historical control rate of 25%, and would provide 82% power to detect a difference of 20% in response rates between the 12-week and 16-week treatment groups (see the Supplementary Appendix for a fuller explanation of the calculation of the historical control rate).

In a secondary analysis that was performed with the use of a Cochran–Mantel–Haenszel test according to the stratification factors at randomization, we compared differences in the rates of

a sustained virologic response at 12 and 16 weeks of treatment in the FUSION study. The modified intention-to-treat analyses included data from all patients who underwent randomization and received at least one dose of study medication.

Multivariable logistic-regression analyses involving baseline demographic and clinical characteristics were performed, and a stepwise procedure was used to identify indepen dent predictors of a sustained virologic response (Tables S5, S6, and S9 through S12 in the Supplementary Appendix).

6 Results

Baseline Characteristics

A total of 410 patients with HCV genotype 2 or 3 infection for whom interferon treatment was not an option were initially screened for the POSITRON trial. Of these patients, 280 underwent randomization, and 278 began treatment (Fig. S1 in the Supplementary Appendix). A total of 277 patients who had received prior treatment for HCV genotype 2 or 3 infection were initially screened for the FUSION study; 202 underwent randomization, and 201 began treatment (Fig. S2 in the Supple mentary Appendix). The demographic and baseline clinical characteristics were balanced between the two groups in each study.

In the POSITRON trial, the distribution of patients on the basis of the classification that interferon therapy was not an option (contraindication, unacceptable side effects, or patient's decision) was similar between the treatment and placebo groups (Table 1). The most common reasons that interferon treatment was not an option were clinically significant psychiatric disorders (in 57% of patients) and autoimmune disorders (in 19%) (Fig. S3 in the Supplementary Appendix).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Two Studies.*

Characteristic	Interferon Treatment Not an Option		Prior Interferon Treatment	
	Placebo (N=71)	12 Wk of Sofosbuvir–Ribavirin (N=207)	12 Wk of Sofosbuvir–Ribavirin (N=103)	16 Wk of Sofosbuvir–Ribavirin (N=98)
Age — yr				
Mean	52	52	54	54
Range	28–67	21–75	30–69	24–70
Body-mass index†				
Mean	28	28	28	29
Range	20–43	18–53	19–43	20–44
Male sex — no. (%)	34 (48)	117 (57)	73 (71)	67 (68)
Race or ethnic group — no. (%)‡				
White	66 (93)	188 (91)	88 (85)	86 (88)
Black	4 (6)	9 (4)	5 (5)	1 (1)
Asian	1 (1)	7 (3)	7 (7)	5 (5)
Other	0	3 (1)	3 (3)	6 (6)
Hispanic or Latino				
Yes	11 (15)	19 (9)	10 (10)	8 (8)
No	60 (85)	188 (91)	93 (90)	89 (91)
HCV genotype — no. (%)				
1§	0	0	3 (3)	3 (3)
2	34 (48)	109 (53)	36 (35)	32 (33)
3	37 (52)	98 (47)	64 (62)	63 (64)
HCV RNA				
Mean — $\log_{10}$ IU/ml	6.3±0.76	6.3±0.77	6.5±0.67	6.5±0.63
≥800,000 IU/ml — no. (%)	55 (77)	150 (72)	80 (78)	77 (79)
IL28B genotype — no. (%)				
CC	29 (41)	97 (47)	31 (30)	30 (31)
CT	36 (51)	84 (41)	53 (51)	56 (57)
TT	6 (8)	26 (13)	19 (18)	12 (12)

Table 1. (Continued.)

Characteristic	Interferon Treatment Not an Option		Prior Interferon Treatment	
	Placebo (N=71)	12 Wk of Sofosbuvir–Ribavirin (N=207)	12 Wk of Sofosbuvir–Ribavirin (N=103)	16 Wk of Sofosbuvir–Ribavirin (N=98)
Cirrhosis — no. (%)	13 (18)	31 (15)	36 (35)	32 (33)
Baseline ALT >1.5× ULN — no. (%)	42 (59)	117 (57)	63 (61)	56 (57)
Interferon classification — no. (%)				
Contraindication¶	33 (46)	88 (43)	—	—
Unacceptable side effects‖	8 (11)	17 (8)	—	—
Patient's decision	30 (42)	102 (49)	—	—
Response to previous treatment — no. (%)				
Nonresponse	2 (3)	2 (1)	25 (24)	25 (26)
Relapse	4 (6)	11 (5)	78 (76)	73 (74)

* No significant differences were found between the groups in either study. ALT denotes alanine aminotransferase, HCV hepatitis C virus, and ULN upper limit of the normal range.

† 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. One patient declined to report ethnic group.

§ These patients, who were found to have genotype 1 infection by deep sequencing after randomization, were excluded from the efficacy analysis but not from the safety analyses.

Common contraindications for interferon treatment included psychiatric disorders (in 57% of patients) and autoimmune disorders (in 19%).

‖ Common unacceptable side effects with interferon treatment included influenza-like symptoms (in 32% of patients), psychiatric disorders (in 20%), thrombocytopenia (in 16%), and local or systemic adverse reactions (in 12%). See Figures S3 and S4 in the Supplementary Appendix for details.

Approximately 75% of the previously treated patients enrolled in the FUSION trial had either virologic breakthrough during the prior treatment or virologic relapse afterward; the remainder did not have a response. A total of 16% of the patients in the POSITRON study and 34% of

those in the FUSION study had cirrhosis. A higher percentage of patients with HCV genotype 3 infection were enrolled in the FUSION study (63% of patients) than in the POSITRON

study (49%).

7 Efficacy

Overall Population

Treatment with sofosbuvir and ribavirin resulted in a rapid decline in circulating HCV RNA levels, with similar reductions in the two studies and among patients with HCV genotype 2 or 3 infection. By week 2 of treatment, 81 to 91% of patients in the sofosbuvir groups had an HCV RNA level that was less than the lower limit of quantification. By week 4, the rates of virologic suppression were 97 to 99%, and at the end of treatment, no patient who could be evaluated had an HCV RNA level that was higher than the lower limit of quantification (Table 2). Among the 402 patients receiving sofosbuvir in these studies, none had virologic breakthrough during treatment, and thus all treatment failures involved virologic relapse after the cessation of therapy.

POSITRON Trial In the population of patients for whom interferon treatment was not an option, the rate of sustained virologic response at 12 weeks after treatment was 78% (95% confidence interval [CI], 72 to 83) among patients receiving sofosbuvir and ribavirin, as compared with 0% among those receiving placebo (P<0.001) (Table 2). There was complete concordance (100%) between rates of sustained virologic response at 12 weeks and at 24 weeks among patients who received sofosbuvir and ribavirin, with none of the 153 patients who could be evaluated having virologic relapse after week 12.

Rates of sustained virologic response in patient subgroups are shown in Figure 1 and in

Tables S3 and S4 in the Supplementary Appendix.

Table 2. Response during and after Treatment in the Two Studies.

Response*	Interferon Treatment Not an Option		Prior Interferon Treatment	
	Placebo (N=71)	12 Wk of Sofosbuvir–Ribavirin (N=207)	12 Wk of Sofosbuvir–Ribavirin (N=100)	16 Wk of Sofosbuvir–Ribavirin (N=95)
HCV RNA <25 IU/ml — no./total no. (%)				
During treatment				
Wk 2	0/70	186/205 (91)	81/100 (81)	83/95 (87)
Wk 4	0/70	202/204 (99)	97/100 (97)	93/95 (98)
Wk 12	0/71	202/202 (100)	100/100 (100)	95/95 (100)
After treatment				
Wk 4	0/68	172/207 (83)	56/100 (56)	73/95 (77)
Wk 12	0/68	161/207 (78)†	50/100 (50)	69/95 (73)
Virologic breakthrough during treatment — no.	—	0	0	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no./total no. (%)				
Patients who completed treatment	—	40/201 (20)	46/99 (46)	26/95 (27)
Patients who did not complete treatment	—	2/4 (50)	1/1 (100)	0

* Data are for patients for whom HCV RNA results were available. An HCV RNA level of 25 IU per milliliter was the

lower
limit of quantification.
† None of the 153 patients who could be evaluated had a relapse after a sustained virologic response at 12 weeks.

Logistic-regression analysis showed that HCV genotype 3 infection was significantly associated with reduced rates of sustained virologic response, as compared with HCV genotype 2 infection (Table S6 in the Supplementary Appendix). Among patients who received sofosbuvir and ribavirin, 93% of patients with HCV genotype 2 infection had a sustained virologic response, as compared with 61% of those with HCV genotype 3 infection. Likewise, 81% of patients without cirrhosis (92% of patients with HCV genotype 2 infection and 68% of those with HCV genotype 3 infection) had a sustained virologic response, as compared with 61% of patients with cirrhosis (94% of patients with HCV genotype 2 infection and 21% of those with HCV genotype 3 nfection).

8 FUSION TRIAL

The rates of sustained virologic response achieved with sofosbuvir and ribavirin in the population of patients with prior treatment were superior to the historical control rate of 25%, with rates of 50% (95% CI, 40 to 60) in the 12-week group and 73% (95% CI, 63 to 81) in the 16-week group (P<0.001 for each comparison). The secondary analysis comparing rates of sustained virologic response between the groups showed that patients receiving 16 weeks of treatment had a significantly higher rate of sustained virologic response than patients receiving 12 weeks of treatment (difference, −23 percentage points; 95% CI, −35 to −11; P<0.001) (Fig. 1).
The rates of sustained virologic response in various patient subgroups are shown in Figure 1and in Tables S7 and S8 in the Supplementary Appendix. Multivariate logistic-regression modeling was performed independently for each treatment group to investigate predefined covariate effects.

HCV genotype 3 infection, as compared with genotype 2 infection, was significantly associated with a lower response rate with both 12 and 16 weeks of treatment (Tables S10 and S12 in the Supplementary Appendix). The rates of sustained virologic response among patients with HCV genotype 2 infection who received 12 weeks of treatment and those who received 16 weeks of treatment were 86% and 94%, respectively (difference, −8 percentage points; 95% CI, −24 to 9), as compared with 30% and 62% for 12 and 16 weeks of treatment, respectively, among patients with HCV genotype 3 infection (difference, −32 percentage points; 95% CI, −48 to −15).

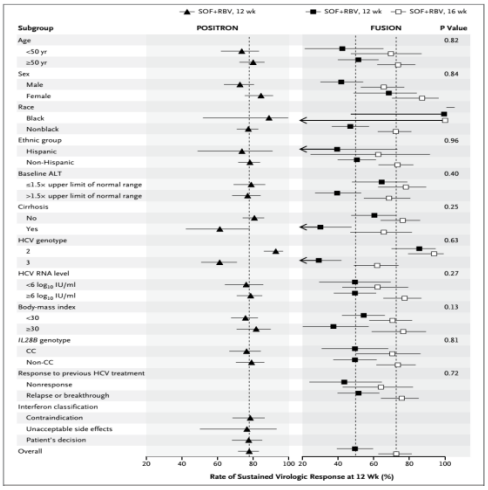

Figure 1. Rates of Sustained Virologic Response, According to Demographic and Baseline Clinical Characteristics
in Both Studies.

The position of each symbol indicates the rate of sustained virologic response 12 weeks after the end of treatment for each prespecified subgroup; the horizontal lines indicate 95% confidence intervals. The vertical dashed lines represent the overall rates of sustained virologic response for the sofosbuvir treatment 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. The P values shown are for the interactions between
treatment durations and subgroups in the FUSION study. There were not enough black patients in the study for the calculation of an interaction P value. For confidence intervals of response rates, see Tables S3 and S7 in the Supplementary Appendix. ALT denotes alanine aminotransferase, HCV hepatitis C virus, RBV ribavirin, and SOF sofosbuvir.

Cirrhosis was associated with a decreased rate of sustained virologic response, particularly among patients with HCV genotype 3 infection who received 12 weeks of treatment. Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with

HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared with 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared with 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection).

9 Virologic Resistance Testing

No patient receiving sofosbuvir in either study had virologic breakthrough during treatment or failed to have a response to treatment. Among the 42 patients in the POSITRON study and the 73 patients in the FUSION study who had a relapse after the end of treatment, sequencing analysis of samples collected at time of relapse showed no resistance-associated variants (see the Supplementary Appendix).

10 Safety

Premature discontinuation of the study drug due to adverse events was uncommon in all groups:
in the FUSION study, one patient in the 12-week group discontinued treatment during the 4-week placebo phase of dosing; in the POSITRON study, four patients who received sofosbuvir and ribavirin (2%) discontinued treatment, as compared with three who received placebo (4%). The rates of serious adverse events in the POSITRON trial were 5% in the group that received sofosbuvir and ribavirin and 3% in the placebo group; in the FUSION study, the rates were 5% in the 12-week group and 3% in the 16-week group (Table 3, and Tables S17 and S18 in the Supplementary Appendix).

In the POSITRON study, the differences in adverse events between the placebo and activetreatment groups included higher rates of fatigue and insomnia among patients receiving sofosbuvir and ribavirin (Table 3, and Table S15 in the Supplementary Appendix). As expected, the incidence of anemia was higher among patients receiving ofosbuvir and ribavirin than among patients receiving placebo (Fig. S7 and S9 in the Supplementary Appendix).11 Otherwise, the rates of laboratory abnormalities, including whitecell, neutrophil, and platelet counts, did not differ significantly between the two groups. The incidences of adverse events and laboratory abnormalities among patients with cirrhosis who received sofosbuvir and ribavirin were similar to those among patients without cirrhosis (Table S19 in the Supplementary Appendix).

In addition, the overall safety profile in patients receiving 16 weeks of therapy was similar to that observed in patients receiving 12 weeks of therapy (Table 3).

11 Discussion

In these phase 3 studies, 12 or 16 weeks of treatment with sofosbuvir and ribavirin resulted in a sustained virologic response in 78% of patients for whom interferon treatment was not an option and in 50 to 73% of patients with prior treatment failure. High response rates were observed among patients with HCV genotype 2 infection in all patient subgroups in both studies. Response rates among patients with HCV genotype 3 infection were lower than the rates among those with HCV genotype 2 infection, especially in the subgroup of patients with cirrhosis.
Extending the duration of treatment from 12 to 16 weeks in patients with prior treatment failure significantly increased the rates of sustained virologic response among patients with HCV genotype 3 infection and among patients with cirrhosis by decreasing the rate of relapse. Relapse accounted for all treatment failures in both studies. No virologic resistance was detected in patients who did not have a sustained virologic response. An explanation for the lower rates of sustained virologic response among patients with HCV genotype 3 infection, as compared with those who had HCV genotype 2 infection — a difference that has also been observed among patients treated with peginterferon and ribavirin12 — remains unclear. Although virologic declines during treatment are similar with the two genotypes, the lower rates of relapse among patients with HCV genotype 2 infection indicate that virologic clearance is likely to be slower in
some patients with HCV genotype 3 infection.

Sofosbuvir for Hepatitis C Genotype 2 or 3

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

Variable	Interferon Treatment Not an Option		Prior Interferon Treatment	
	Placebo (N=71)	12 Wk of Sofosbuvir–Ribavirin (N=207)	12 Wk of Sofosbuvir–Ribavirin (N=103)	16 Wk of Sofosbuvir–Ribavirin (N=98)
Mean duration of treatment — wk	12±1.3	12±1.6	12±0.6	16±0.2
Discontinuation of treatment due to adverse event — no. (%)	3 (4)	4 (2)	1 (1)	0
Serious adverse event — no. (%)	2 (3)	11 (5)	5 (5)	3 (3)
Common adverse events — no. (%)†				
Fatigue	17 (24)	91 (44)	46 (45)	46 (47)
Nausea	13 (18)	46 (22)	22 (21)	20 (20)
Headache	14 (20)	43 (21)	26 (25)	32 (33)
Insomnia	3 (4)	39 (19)	21 (20)	28 (29)
Pruritus	6 (8)	23 (11)	12 (12)	7 (7)
Anemia	0	27 (13)	11 (11)	4 (4)
Irritability	1 (1)	19 (9)	15 (15)	11 (11)
Cough	2 (3)	11 (5)	10 (10)	13 (13)
Diarrhea	4 (6)	19 (9)	15 (15)	6 (6)
Rash	6 (8)	18 (9)	7 (7)	12 (12)
Arthralgia	1 (1)	16 (8)	11 (11)	9 (9)
Hematologic event — no. (%)				
Decreased hemoglobin concentration				
<10.0 g/dl	0	15 (7)	10 (10)	5 (5)
<8.5 g/dl	0	2 (1)	2 (2)	0
Decreased lymphocyte count				
350 to <500/mm³	0	1 (<1)	4 (4)	0
<350/mm³	0	0	2 (2)	0
Decreased neutrophil count				
500 to <750/mm³	1 (1)	0	0	0
<500/mm³	0	0	1 (1)	0
Decreased white-cell count				
1000 to 1500/mm³	0	0	0	0
<1000/mm³	0	0	1 (1)	0
Decreased platelet count: 25,000 to <50,000/mm³	2 (3)	0	2 (2)	0

* Plus–minus values are means ±SD.
† Data shown are for adverse events occurring in at least 10% of patients in any group.

Thus, a longer period of virologic suppression may be required to eliminate residual viral reservoirs in patients with HCV genotype 3 infection. This is supported by the observation that prolonging the treatment duration by as short a period as 4 weeks significantly improved the rates of sustained virologic response among the patients with HCV genotype 3 infection in whom prior treatment had failed, especially among those with factors associated with a poor response, such as cirrhosis. Studies exploring 24 weeks of treatment with sofosbuvir plus ribavirin in pa tients with HCV genotype 3 infection will help determine whether response rates can be increased by extending the duration of treatment.

An alternative hypothesis is that patients with HCV genotype 3 infection may require additional immune modulation or more potent antiviral suppression to enhance virologic clearance with a shorter, 12-week duration of treatment. Thus, another possible approach to improving the response in patients with HCV genotype 3 infection is the addition of other direct-acting antiviral agents or peginterferon to the regimen. A study evaluating such a regimen, also now reported in the Journal, showed high rates of sustained virologic response among patients with HCV genotype 1, 4, 5, or 6 infection.13 On the basis of these findings, a combined regimen warrants exploration in future clinical trials involving patients with HCV genotype 3 infection. In both of our studies, the rate of premature discontinuation of treatment with sofosbuvir and ribavirin due to adverse events was low (1 to 2%) and was similar to the rate among patients receiving placebo in the POSITRON trial (4%). Whereas adverse events associated with ribavirin therapy — fatigue, insomnia, and anemia were higher in the groups that received sofosbuvir plus ribavirin, other common adverse events occurred at similar rates in the treatment and placebo groups.3,14 There were no notable differences in adverse events during treatment with sofosbuvir and ribavirin among patients receiving 16 weeks of treatment or among those with cirrhosis.

There are currently no effective treatment options for patients with HCV genotype 2 or 3 infection who do not have a sustained virologic response with the current standard of care of 24 weeks of treatment with peginterferon and ribavirin and for those who have medical contraindications to interferon therapy or decide against it. Our findings suggest that 12 weeks of treatment with sofosbuvir and ribavirin can be an effective option for patients with HCV genotype 2 infection. However, for patients with genotype 3 infection, particularly those who have cirrhosis or who have not had a response to prior treatment with interferon, extending the duration of treatment to 16 weeks may provide an additional benefit.

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