ORIGINAL ARTICLE

Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection

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ABSTRACT

BACKGROUND

In phase 2 trials, treatment with the combination of the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir resulted in high rates of sustained virologic response in patients chronically infected with hepatitis C virus (HCV) genotype 2 or 3.

METHODS

We conducted two randomized, phase 3, open-label studies involving patients who had received previous treatment for HCV genotype 2 or 3 and those who had not received such treatment, including patients with compensated cirrhosis. In one trial, patients with HCV genotype 2 were randomly assigned in a 1:1 ratio to receive sofosbuvir–velpatasvir, in a once-daily, fixed-dose combination tablet (134 patients), or sofosbuvir plus weight-based ribavirin (132 patients) for 12 weeks. In a second trial, patients with HCV genotype 3 were randomly assigned in a 1:1 ratio to receive sofosbuvir–velpatasvir for 12 weeks (277 patients) or sofosbuvir–ribavirin for 24 weeks (275 patients). The primary end point for the two trials was a sustained virologic response at 12 weeks after the end of therapy.

RESULTS

Among patients with HCV genotype 2, the rate of sustained virologic response in the sofosbuvir–velpatasvir group was 99% (95% confidence interval [CI], 96 to 100), which was superior to the rate of 94% (95% CI, 88 to 97) in the sofosbuvir–ribavirin group (P=0.02). Among patients with HCV genotype 3, the rate of sustained virologic response in the sofosbuvir–velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) in the sofosbuvir–ribavirin group (P<0.001). The most common adverse events in the two studies were fatigue, headache, nausea, and insomnia.

CONCLUSIONS

Among patients with HCV genotype 2 or 3 with or without previous treatment, including those with compensated cirrhosis, 12 weeks of treatment with sofosbuvir–velpatasvir resulted in rates of sustained virologic response that were superior to those with standard treatment with sofosbuvir–ribavirin. (Funded by Gilead Sciences; ASTRAL-2 ClinicalTrials.gov number, NCT02220998; and ASTRAL-3, NCT02201953.)

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*A complete list of investigators in the ASTRAL-2 and ASTRAL-3 trials is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on November 17, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1512612

Hepatitis C virus (HCV) genotypes 2 and 3 account for an estimated 35% of global HCV infections, affecting up to 58 million persons.[1,2] Unlike HCV genotype 1, genotypes 2 and 3 are common in low-income regions in Asia, sub-Saharan Africa, Latin America, and Eastern Europe.[1] Before the advent of direct-acting antiviral agents, HCV genotypes 2 and 3 were grouped together in treatment guidelines as "easy-to-treat" genotypes. However, recent studies have shown that HCV genotype 3 is associated with more rapid disease progression and lower rates of response to treatment than is HCV genotype 2, especially in patients with cirrhosis and those who have not had a response to previous treatment.[3,4] The current standard treatment is 12 to 20 weeks of sofosbuvir–ribavirin for patients with HCV genotype 2 and 24 weeks of sofosbuvir–ribavirin for patients with HCV genotype 3.[5,6] The inclusion of ribavirin, which has known hematologic and other toxic effects, as well as teratogenic effects, limits the use of this regimen, particularly among patients of childbearing age, those with heart disease, and those who live in regions where hemoglobinopathies are highly prevalent.[7] A simple, ribavirin-free regimen that would be effective across HCV genotypes might allow clinicians to dispense with pretreatment genotype testing and on-treatment monitoring, which would potentially allow for the expansion of access to treatment in low- and middle-income regions.

Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor that is approved for the treatment of HCV genotypes 2 and 3 in combination with ribavirin.[8] Velpatasvir (formerly GS-5816, Gilead Sciences) is a new NS5A inhibitor with antiviral activity against all HCV genotypes.[9-11] In phase 2 trials, 12 weeks of treatment with the combination of sofosbuvir and velpatasvir resulted in high rates of sustained virologic response in patients with HCV genotype 2 or 3.[12,13]

Here, we present the results of two randomized, controlled, phase 3 trials (ASTRAL-2 and ASTRAL-3) in which treatment with a fixed-dose combination tablet of sofosbuvir and velpatasvir for 12 weeks was compared with standard treatment with sofosbuvir plus ribavirin for 12 or 24 weeks in patients who had received prior treatment for HCV genotype 2 or 3 infection and in those who had not received such treatment, including those with compensated cirrhosis.

Methods

Patients

Eligibility criteria for the two trials were identical, except that the ASTRAL-2 trial enrolled patients with HCV genotype 2 and the ASTRAL-3 trial enrolled patients with HCV genotype 3. Eligible patients were 18 years of age or older and had at least a 6-month history of HCV infection. The two protocols specified that patients who did not have a sustained virologic response after previous treatment with an interferon-containing regimen could account for approximately 20% of the study population, although patients who discontinued previous therapy because of an adverse event were not eligible. The two studies had an intended enrollment of patients with compensated cirrhosis of approximately 20%, with the presence of compensated cirrhosis determined on liver biopsy showing cirrhosis (Metavir stage 4 or Ishak score of 5 or 6), a FibroTest score of more than 0.75 and a ratio of aspartate aminotransferase to platelets of more than 2, or a FibroScan result of more than 12.5 kPa. Patients with clinical evidence of hepatic decompensation (i.e., ascites, encephalopathy, or variceal hemorrhage) were excluded. There were no upper limits on age or body-mass index. All patients provided written informed consent. Full eligibility criteria are provided in the study protocol, available with the full text of this article at NEJM.org.

Study Oversight

The two 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. The studies were designed and conducted by the sponsor (Gilead Sciences) in collaboration with the principal investigators, according to the protocol. The sponsor collected the data, monitored study conduct, and performed the statistical analyses. Independent data and safety monitoring committees reviewed the progress of the studies. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors had access to the data and assumed responsibility for the integrity and completeness of the reported data. The initial draft

of the manuscript was prepared by a writer employed by Gilead Sciences and the primary investigators with input from all the authors. The studies were conducted and reported with fidelity to the study protocol.

STUDY DESIGNS

In the two multicenter trials, patients with chronic HCV infection were randomly assigned in a 1:1 ratio to receive a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir once daily for 12 weeks or 400 mg of sofosbuvir plus ribavirin (RibaSphere, Kadmon) for 12 weeks (for patients with HCV genotype 2) or 24 weeks (for patients with HCV genotype 3). 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). All investigators, patients, and trial personnel were aware of the treatment assignments at all points in the two trials.

In ASTRAL-2, patients were enrolled at 51 sites in the United States from October 15, 2014, through December 18, 2014. In ASTRAL-3, patients were enrolled at 76 sites in the United States, Canada, Europe (France, Germany, Italy, and the United Kingdom), Australia, and New Zealand from July 30, 2014, through December 17, 2014. In the two studies, randomization was stratified according to the presence or absence of cirrhosis at screening and status regarding previous treatment.

STUDY ASSESSMENTS

For the two trials, screening assessments included measurement of serum HCV RNA levels and *IL28B* genotyping in addition to standard laboratory and clinical testing. Serum HCV RNA was measured with the use of the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Molecular Systems), with a lower limit of quantification of 15 IU per milliliter. The HCV genotype and subtype were determined with the use of the VERSANT HCV Genotype 2.0 Assay (Siemens). For patients for whom genotyping data could not be provided with the VERSANT assay, the TRUGENE HCV 5′NC Genotyping Kit was used. If genotyping with the TRUGENE test was unsuccessful, NS5B sequencing was performed. *IL28B* genotyping was performed by means of polymerase-chain-reaction amplification and sequencing of the rs12979860 single-nucleotide polymorphism.

On-treatment assessments included standard laboratory testing, along with measurement of serum HCV RNA levels, recording of vital signs, electrocardiography, and symptom-directed physical examinations. All adverse events were recorded and graded according to a standardized scale. (Details are provided in the study protocol.)

Deep sequencing of the HCV NS5A and NS5B coding regions was performed on samples obtained from all patients at baseline and again for all patients with virologic failure. Sequences that were obtained at the time of virologic failure were compared with sequences from baseline samples to detect resistance-associated variants that emerged during treatment. We report resistance-associated variants that were present in more than 1% of the sequence reads.

PRIMARY END POINT

The primary efficacy end point for the two trials was a sustained virologic response, which was defined as an HCV RNA level of less than 15 IU per milliliter at 12 weeks after the end of treatment. All patients who underwent randomization and received at least one dose of a study drug were included in the analysis of the primary end point.

STATISTICAL ANALYSIS

We used the same statistical methods in the two studies. Efficacy and safety were assessed in all patients who underwent randomization and received at least one dose of a study drug.

In the two studies, the primary efficacy hypothesis was that the rate of sustained virologic response among patients receiving sofosbuvir–velpatasvir would be noninferior to that among patients receiving sofosbuvir–ribavirin, with a noninferiority margin of 10 percentage points. If the lower boundary of the 95% confidence interval for the strata-adjusted between-group difference in proportions was more than –10%, a two-sided stratified Cochran–Mantel–Haenszel test would be used to test for the superiority of sofosbuvir–velpatasvir over sofosbuvir–ribavirin at a significance level of 0.05.

For ASTRAL-2, we determined that enrollment of 120 patients in each treatment group would provide a power of 90% to establish noninferiority between the two groups on the basis

of a rate of sustained virologic response of 94%, with the use of a one-sided test at a significance level of 0.025. For ASTRAL-3, we determined that enrollment of 250 patients in each treatment group would provide a power of 94% to establish noninferiority between the two groups on the basis of a rate of sustained virologic response of 89%, with the use of a one-sided test at a significance level of 0.025. Point estimates and two-sided 95% exact confidence intervals that are based on the Clopper–Pearson method are provided for rates of sustained virologic response for all treatment groups, as well as selected subgroups.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 317 patients with HCV genotype 2 were initially screened for the ASTRAL-2 trial. Of these patients, 269 underwent randomization, and 266 began treatment (Table S1 and Fig. S1 in the Supplementary Appendix, available at NEJM.org). Most of the patients were white men and had a non-CC *IL28B* genotype (Table 1). (The non-CC genotype has been associated with a reduced response to HCV treatment.) A total of 14% of the patients had cirrhosis, and 14 to 15% had received unsuccessful treatment for HCV.

A total of 652 patients with HCV genotype 3 were initially screened for the ASTRAL-3 trial. Of these patients, 558 underwent randomization and 552 began treatment (Table S2 and Fig. S2 in the Supplementary Appendix). As in the ASTRAL-2 trial, most of the patients were white men with a non-CC *IL28B* genotype. However, a larger percentage of patients than in the ASTRAL-2 trial had cirrhosis (29 to 30%) and had undergone unsuccessful treatment (26%).

EFFICACY

ASTRAL-2 Trial

Among patients with HCV genotype 2, the rate of sustained virologic response at 12 weeks after treatment was 99% (95% confidence interval [CI], 96 to 100) among those who had received sofosbuvir–velpatasvir for 12 weeks, as compared with 94% (95% CI, 88 to 97) among those who had received sofosbuvir–ribavirin for 12 weeks (Table 2). Thus, the group of patients who had received sofosbuvir–velpatasvir met the primary end point with a rate of sustained virologic response that was significantly superior to that among patients who had received the standard treatment of sofosbuvir–ribavirin for 12 weeks, with a strata-adjusted absolute difference of 5.2 percentage points (95% CI, 0.2 to 10.3; P=0.02 with the Cochran–Mantel–Haenszel test stratified according to cirrhosis status and previous treatment).

There were no virologic failures among patients receiving sofosbuvir–velpatasvir. One 57-year-old black man discontinued study treatment on day 1 after receiving one dose of the study drug because of adverse events (as described in the Safety section). Of the 132 patients who received sofosbuvir–ribavirin, 6 (5%) had a virologic relapse after the end of treatment, and 2 other patients were lost to follow-up.

ASTRAL-3 Trial

Among patients with HCV genotype 3, the rate of sustained virologic response at 12 weeks after treatment was 95% (95% CI, 92 to 98) among those who had received sofosbuvir–velpatasvir for 12 weeks, as compared with 80% (95% CI, 75 to 85) among those who had received 24 weeks of sofosbuvir–ribavirin (Table 2). The sustained virologic response rate with 12 weeks of sofosbuvir–velpatasvir was significantly superior to that with 24 weeks of sofosbuvir–ribavirin. The strata-adjusted absolute difference was 14.8 percentage points (95% CI, 9.6 to 20.0; P<0.001 with the Cochran–Mantel–Haenszel test stratified according to cirrhosis status and previous treatment).

Among the 277 patients who received sofosbuvir–velpatasvir, 11 (4%) had virologic failure after the end of treatment, and 2 patients were lost to follow-up. Characteristics of the 11 patients in the sofosbuvir–velpatasvir group who had a relapse are provided in Table S4 in the Supplementary Appendix. Among the 275 patients who received sofosbuvir–ribavirin, 38 (14%) had a relapse after treatment, 1 had virologic failure during treatment, 6 were lost to follow-up, 4 discontinued treatment because of adverse events, 2 withdrew consent, 2 died, and 1 discontinued treatment before achieving undetectable HCV RNA.

The rates of sustained virologic response in various patient subgroups are shown in Table S3 in the Supplementary Appendix. Among patients who received sofosbuvir–velpatasvir, the rate of sustained virologic response was 91% among

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	HCV Genotype 2		HCV Genotype 3	
	Sofosbuvir–Velpatasvir for 12 Wk (N=134)	Sofosbuvir–Ribavirin for 12 Wk (N=132)	Sofosbuvir–Velpatasvir for 12 Wk (N=277)	Sofosbuvir–Ribavirin for 24 Wk (N=275)
Mean age (range) — yr	57 (26–81)	57 (23–76)	49 (21–76)	50 (19–74)
Male sex — no. (%)	86 (64)	72 (55)	170 (61)	174 (63)
Mean body-mass index (range)†	28 (17–45)	29 (19–61)	26 (17–48)	27 (17–56)
Race — no. (%)‡				
White	124 (93)	111 (84)	250 (90)	239 (87)
Black	6 (4)	12 (9)	3 (1)	1 (<1)
Asian	1 (1)	5 (4)	23 (8)	29 (11)
Other	3 (2)	4 (3)	1 (<1)	6 (2)
HCV RNA				
Mean — $\log_{10}$ IU/ml	6.5±0.78	6.4±0.74	6.2±0.72	6.3±0.71
≥800,000 IU/ml — no. (%)	111 (83)	101 (77)	191 (69)	194 (71)
IL28B genotype — no. (%)				
CC	55 (41)	46 (35)	105 (38)	111 (40)
CT	61 (46)	64 (48)	148 (53)	133 (48)
TT	18 (13)	22 (17)	24 (9)	31 (11)
Compensated cirrhosis — no. (%)	19 (14)	19 (14)	80 (29)	83 (30)
Previous HCV treatment — no. (%)				
No	115 (86)	112 (85)	206 (74)	204 (74)
Yes	19 (14)	20 (15)	71 (26)	71 (26)
Response to previous HCV treatment — no./total no. (%)				
No response	3/19 (16)	3/20 (15)	20/71 (28)	24/71 (34)
Relapse or breakthrough	16/19 (84)	17/20 (85)	51/71 (72)	47/71 (66)

* Plus–minus values are means ±SD. Patients with hepatitis C virus (HCV) genotype 2 were evaluated in the ASTRAL-2 trial, and those with genotype 3 in the ASTRAL-3 trial. There were no significant differences between the two groups.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was self-reported.

those with cirrhosis, as compared with 97% among those without cirrhosis. Among patients who received sofosbuvir–ribavirin, the rates of sustained virologic response among patients with and those without cirrhosis were 66% and 87%, respectively. A similar pattern of response was seen according to whether patients had received previous treatment. Among patients in the sofosbuvir–velpatasvir group, the rate of sustained virologic response was 90% among those who had received previous HCV treatment, as compared with 97% among those who had received no previous treatment. The corresponding rates among patients in the sofosbuvir–ribavirin group were 63% and 86%. The rate of sustained virologic response among patients who had received previous treatment and who had evidence of cirrhosis was 89% in the sofosbuvir–velpatasvir group as compared with 58% in the sofosbuvir–ribavirin group (Fig. 1). Sustained virologic response did not appear to be correlated with the *IL28B* genotype or early viral kinetics.

VIRAL RESISTANCE TESTING

In the ASTRAL-2 trial, deep sequencing indicated that approximately 60% of the 134 patients in the sofosbuvir–velpatasvir group had NS5A resistance-associated variants and 10% had NS5B resistance-associated variants at baseline. The most prevalent NS5A variant observed at base-

Table 2. Response during and after Treatment.

Response	HCV Genotype 2		HCV Genotype 3	
	Sofosbuvir–Velpatasvir for 12 Wk (N=134)	Sofosbuvir–Ribavirin for 12 Wk (N=132)	Sofosbuvir–Velpatasvir for 12 Wk (N=277)	Sofosbuvir–Ribavirin for 24 Wk (N=275)
HCV RNA <15 IU/ml — no. (%)				
During treatment period				
At 2 wk	76 (57)	79 (60)	171 (62)	137 (50)
At 4 wk	120 (90)	119 (90)	253 (91)	240 (87)
After end of treatment				
At 4 wk	133 (99)	127 (96)	268 (97)	225 (82)
At 12 wk*	133 (99)	124 (94)	264 (95)	221 (80)
95% CI at 12 wk	96–100	88–97	92–98	75–85
Virologic failure — no./total no. (%)				
On-treatment failure	0	0	0	1/275 (<1)
Relapse	0	6/132 (5)	11/276 (4)	38/272 (14)

* The primary efficacy end point was a sustained virologic response (HCV RNA level of <15 IU per milliliter) at 12 weeks after the end of treatment.

line was L31M in 52% of the patients. Despite the presence of pretreatment NS5A and NS5B resistance-associated variants in the ASTRAL-2 trial, no patient receiving sofosbuvir–velpatasvir had virologic failure.

In the ASTRAL-3 trial, of the 274 patients in the sofosbuvir–velpatasvir group who had available data on virologic outcome (sustained virologic response or virologic failure) with deep sequencing data, 43 (16%) had detectable NS5A resistance-associated variants (A30K, L31M, and Y93H) at baseline. Of these patients, 38 (88%) had a sustained virologic response. Of the 25 patients with the Y93H variant at baseline, 21 (84%) had a sustained virologic response. Of the 231 patients without NS5A resistance-associated variants at baseline, 225 (97%) had a sustained virologic response. All 10 patients with baseline NS5B resistance-associated variants (N142T, L159F, E237G, L320I, and V321A/I) had a sustained virologic response (Fig. S3 in the Supplementary Appendix).

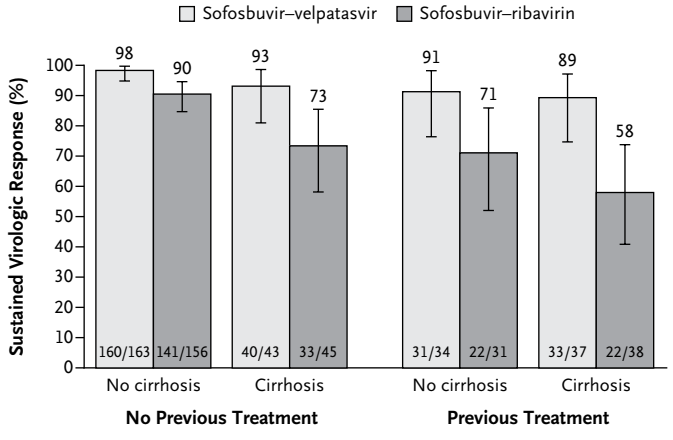

Figure 1. Sustained Virologic Response among Patients with HCV Genotype 3, According to Cirrhosis Status and Previous Treatment.

Shown are the rates of sustained virologic response at 12 weeks after treatment among patients with HCV genotype 3 who were treated with sofosbuvir–velpatasvir or sofosbuvir–ribavirin in the ASTRAL-3 study. Data for five patients in the sofosbuvir–ribavirin group for whom cirrhosis status was not available are not included in the analysis. The I bars represent 95% confidence intervals.

SAFETY

In the two trials, 1 patient receiving sofosbuvir–velpatasvir discontinued all treatment prematurely because of an adverse event. This patient, a 57-year-old black man in the sofosbuvir–velpatasvir group in the ASTRAL-2 trial, discontinued on day 1 of treatment because of anxiety, headache, and difficulty concentrating. A total of 9 of 275 patients (3%) in the sofosbuvir–ribavirin group in the ASTRAL-3 trial discontinued ribavirin because of adverse events (Table 3).

Serious adverse events were reported in 4 patients in the ASTRAL-2 trial, including 2 in the

Table 3. Discontinuations, Adverse Events, and Selected Laboratory Abnormalities.

Variable	HCV Genotype 2		HCV Genotype 3	
	Sofosbuvir–Velpatasvir for 12 Wk (N=134)	Sofosbuvir–Ribavirin for 12 Wk (N=132)	Sofosbuvir–Velpatasvir for 12 Wk (N=277)	Sofosbuvir–Ribavirin for 24 Wk (N=275)
	number (percent)			
Patients discontinuing treatment because of adverse event	1 (1)	0	0	9 (3)
Patients with event up to 30 days after last dose				
Any adverse event	92 (69)	101 (77)	245 (88)	260 (95)
Serious adverse event	2 (1)	2 (2)	6 (2)	15 (5)
Death	2 (1)	0	0	3 (1)
Common adverse events*				
Fatigue	20 (15)	47 (36)	71 (26)	105 (38)
Headache	24 (18)	29 (22)	90 (32)	89 (32)
Nausea	14 (10)	19 (14)	46 (17)	58 (21)
Insomnia	6 (4)	18 (14)	31 (11)	74 (27)
Irritability	4 (3)	9 (7)	23 (8)	40 (15)
Pruritus	6 (4)	7 (5)	8 (3)	35 (13)
Nasopharyngitis	8 (6)	2 (2)	34 (12)	33 (12)
Cough	4 (3)	6 (5)	14 (5)	35 (13)
Dyspepsia	1 (1)	5 (4)	9 (3)	30 (11)
Selected laboratory abnormalities				
Hemoglobin concentration <10 g/dl	0	6 (5)	0	10 (4)
Lymphocyte count				
350 to <500 per mm^3	0	1 (1)	2 (1)	3 (1)
<500 per mm^3	0	0	1 (<1)	1 (<1)
Platelet count 25,000 to <50,000 per mm^3	0	0	1 (<1)	1 (<1)
Total bilirubin				
>2.5 to 3.0 mg/dl	0	3 (2)	0	2 (1)
>3.0 mg/dl	0	0	0	1 (<1)

* Adverse events were considered to be common if they occurred in at least 10% of patients in any group. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

sofosbuvir–velpatasvir group (pneumonia in 1 patient and enteritis and abdominal pain in 1 patient) and 2 in the sofosbuvir–ribavirin group (arthralgia in 1 patient and depression in 1 patient) (Table 3, and Table S5 in the Supplementary Appendix). In the ASTRAL-3 trial, serious adverse events were reported in 6 patients (2%) receiving sofosbuvir–velpatasvir and in 15 patients (5%) receiving sofosbuvir–ribavirin (Table 3, and Table S6 in the Supplementary Appendix). Across the two trials, the only serious adverse event that occurred in more than 1 patient was depression in 2 patients receiving sofosbuvir–ribavirin (1 in each study).

In the ASTRAL-2 trial, 2 patients receiving sofosbuvir–velpatasvir died during the post-treatment follow-up: a 56-year-old white woman died of cardiac arrest 131 days after the end of treatment, and a 58-year-old white man died of complications related to metastatic lung cancer 112 days after the end of treatment. In the ASTRAL-3 trial, 3 patients receiving sofosbuvir–ribavirin

died, 2 during treatment (1 from unknown causes and 1 from gunshot wounds) and 1 during follow-up (from unknown causes).

In the two trials, the rates of adverse events were lower among patients receiving sofosbuvir–velpatasvir than among those receiving sofosbuvir–ribavirin (Table 3). Overall, the most common events in the two treatment groups were fatigue, headache, and nausea. Patients receiving 24 weeks of sofosbuvir–ribavirin in the ASTRAL-3 trial had increased rates of insomnia, irritability, and cough, all of which are known to be associated with ribavirin treatment.

Among patients receiving sofosbuvir–ribavirin, 6 (5%) in the ASTRAL-2 trial and 10 (4%) in the ASTRAL-3 trial had decreased hemoglobin values (<10 g per deciliter); no patients receiving sofosbuvir–velpatasvir in either study had hemoglobin values of less than 10 g per deciliter (Table 3). Grade 3 or 4 hyperbilirubinemia, a known side effect of ribavirin-associated hemolysis, was seen in 6 patients receiving sofosbuvir–ribavirin in the two studies. No grade 3 or 4 elevations in bilirubin were observed among patients receiving sofosbuvir–velpatasvir.

DISCUSSION

In these multicenter, randomized, phase 3 trials, rates of sustained virologic response among patients with HCV genotype 2 or 3 who received 12 weeks of treatment with a fixed-dose combination of sofosbuvir–velpatasvir once daily were superior to those among patients who received standard treatment with sofosbuvir–ribavirin. The rates of adverse events and laboratory abnormalities were lower among patients receiving sofosbuvir–velpatasvir than among those receiving sofosbuvir–ribavirin.

Although the current standard treatment of 12 weeks of sofosbuvir plus ribavirin is effective in patients with HCV genotype 2, with rates of sustained virologic response of more than 90% in most subgroups, patients with cirrhosis and those who have not had a response to previous HCV treatment have an increased likelihood of HCV relapse. Furthermore, some patients are not eligible for sofosbuvir–ribavirin treatment because of contraindications to the use of ribavirin. None of the 134 patients with HCV genotype 2 who received sofosbuvir–velpatasvir had virologic failure in a population that included patients with cirrhosis and previous treatment failure, and anemia was not observed. Also now reported in the *Journal* are the results of the ASTRAL-1 trial,[14] which assesses the efficacy of 12 weeks of sofosbuvir–velpatasvir in patients with HCV genotypes 1, 2, 4, 5, or 6, including patients with cirrhosis and those with previous treatment failure. Of the 104 patients in that study with HCV genotype 2, 100% had a sustained virologic response. The rate of sustained virologic response among patients who received 12 weeks of sofosbuvir–ribavirin in our active-comparator group was 94%, which is similar to the rate of 93% that was reported in a similar population receiving the same treatment in the phase 3 VALENCE trial.[15]

The treatment of patients with HCV genotype 3 has remained a clinical challenge in the era of direct-acting antiviral agents. Patients with HCV genotype 3, especially those who have not had a response to previous treatment and those with cirrhosis, have relatively poor rates of response to standard treatment with sofosbuvir–ribavirin. In the ALLY-3 phase 3 trial, among patients with HCV genotype 3 who received 12 weeks of sofosbuvir with the NS5A inhibitor daclatasvir, a sustained virologic response was reported in 90% of previously untreated patients and in 86% of previously treated patients. However, the response rate fell to 63% among patients with compensated cirrhosis.[16] The addition of peginterferon to sofosbuvir–ribavirin has been shown to improve outcomes but at the expense of greater toxic effects and the exclusion of patients who have unacceptable side effects from interferon.[17] In this context, the finding that the rates of sustained virologic response in every subgroup of patients with HCV genotype 3 were substantially higher among those who had received sofosbuvir–velpatasvir, including patients with cirrhosis and previous treatment failure, represents an improvement over standard treatment with 24 weeks of sofosbuvir–ribavirin, with a shorter duration of treatment and fewer side effects owing to the removal of ribavirin from the regimen. The rates of response in the sofosbuvir–ribavirin group in our study and in a similar population receiving the same regimen in the phase 3 VALENCE trial were 80% and 85%, respectively.[15]

Among patients with HCV genotype 2 who received sofosbuvir–velpatasvir, the presence of baseline NS5A or NS5B resistance-associated

variants was not associated with virologic failure. However, among patients with HCV genotype 3, the rate of sustained virologic response was 88% among patients who had NS5A resistance-associated variants at baseline and 97% among those who did not, with the lowest rate (84%) observed among patients with the Y93H variant at baseline. Further research is needed to evaluate potential strategies to increase the rate of sustained virologic response, such as prolongation of therapy or the addition of a third antiviral drug (e.g., ribavirin or an active direct-acting antiviral agent with a different mechanism of action) in these patients.

In both the ASTRAL-2 and ASTRAL-3 trials, the generalizability of the results may be limited by the small number of black patients who were enrolled, which primarily was the result of the low prevalence of infection with HCV genotype 2 or 3 among blacks in certain regions, including the United States. In addition, although patients with compensated cirrhosis were evaluated in these studies, patients with decompensated liver disease were excluded. However, in the ASTRAL-4 trial,[18] another phase 3 study now reported in the *Journal*, investigators evaluated the use of sofosbuvir–velpatasvir with or without ribavirin in patients with decompensated cirrhosis.

In conclusion, the results of the two trials reported here combined with the results of the ASTRAL-1 trial show that treatment with sofosbuvir–velpatasvir for 12 weeks was highly effective regardless of HCV genotype.

Supported by Gilead Sciences.

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, the support personnel at each study site, and David McNeel of Gilead Sciences for his editorial assistance.

APPENDIX

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