ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

Kris V. Kowdley, M.D., Stuart C. Gordon, M.D., K. Rajender Reddy, M.D., Lorenzo Rossaro, M.D., David E. Bernstein, M.D., Eric Lawitz, M.D., Mitchell L. Shiffman, M.D., Eugene Schiff, M.D., Reem Ghalib, M.D., Michael Ryan, M.D., Vinod Rustgi, M.D., Mario Chojkier, M.D., Robert Herring, M.D., Adrian M. Di Bisceglie, M.D., Paul J. Pockros, M.D., G. Mani Subramanian, M.D., Ph.D., Di An, Ph.D., Evguenia Svarovskaia, Ph.D., Robert H. Hyland, D.Phil., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., David Pound, M.D., and Michael W. Fried, M.D., for the ION-3 Investigators*

ABSTRACT

BACKGROUND

High rates of sustained virologic response were observed among patients with hepatitis C virus (HCV) infection who received 12 weeks of treatment with the nucleotide polymerase inhibitor sofosbuvir combined with the NS5A inhibitor ledipasvir. This study examined 8 weeks of treatment with this regimen.

METHODS

In this phase 3, open-label study, we randomly assigned 647 previously untreated patients with HCV genotype 1 infection without cirrhosis to receive ledipasvir and sofosbuvir (ledipasvir–sofosbuvir) for 8 weeks, ledipasvir–sofosbuvir plus ribavirin for 8 weeks, or ledipasvir–sofosbuvir for 12 weeks. The primary end point was sustained virologic response at 12 weeks after the end of therapy.

RESULTS

The rate of sustained virologic response was 94% (95% confidence interval [CI], 90 to 97) with 8 weeks of ledipasvir–sofosbuvir, 93% (95% CI, 89 to 96) with 8 weeks of ledipasvir–sofosbuvir plus ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir–sofosbuvir. As compared with the rate of sustained virologic response in the group that received 8 weeks of ledipasvir–sofosbuvir, the rate in the 12-week group was 1 percentage point higher (97.5% CI, −4 to 6) and the rate in the group that received 8 weeks of ledipasvir–sofosbuvir with ribavirin was 1 percentage point lower (95% CI, −6 to 4); these results indicated noninferiority of the 8-week ledipasvir–sofosbuvir regimen, on the basis of a noninferiority margin of 12 percentage points. Adverse events were more common in the group that received ribavirin than in the other two groups. No patient who received 8 weeks of only ledipasvir–sofosbuvir discontinued treatment owing to adverse events.

CONCLUSIONS

Ledipasvir–sofosbuvir for 8 weeks was associated with a high rate of sustained virologic response among previously untreated patients with HCV genotype 1 infection without cirrhosis. No additional benefit was associated with the inclusion of ribavirin in the regimen or with extension of the duration of treatment to 12 weeks. (Funded by Gilead Sciences; ION-3 ClinicalTrials.gov number, NCT01851330.)

From the Digestive Disease Institute, Virginia Mason Medical Center, Seattle (K.V.K.); Henry Ford Health Systems, Detroit (S.C.G.); University of Pennsylvania, Philadelphia (K.R.R.); University of California Davis Medical Center, Sacramento (L.R.), University of California at San Diego Medical Center, San Diego (M.C.), Scripps Clinic, La Jolla (P.J.P.), and Gilead Sciences, Foster City (G.M.S., D.A., E.S., R.H.H., P.S.P., W.T.S., J.G.M.) — all in California; Hofstra North Shore–Long Island Jewish School of Medicine, Manhasset, NY (D.E.B.); Texas Liver Institute and University of Texas Health Science Center, San Antonio (E.L.), and Texas Clinical Research Institute, Arlington (R.G.) — both in Texas; Liver Institute of Virginia, Bon Secours Health System, Richmond and Newport News (M.L.S.), Digestive and Liver Disease Specialists, Norfolk (M.R.), and Metropolitan Liver Diseases, Fairfax (V.R.) — all in Virginia; Center for Liver Diseases, School of Medicine, University of Miami, Miami (E.S.); Quality Medical Research, Nashville (R.H.); Saint Louis University, St. Louis (A.M.D.); Duke University Medical Center, Durham (A.J.M.), and University of North Carolina, Chapel Hill (M.W.F.) — both in North Carolina; and Indianapolis Gastroenterology Research Foundation, Indianapolis (D.P.). Address reprint requests to Dr. Kowdley at the Digestive Disease Institute, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101, or at kris.kowdley@vmmc.org.

*A complete list of the principal investigators for the ION-3 study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 11, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1402355

More than 3 million people in the United States are chronically infected with the hepatitis C virus (HCV).[1,2] Although the number of new infections has been declining for decades, HCV-related morbidity and mortality are projected to continue rising for another 20 years.[3] One half to three quarters of persons currently infected with HCV have not received a diagnosis and are untreated; many will have progression to decompensated cirrhosis, hepatocellular carcinoma, and other liver complications.[3,4] Early diagnosis and treatment are essential to improve long-term health outcomes in this population. New guidelines from the Centers for Disease Control and Prevention and the U.S. Community Preventive Services Task Force have broadened recommendations for screening to include all adults born between 1945 and 1965.[5,6] To accompany this expanded screening program, there is a recognized need for a simple, safe regimen of short duration that can provide high cure rates in a broad range of patients.[7]

Sofosbuvir (Gilead Sciences), an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase, has recently been approved for the treatment of chronic HCV infection.[8] The labeled use for patients with HCV genotype 1 infection is sofosbuvir with peginterferon alfa and ribavirin for 12 weeks, or sofosbuvir plus ribavirin for 24 weeks in patients who are ineligible to receive interferon therapy. Ledipasvir (Gilead Sciences) is a new HCV NS5A inhibitor with demonstrated antiviral activity against HCV genotypes 1a and 1b.[9]

In the phase 2 LONESTAR trial, patients with HCV genotype 1 infection without cirrhosis who received 8 or 12 weeks of ledipasvir–sofosbuvir, with or without ribavirin, had rates of sustained virologic response of 95 to 100%.[10] The phase 3 ION-1 and ION-2 trials (also reported in the *Journal*)[11,12] showed that 12 weeks of treatment with ledipasvir–sofosbuvir was associated with response rates that were similar to those among patients who received 24 weeks of treatment.

We conducted a phase 3 trial involving previously untreated patients with HCV genotype 1 infection without cirrhosis to explore the feasibility of shortening the treatment duration. We assessed the single-tablet regimen of ledipasvir–sofosbuvir administered for 8 weeks, with or without ribavirin (Ribasphere, Kadmon Pharmaceuticals), as compared with ledipasvir–sofosbuvir alone administered for 12 weeks.

Methods

Patients

Patients were enrolled between May 20, 2013, and June 19, 2013, at 58 sites in the United States. Eligible patients were 18 years of age or older, with chronic HCV genotype 1 infection without cirrhosis, who had not received treatment for HCV infection previously. Patients were required to have an HCV RNA level of at least 10^4 IU per milliliter at the time of screening, alanine and aspartate aminotransferase levels of no more than 10 times the upper limit of the normal range, a platelet count of more than 90,000 per cubic millimeter, and a hemoglobin level of at least 11 g per deciliter (in women) or at least 12 g per deciliter (in men). There were no upper limits on age or body-mass index. Full eligibility criteria, including details of the assessment of the absence of cirrhosis, are provided in the study protocol, available with the full text of this article at NEJM.org. All the patients provided written informed consent.

Study Design

In this multicenter, randomized, open-label trial, all the patients received a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir, administered orally once daily. Ribavirin was administered orally twice daily, with the dose 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).

Patients were randomly assigned in a 1:1:1 ratio to one of three treatment groups: ledipasvir–sofosbuvir for 8 weeks, ledipasvir–sofosbuvir plus ribavirin for 8 weeks, or ledipasvir–sofosbuvir for 12 weeks. Randomization was stratified according to HCV genotype (1a or 1b).

Study Assessments

The primary efficacy end point was an HCV RNA level of less than 25 IU per milliliter at 12 weeks after the end of therapy (sustained virologic response). This end point was assessed in all the patients who underwent randomization and received at least one dose of a study drug. In the primary efficacy analysis, the rate of sustained virologic response in each of the three treatment groups was compared with a calculated historical response rate of 60%. A key secondary end point was the noninferiority of 8 weeks

of ledipasvir–sofosbuvir to the other treatment regimens.

Screening assessments included measurement of the serum HCV RNA level and *IL28B* (rs12979860) genotyping, as well as standard laboratory and clinical tests. The serum HCV RNA level was measured with the COBAS TaqMan HCV Test, version 2.0, for use with the High Pure System (Roche Molecular Systems), which has a lower limit of quantification of 25 IU per milliliter. HCV genotype and subtype were determined with the use of the Versant HCV Genotype INNO-LiPA 2.0 assay (Siemens Healthcare Diagnostics).

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

Deep sequencing of the NS5A and NS5B regions of the HCV RNA was performed in all the patients at baseline, and again at the time of failure in those who had virologic failure. The resulting sequences were compared to detect resistance-associated variants that emerged during treatment. We report resistance-associated variants that were present in more than 1% of sequence reads.

STUDY OVERSIGHT

This trial was approved by the institutional review board or independent ethics committees at each participating site and was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. The study was designed and conducted according to the protocol by the sponsor (Gilead Sciences) in collaboration with the principal investigators. The sponsor collected the data, monitored the study conduct, and performed the statistical analyses. An independent data and safety monitoring committee reviewed the progress of the study. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors had access to the data and assume responsibility for the integrity and completeness of the reported data. The manuscript was prepared by a medical writer who was an employee of the sponsor, with input from all the authors. The first author made the decision to submit the manuscript for publication.

STATISTICAL ANALYSIS

The Kruskal–Wallis test was used to test for overall differences in continuous variables across treatment groups; the Cochran–Mantel–Haenszel test was used to test for overall differences in categorical variables across treatment groups. We determined that a sample of 200 patients in each treatment group would provide the study with more than 90% power to detect an improvement of at least 30 percentage points in the rate of sustained virologic response, as compared with a calculated control rate of 60%. This 60% rate was based on rates of sustained virologic response in phase 3 trials of telaprevir[13] and boceprevir,[14] allowing for a rate of sustained virologic response that was 5 percentage points lower than the adjusted rate of 65%, in exchange for an expected improved safety profile and shorter duration of treatment. The comparison with the calculated control rate was performed with the use of a two-sided, exact one-sample binomial test at a significance level of 0.025. In addition, noninferiority between the groups was assessed with the use of the conventional confidence-interval approach and a noninferiority margin of 12 percentage points. For details concerning the calculation of the control rate and the noninferiority margin, see the Supplementary Appendix, available at NEJM.org. The two-sided 95% exact confidence interval calculated by the Clopper–Pearson method is provided for the rate of sustained virologic response at 12 weeks after the end of treatment in each of the three treatment groups and in all patient subgroups.

RESULTS

BASELINE CHARACTERISTICS

Of the 831 patients who were initially screened, 647 underwent randomization and began treatment (Fig. S1 in the Supplementary Appendix). Most of the patients who were screened but not enrolled were excluded for not meeting eligibility criteria (Table S1 in the Supplementary Appendix). The demographic and baseline clinical characteristics of the patients were generally balanced among the three treatment groups (Table 1). The population was reflective of the popula-

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

Characteristic	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
Age — yr			
Mean	53	51	53
Range	22–75	21–71	20–71
Body-mass index†			
Mean	28	28	28
Range	18–43	18–56	19–45
Male sex — no. (%)	130 (60)	117 (54)	128 (59)
Race — no. (%)‡			
White	164 (76)	176 (81)	167 (77)
Black	45 (21)	36 (17)	42 (19)
Other	6 (3)	4 (2)	7 (3)
Ethnic group — no. (%)‡			
Hispanic	13 (6)	12 (6)	14 (6)
Non-Hispanic	200 (93)	204 (94)	202 (94)
Not reported	2 (1)	0	0
HCV genotype — no. (%)			
1a	171 (80)	172 (80)	172 (80)
1b	43 (20)	44 (20)	44 (20)
1 without confirmed subtype	1 (<1)	0	0
HCV RNA — $\log_{10}$ IU/ml	6.5±0.8	6.4±0.7	6.4±0.8
HCV RNA ≥800,000 IU/ml — no. (%)	181 (84)	171 (79)	172 (80)
IL28B genotype — no. (%)			
CC	56 (26)	60 (28)	56 (26)
CT	120 (56)	128 (59)	124 (57)
TT	39 (18)	28 (13)	36 (17)
Alanine aminotransferase >1.5× ULN — no. (%)	87 (40)	95 (44)	99 (46)
Fibrosis score — no. (%)§	156 (73)	136 (63)	156 (72)
F0–F2	127 (59)	108 (50)	127 (59)
F3	29 (13)	28 (13)	29 (13)
Interferon eligibility — no. (%)¶			
Eligible	202 (94)	203 (94)	203 (94)
Ineligible	13 (6)	13 (6)	15 (7)

* Plus–minus values are means ±SD. The Kruskal–Wallis test was used to test for overall differences in continuous variables across treatment groups; the Cochran–Mantel–Haenszel test was used to test for overall differences in categorical variables across treatment groups. There were no significant differences (at the significance level of 0.05) among the treatment groups with regard to any of the baseline characteristics. HCV denotes hepatitis C virus, LDV ledipasvir, RBV ribavirin, SOF sofosbuvir, 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.

§ The presence of fibrosis was determined by means of liver biopsy (Metavir stage, on a scale from F0 to F4, with higher stages indicating a greater degree of fibrosis). No patient in this study had a fibrosis score of F4.

¶ Interferon eligibility was determined by the site investigator on the basis of whether, in the investigator's judgment, the patient had contraindications to interferon therapy.

Table 2. Response during and after Treatment.

Response	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
HCV RNA <25 IU/ml			
During treatment period — no./total no. (%)*			
At wk 2	190/215 (88)	195/214 (91)	197/216 (91)
At wk 4	215/215 (100)	211/213 (99)	216/216 (100)
After end of treatment — no. (%)			
At wk 4	207 (96)	205 (95)	208 (96)
At wk 12	202 (94)	201 (93)	206 (95)
Virologic failure during treatment — no.	0	0	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no. (%)	11 (5)	9 (4)	3 (1)
Lost to follow-up — no.	1	5	7
Withdrew consent — no.	1	1	0

* Data shown are for patients for whom HCV RNA results were available.

tion of patients with HCV infection in the United States: 80% had HCV genotype 1a infection, 19% were black, and 6% were Hispanic. Approximately three quarters of the patients had a non-CC *IL28B* genotype.

EFFICACY

The criterion for the primary end point was met in all three treatment groups, with rates of sustained virologic response that were superior to the adjusted historical control rate of 60% (P<0.001 for all comparisons). Among the 215 patients who received 8 weeks of ledipasvir–sofosbuvir, 202 had a sustained virologic response at 12 weeks after the end of treatment (94%; 95% confidence interval [CI], 90 to 97); among the 216 who received 8 weeks of ledipasvir–sofosbuvir plus ribavirin, 201 had a sustained virologic response (93%; 95% CI, 89 to 96); and among the 216 who received 12 weeks of ledipasvir–sofosbuvir, 206 had a sustained virologic response (95%; 95% CI, 92 to 98) (Table 2).

In the secondary analysis of noninferiority, the rate of sustained virologic response among patients who received 8 weeks of ledipasvir–sofosbuvir without ribavirin was noninferior to the response rates in the other two treatment groups, as evidenced by the fact that the lower boundaries of the confidence intervals for the difference in proportions between the groups were greater than the prespecified noninferiority margin of –12 percentage points. As compared with the rate of sustained virologic response in the group that received 8 weeks of ledipasvir–sofosbuvir, the rate in the group that received 12 weeks of ledipasvir–sofosbuvir was 1 percentage point higher (97.5% CI, –4 to 6) and the rate in the group that received 8 weeks of ledipasvir–sofosbuvir with ribavirin was 1 percentage point lower (95% CI, –6 to 4) (Table S3 in the Supplementary Appendix).

The patients' responses according to baseline characteristics are shown in Figure 1, and in Table S2 in the Supplementary Appendix. The rates of sustained virologic response in prespecified subgroups across the three treatment groups were generally similar to those observed in the overall population. Patients with characteristics historically associated with a poor response to interferon-based treatment — non-CC *IL28B* genotype, high viral load at baseline, black race, and HCV genotype 1a infection — had rates of sustained virologic response that were similar to the rates among patients without these characteristics. Among patients who received 8 weeks of ledipasvir–sofosbuvir alone, the rates of response in all the subgroups ranged from 89% to 100%. The fibrosis score (which was used as a measure of liver damage) had no discernible effect on the rate of sustained virologic response

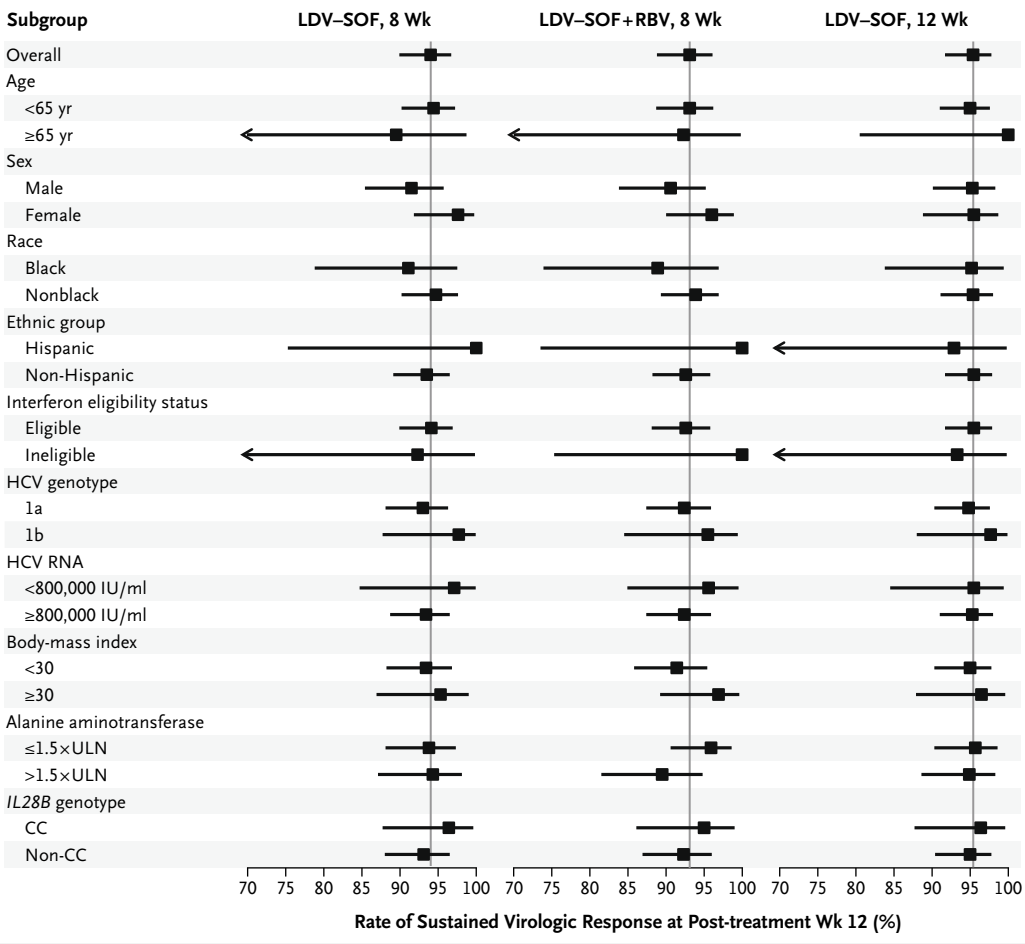

Figure 1. Rates of Sustained Virologic Response According to Subgroup.

The position of the square indicates the rate of sustained virologic response at 12 weeks after the end of treatment in each subgroup; the horizontal lines indicate 95% confidence intervals. The vertical lines represent the overall rate of sustained virologic response in each treatment group. Race or ethnic group was self-reported. Data from patients with other (i.e., nonwhite and nonblack) race, unreported ethnic group, and unconfirmed HCV genotype (1a or 1b) are not included. Interferon eligibility was determined by the site investigator on the basis of whether, in the investigator's judgment, the patient had contraindications to interferon therapy. The body-mass index is the weight in kilograms divided by the square of the height in meters. HCV denotes hepatitis C virus, LDV ledipasvir, RBV ribavirin, SOF sofosbuvir, and ULN upper limit of the normal range.

at post-treatment week 12 (Table S7 in the Supplementary Appendix).

Among the 647 patients treated, no patient had virologic breakthrough during study treatment. Overall, 23 patients had a virologic relapse after the end of therapy: 11 patients (5%) in the group that received 8 weeks of ledipasvir–sofosbuvir, 9 (4%) in the group that received 8 weeks of ledipasvir–sofosbuvir plus ribavirin, and 3 (1%) in the 12-week group. The characteristics of the patients who had a relapse are provided in Table S4 in the Supplementary Appendix. The majority of these patients were, like the majority of patients in the study population, non-Hispanic white men with HCV genotype 1a infection.

VIROLOGIC RESISTANCE TESTING

Variants associated with resistance to NS5A inhibitors were detected at baseline by means of deep sequencing in 116 of the 647 patients (18%) for whom data were available. Of the 116 patients, 104 (90%) had a sustained virologic response. Of the 23 patients who had a relapse, 15 had NS5A resistance–associated variants at the

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

Variable	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
Duration of treatment — wk	8.1±0.2	8.0±0.9	12.0±0.9
Discontinuation of ledipavir–sofosbuvir owing to adverse event — no. of patients (%)	0	1 (<1)	2 (1)
Serious adverse event — no. of patients (%)	4 (2)	1 (<1)	5 (2)
Any adverse event — no. of patients (%)	145 (67)	165 (76)	149 (69)
Common adverse event — no. of patients (%)†			
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	9 (4)
Diarrhea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	11 (5)	16 (7)
Constipation	9 (4)	13 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	19 (9)	5 (2)
Pruritus	2 (1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anemia	2 (1)	17 (8)	2 (1)
Muscle spasms	3 (1)	11 (5)	6 (3)
Dyspnea	0	11 (5)	1 (<1)
Hematologic abnormality — no. of patients (%)			
Hemoglobin level <10 g/dl	0	11 (5)	1 (<1)
Lymphocyte count 350 to <500 per mm^3	0	1 (<1)	0
Neutrophil count 500 to <750 per mm^3	0	1 (<1)	1 (<1)

* Plus–minus values are means ±SD.
† Common adverse events were those that occurred in at least 5% of the patients in any treatment group.

time of relapse and 8 did not. Of the 15 patients with NS5A resistance–associated variants at relapse, 9 had the variants at baseline and 6 did not. The NS5B S282T variant, which is associated with reduced susceptibility to sofosbuvir, was not detected by means of deep sequencing in any patient at baseline or at the time of virologic failure (Table S6 in the Supplementary Appendix).

SAFETY

Of the 647 patients in the study, 3 discontinued ledipasvir–sofosbuvir prematurely owing to adverse events: 1 patient in the group that received 8 weeks of ledipasvir–sofosbuvir plus ribavirin (owing to a road accident), and 2 in the group that received 12 weeks of ledipasvir–sofosbuvir (1 owing to arthralgia and 1 owing to lung cancer). A total of 10 patients had serious adverse events; no single serious adverse event occurred in more than 1 patient. A full list of serious adverse events is provided in Table S5 in the Supplementary Appendix.

Fatigue, headache, and nausea were the most common adverse events. The incidence of adverse events was lower among patients receiving ledipasvir–sofosbuvir alone (67% and 69% of patients receiving 8 weeks and 12 weeks of treatment, respectively) than among those receiving 8 weeks of ledipasvir–sofosbuvir plus ribavirin (76%) (Table 3). Patients in the group that received ledipasvir–sofosbuvir plus ribavirin had higher rates of events that are generally associated with

ribavirin therapy — fatigue, headache, nausea, insomnia, irritability, rash, pruritus, cough, and anemia — than did patients who received ledipasvir–sofosbuvir alone (Table 3).[15] A total of 2 patients (1%) receiving 8 weeks of ledipasvir–sofosbuvir, 8 (4%) receiving 8 weeks of ledipasvir–sofosbuvir plus ribavirin, and 7 (3%) receiving 12 weeks of ledipasvir–sofosbuvir had grade 3 (severe) or grade 4 (life-threatening) adverse events.

In the groups that received 8 weeks of treatment, the mean change in the hemoglobin level from baseline to week 8 was −0.2 g per deciliter among those who received ledipasvir–sofosbuvir alone and −1.9 g per deciliter among those who received ledipasvir–sofosbuvir plus ribavirin. Patients in the 12-week group had a mean change in the hemoglobin level of −0.4 g per deciliter from baseline to week 12. A total of 11 patients (5%) in the group that received 8 weeks of ledipasvir–sofosbuvir plus ribavirin had a reduction in the hemoglobin level during treatment to less than 10 g per deciliter, as compared with no patients in the group that received 8 weeks of ledipasvir–sofosbuvir alone and 1 (<1%) in the group that received 12 weeks of ledipasvir–sofosbuvir. A total of 3 patients (1%) who received 8 weeks of ledipasvir–sofosbuvir plus ribavirin had grade 3 hyperbilirubinemia; no other grade 3 or 4 hyperbilirubinemia occurred in any treatment group. The rates of laboratory abnormalities were otherwise similar among the three treatment groups (Table S8 in the Supplementary Appendix).

DISCUSSION

In this phase 3 trial, all three groups of previously untreated patients with HCV genotype 1 infection without cirrhosis who received treatment with ledipasvir–sofosbuvir had rates of sustained virologic response that were higher than 90%. The results of the noninferiority analysis suggested that adding ribavirin to the 8-week regimen of ledipasvir–sofosbuvir or extending the duration of treatment with ledipasvir–sofosbuvir from 8 weeks to 12 weeks did not result in improved rates of sustained virologic response.

In these previously untreated patients without cirrhosis, the rates of response were high in all patient subgroups and did not vary substantially according to patients' demographic or clinical characteristics at baseline, including characteristics historically associated with a poor response to interferon-based treatment. This uniformity of response suggests that the regimen of ledipasvir–sofosbuvir may be appropriate for a broad range of previously untreated patients, reducing the need to tailor the regimen according to the characteristics of individual patients. Although relapse was more common among patients who received 8 weeks of treatment than among those who received 12 weeks of treatment, the small numbers of patients who had a relapse were not sufficient to identify baseline characteristics or response variables during treatment that were associated with relapse (Table S4 in the Supplementary Appendix).

Variants associated with resistance to NS5A inhibitors were detected at baseline by means of deep sequencing in 116 of the 647 patients (18%) for whom data were available; of these 116 patients, 104 (90%) had a sustained virologic response. The presence of any given NS5A resistance–associated variant at baseline was not associated with relapse. Variants associated with resistance to NS5A inhibitors developed in most but not all the patients who had a relapse. An ongoing trial in which patients who did not have a response to an 8-week or 12-week regimen of ledipasvir–sofosbuvir are retreated with ledipasvir–sofosbuvir for 24 weeks (ClinicalTrials.gov number, NCT01987453) may provide further insight into the clinical significance of NS5A resistance–associated variants for this particular regimen.

The results of this phase 3 study exploring the efficacy of an 8-week regimen for the treatment of HCV infection appear to support the rationale for the development of this regimen — namely, that two direct-acting antiviral agents with distinct viral targets and mechanisms of action can provide high efficacy and complementary resistance profiles. The rapidity and durability of viral suppression attained with this regimen appear to allow a shorter course of treatment for previously untreated patients without cirrhosis than has proved possible with interferon-based regimens. The feasibility of a regimen shorter than 8 weeks has been explored previously in the Electron trial, in which a group of previously untreated patients with HCV genotype 1 infection received 6 weeks of treatment with ledipasvir–sofosbuvir plus ribavirin.[16] The result — 17 of the 25 patients treated (68%) had a sustained virologic response, and 8 (32%) had a relapse after

the end of treatment — appears to establish that 8 weeks is the shortest effective duration for this regimen. Recent evidence, however, suggests that the addition of a third direct-acting antiviral agent to ledipasvir–sofosbuvir may allow further shortening of the duration of treatment to 6 weeks.[17]

The higher rates of hemolytic anemia, fatigue, headache, rash, pruritus, and insomnia among patients in the ribavirin-containing group are consistent with the well-known side effects of ribavirin treatment. Eliminating ribavirin from this regimen would therefore appear to result in better adherence to therapy with no loss of efficacy. Moreover, without ribavirin, the ledipasvir–sofosbuvir regimen would probably require little monitoring of hemoglobin levels during treatment, reduce the need for colony-stimulating factors and transfusions, and decrease the risk of teratogenicity among women of childbearing age.

In conclusion, in this phase 3 trial, 8 weeks of treatment with a single-tablet regimen of ledipasvir–sofosbuvir resulted in a high rate of sustained virologic response among previously untreated patients with HCV genotype 1 infection without cirrhosis. Our results show that ribavirin worsens the treatment burden without enhancing efficacy. A 12-week duration of treatment with ledipasvir–sofosbuvir was not more effective than 8 weeks of treatment. The uniformly high rates of response in all the patient subgroups suggest the efficacy of this regimen across a broad range of previously untreated patients with HCV genotype 1 infection without cirrhosis. The 8-week regimen of ledipasvir–sofosbuvir has not been evaluated in patients with cirrhosis.

Supported by Gilead Sciences.

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

Dr. Kowdley reports receiving fees for serving on advisory boards through his institution from Boehringer Ingelheim, Gilead Sciences, Ikaria Pharmaceuticals, Janssen, Merck, Vertex Pharmaceuticals, Trio Health, Pharmasset, and Tekmira Pharmaceuticals, consulting fees through his institution from Novartis, and grant support through his institution from Beckman Coulter, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Ikaria Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck, Mochida, Vertex Pharmaceuticals, Pharmasset, Conatus Pharmaceuticals, Genentech, and GlaxoSmithKline. Dr. Gordon reports receiving fees for serving on a data monitoring board from Janssen-Cilag, consulting fees from AbbVie, Bristol-Myers Squibb, Amgen, CVS Caremark, Merck, Novartis, and Vertex Pharmaceuticals, and grant support through his institution from AbbVie, Bristol-Myers Squibb, Merck, Vertex Pharmaceuticals, GlaxoSmithKline, and Intercept Pharmaceuticals. Dr. Reddy reports receiving fees for serving on advisory boards from Idenix Pharmaceuticals and Novartis, fees for serving on advisory boards through his institution from Bristol-Myers Squibb, Merck, Vertex Pharmaceuticals, Janssen, Genentech, and AbbVie, fees for the preparation of education material and participation in continuing medical education meetings from ViralEd, and grant support through his institution from Bristol-Myers Squibb, Merck, Vertex Pharmaceuticals, Janssen, Genentech, AbbVie, Genfit, Ikaria Pharmaceuticals, and Hyperion Therapeutics. Dr. Rossaro reports receiving fees for serving on advisory boards from Gilead Sciences, Vertex Pharmaceuticals, Merck, Janssen, Genentech, Novartis, and AbbVie, lecture fees from Gilead Sciences, Vertex Pharmaceuticals, Merck, Janssen, and Genentech, and grant support from Gilead Sciences, Vertex Pharmaceuticals, Merck, Genentech, Bristol-Myers Squibb, Novartis, and AbbVie. Dr. Bernstein reports receiving personal fees from Gilead Sciences, AbbVie, Vertex Pharmaceuticals, and Merck, and grant support from Gilead Sciences, AbbVie, Janssen, Vertex Pharmaceuticals, Merck, and Bristol-Myers Squibb. Dr. Lawitz reports receiving personal fees and grant support from Gilead Sciences. Dr. Shiffman reports receiving fees for serving on advisory boards from AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, and Salix Pharmaceuticals, lecture fees from Bayer, GlaxoSmithKline, Janssen, Genentech, Salix Pharmaceuticals, and Vertex Pharmaceuticals, and grant support from AbbVie, Achillion Pharmaceuticals, Beckman Coulter, Bristol-Myers Squibb, Boehringer Ingelheim, Gen-Probe, Intercept Pharmaceuticals, Lumena Pharmaceuticals, and Novartis. Dr. Schiff reports receiving fees for serving on an advisory board and grant support from Gilead Sciences. Dr. Ghalib reports receiving grant support from Gilead Sciences, Pharmasset, Bristol-Myers Squibb, Idenix Pharmaceuticals, Idera Pharmaceuticals, Merck, Novartis, Boehringer Ingelheim, Salix Pharmaceuticals, Takeda Pharmaceuticals, Janssen, Vertex Pharmaceuticals, ViroChem Pharma, Achillion Pharmaceuticals, Inhibitex, ZymoGenetics, Biolex Therapeutics, and Anadys Pharmaceuticals. Dr. Rustgi reports receiving fees for serving on advisory boards from AbbVie and Merck, lecture fees from Janssen and Genentech, and grant support from AbbVie, Vertex Pharmaceuticals, and Bristol-Myers Squibb. Dr. Di Bisceglie reports receiving personal fees from Genentech, Gilead Sciences, Vertex Pharmaceuticals, AbbVie, Bayer, Salix Pharmaceuticals, and Janssen, and grant support from Genentech, Gilead Sciences, Idenix Pharmaceuticals, Vertex Pharmaceuticals, Bristol-Myers Squibb, AbbVie, GlobeImmune, Transgene, Salix Pharmaceuticals, and Janssen. Dr. Pockros reports receiving fees for serving on an advisory board, lecture fees, and grant support from Gilead Sciences. Drs. Subramanian, An, Svarovskaia, Hyland, Pang, Symonds, and McHutchison report being employees of and owning stock in Gilead Sciences. Dr. Muir reports receiving personal fees from AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, and Vertex Pharmaceuticals, and grant support from AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Roche, and Vertex Pharmaceuticals. Dr. Fried reports receiving personal fees and grant support from Gilead Sciences, AbbVie, Bristol-Myers Squibb, Janssen, Merck, Vertex Pharmaceuticals, and Genentech. No other potential conflict of interest relevant to this article was reported.

We thank the patients, their families, and the study-site personnel; Reena Chhatre (Gilead Sciences) for contributions to the conduct of the study; and David McNeel (Gilead Sciences) for providing editorial assistance with an earlier version of the manuscript.

REFERENCES

1. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med 2013;368:1859-61.

2. Institute of Medicine. Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. Washington, DC: National Academies Press, 2010.

3. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513-21.

4. Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of precirrhotic chronic hepatitis C in the United States. Dig Liver Dis 2011;43:66-72.

5. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR Recomm Rep 2012;61(RR-4):1-32.

6. Screening for hepatitis C virus infection in adults: final recommendation statement. Rockville, MD: U.S. Preventive Services Task Force, June 25, 2013 (http://www.uspreventiveservicestaskforce.org/uspstf12/hepc/hepcfinalrs.htm).

7. Aronsohn A, Jensen D. Expanding access to hepatitis C virus care: a call to deconstruct individualized therapy. Hepatology 2014;59:13-5.

8. Sovaldi (sofosbuvir) tablets: U.S. prescribing information. Foster City, CA: Gilead Sciences, December 2013 (http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf).

9. Lawitz EJ, Gruener D, Hill JM, et al. A phase 1, randomized, placebo-controlled, 3-day, dose-ranging study of GS-5885, an NS5A inhibitor, in patients with genotype 1 hepatitis C. J Hepatol 2012;57:24-31.

10. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C: an open-label, randomized, phase 2 trial (LONESTAR). Lancet 2014;383:515-23. [Erratum, Lancet 2014;383:870.]

11. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. DOI: 10.1056/NEJMoa1402454.

12. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. DOI: 10.1056/NEJMoa1316366.

13. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.

14. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.

15. Rebetol (ribavirin) capsules: U.S. prescribing information. Whitehouse Station, NJ: Merck, 2003 (https://www.merck.com/product/usa/pi_circulars/r/rebetol/rebetol_pi.pdf).

16. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014;146:736-43, e1.

17. Kohli A, Sims Z, Marti M, et al. Combination oral, ribavirin free, antiviral therapy to optimize treatment outcomes for hepatitis C treatment naive patients: interim results from the NIAID SYNERGY trial. Presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, November 1–5, 2013. abstract.