ORIGINAL ARTICLE

ABT-450/r–Ombitasvir and Dasabuvir with or without Ribavirin for HCV

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ABSTRACT

BACKGROUND

The interferon-free regimen of ABT-450 with ritonavir (ABT-450/r), ombitasvir, and dasabuvir with or without ribavirin has shown efficacy in inducing a sustained virologic response in a phase 2 study involving patients with hepatitis C virus (HCV) genotype 1 infection. We conducted two phase 3 trials to examine the efficacy and safety of this regimen in previously untreated patients with HCV genotype 1 infection and no cirrhosis.

METHODS

We randomly assigned 419 patients with HCV genotype 1b infection (PEARL-III study) and 305 patients with genotype 1a infection (PEARL-IV study) to 12 weeks of ABT-450/r–ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir), dasabuvir (250 mg twice daily), and ribavirin administered according to body weight or to matching placebo for ribavirin. The primary efficacy end point was a sustained virologic response (an HCV RNA level of <25 IU per milliliter) 12 weeks after the end of treatment.

RESULTS

The study regimen resulted in high rates of sustained virologic response among patients with HCV genotype 1b infection (99.5% with ribavirin and 99.0% without ribavirin) and among those with genotype 1a infection (97.0% and 90.2%, respectively). Of patients with genotype 1b infection, 1 had virologic failure, and 2 did not have data available at post-treatment week 12. Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the ribavirin group (7.8% vs. 2.0%). In both studies, decreases in the hemoglobin level were significantly more common in patients receiving ribavirin. Two patients (0.3%) discontinued the study drugs owing to adverse events. The most common adverse events were fatigue, headache, and nausea.

CONCLUSIONS

Twelve weeks of treatment with ABT-450/r–ombitasvir and dasabuvir without ribavirin was associated with high rates of sustained virologic response among previously untreated patients with HCV genotype 1 infection. Rates of virologic failure were higher without ribavirin than with ribavirin among patients with genotype 1a infection but not among those with genotype 1b infection. (Funded by AbbVie; PEARL-III and PEARL-IV ClinicalTrials.gov numbers, NCT01767116 and NCT01833533.)

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Hepatitis C virus (HCV) infection is a worldwide health issue, with 3 million to 4 million new infections yearly and infection rates as high as 5% in some countries.[1] Chronic infection leads to liver disease, cirrhosis, or liver cancer in a large proportion of infected persons, and hepatitis C accounts for 25% of all liver cancers, representing the leading indication for liver transplantation.[1-3] Genotype 1 is the most common HCV genotype worldwide and includes 11 subgenotypes, of which 1a and 1b are responsible for the vast majority of infections.[4] Genotype 1b infection is the most prevalent form worldwide, particularly in Europe and East Asia, whereas genotype 1a infection is more prevalent in North America.[4]

Approved treatments for HCV genotype 1 infection include peginterferon and ribavirin combined with a direct-acting antiviral agent.[5-9] Peginterferon is associated with substantial adverse events, including influenza-like symptoms, depression, fatigue, and cytopenias that make it difficult for patients to adhere to treatment.[10] Cure rates for genotype 1a and 1b infection may differ depending on the treatment regimen; rates are generally lower among patients with genotype 1a infection when the treatment regimen includes an NS3 protease inhibitor or an NS5A replication complex inhibitor[6,8,11,12] and among patients with genotype 1b infection when the regimen includes the nucleotide analogue sofosbuvir.[9] Data suggest that genotype 1a infection is more difficult to cure than genotype 1b infection owing to the development of resistance.[7,13-17] Thus, careful assessment of the efficacy of individual regimens in patients with different subgenotypes of HCV infection is warranted.

Ribavirin is an important component of peginterferon-based therapy with first-generation protease inhibitors, but phase 2 clinical trials of interferon-free regimens based on direct-acting antiviral agents suggest that ribavirin may not always be required.[16,18-20] Although ribavirin appears to have less toxicity in the absence of peginterferon,[9,21] ribavirin is teratogenic and is associated with hemolytic anemia. Therefore, identifying patients who could be successfully treated without ribavirin is of great importance.

ABT-450, an inhibitor of the HCV nonstructural 3/4A (NS3/4A) protease, is administered with ritonavir (ABT-450/r) to increase ABT-450 plasma levels and half-life, permitting once-daily dosing.[22] Ombitasvir (ABT-267) is an inhibitor of the HCV NS5A replication complex, and dasabuvir (ABT-333) is a nonnucleoside NS5B polymerase inhibitor. All three agents have potent activity against HCV genotype 1 in vitro.[23] In a randomized, controlled, phase 2b study, a regimen of ABT-450/r, ombitasvir, and dasabuvir with ribavirin, administered for 12 weeks, was efficacious in previously untreated patients with HCV genotype 1 infection.[18] In addition, all 25 patients with genotype 1b infection who were treated without ribavirin had undetectable HCV RNA levels 24 weeks after the end of therapy.

On the basis of these data, two separate phase 3 trials were designed to evaluate the role of ribavirin in the treatment of patients with genotype 1a or 1b infection. We assessed the efficacy and safety of a 12-week treatment regimen of coformulated ABT-450/r–ombitasvir and dasabuvir with or without ribavirin in previously untreated patients without cirrhosis who had HCV genotype 1a infection (PEARL-IV study) or genotype 1b infection (PEARL-III study). The double-blind, placebo-controlled design of these studies permitted a thorough assessment of the contribution of ribavirin to the adverse-event profile of the combination regimen.

METHODS

PATIENTS

Patients 18 to 70 years of age were eligible for enrollment if they had chronic HCV genotype 1 infection with an HCV RNA level of more than 10,000 IU per milliliter and had never received any antiviral treatment for HCV. Patients with genotype 1a infection were screened at 53 sites in Canada, the United States, and the United Kingdom (PEARL-IV study). Patients with genotype 1b infection were screened at 50 sites in Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, the Russian Federation, Spain, and the United States (PEARL-III study). For both studies, eligible patients had no evidence of cirrhosis as documented by means of a liver biopsy within the previous 24 months, transient elastography (FibroScan), or noninvasive assessment of serum markers (FibroTest). Patients were excluded if they had coinfection with human immunodeficiency virus or hepatitis B virus or if they had infection with any HCV genotype other than 1a (PEARL-IV study) or 1b (PEARL-III study). Detailed eligibility

criteria and information on fibrosis scoring are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY DESIGNS

Patients in both studies were stratified according to *IL28B* genotype (CC vs. non-CC) and randomly assigned in a 1:2 ratio (genotype 1a study) or a 1:1 ratio (genotype 1b study) to receive either ribavirin twice daily according to body weight (1000 mg daily if the body weight was <75 kg and 1200 mg daily if the body weight was ≥75 kg) or matching placebo for 12 weeks. All the patients received open-label ABT-450/r–ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir) and dasabuvir (250 mg twice daily) for 12 weeks (Fig. 1). Visits were scheduled at weeks 0, 1, 2, 4, 6, 8, 10, and 12 of the treatment period, and patients were followed for 48 weeks after the treatment period. The investigators, patients, and study sponsor (AbbVie) were unaware of the treatment assignments and hemoglobin or hematocrit values. If a predefined toxicity criterion for hemoglobin values was met, all hematologic laboratory data were disclosed to the site investigator to allow for appropriate patient care. Additional details on study designs are provided in the Supplementary Appendix.

The studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and guidelines governing clinical-study conduct and ethical principles that have their origin in the Declaration of Helsinki. All the patients provided written informed consent. The studies were designed by the study sponsor. The investigators and sponsor jointly conducted the study and gathered the data. The sponsor conducted the data analyses. All the authors signed a confidentiality agreement with the sponsor. The first draft of the manuscript was written by a sponsor-employed medical writer, with input from all the authors. All the authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the studies to the protocol, available at NEJM.org.

EFFICACY AND SAFETY ASSESSMENTS

Details of the collection of plasma samples, HCV RNA measurement, virologic-failure criteria, resistance testing, and logistic-regression analyses of response predictors are available in the Supplementary Appendix. Adverse-event assessment and clinical laboratory testing were performed at each study visit during treatment and in the follow-up period. Adverse events were reported from the time of study-treatment initiation until 30 days after the last dose. Data on serious adverse events were collected throughout the study.

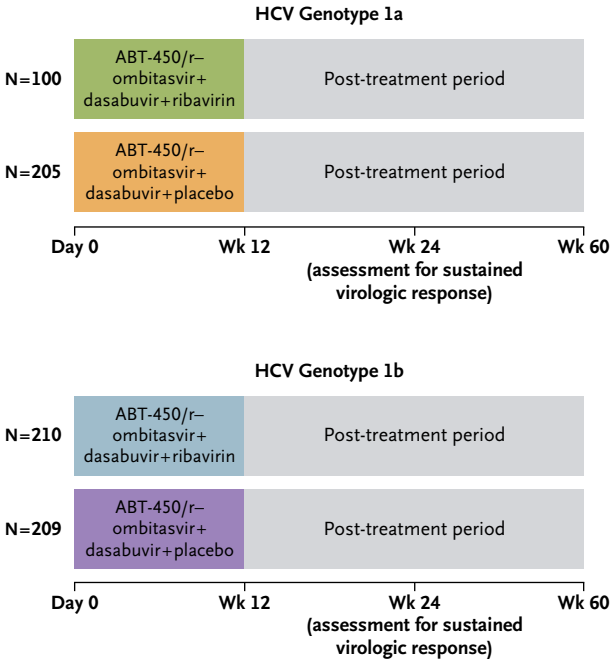

Figure 1. Study Designs.

Patients with hepatitis C virus (HCV) genotype 1a infection (PEARL-IV study) or genotype 1b infection (PEARL-III study) and no cirrhosis were randomly assigned to receive ribavirin (1000 or 1200 mg daily according to body weight) or matching placebo for 12 weeks. All patients received ABT-450 with ritonavir (ABT-450/r)–ombitasvir (at a once-daily dose of 150 mg of ABT-450, 100 mg of ritonavir, and 25 mg of ombitasvir) and dasabuvir (250 mg twice daily) for 12 weeks.

EFFICACY END POINTS

The primary efficacy end point for both studies was a sustained virologic response (a plasma HCV RNA level of <25 IU per milliliter) 12 weeks after the end of treatment. The primary objective of both studies was to assess the noninferiority of the rate of sustained virologic response at post-treatment week 12 in each study group, as compared with the historical rate with telaprevir plus peginterferon–ribavirin among previously

untreated patients with the corresponding HCV subgenotype. The historical rate was 72% among patients with genotype 1a infection (95% confidence interval [CI], 68 to 75) and 80% among those with genotype 1b infection (95% CI, 75 to 84) (see the Supplementary Appendix for details). Secondary efficacy objectives in each study were to assess the noninferiority of the sustained-virologic-response rate in the group that did not receive ribavirin as compared with the group that received ribavirin, the superiority of the rate at post-treatment week 12 in each group as compared with the historical rate with telaprevir plus peginterferon–ribavirin in the corresponding patient population, the percentage of patients in each group with a hemoglobin level below the lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after treatment.

STATISTICAL ANALYSIS

Efficacy analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of a study drug. For the analysis of whether the rate of sustained virologic response with the interferon-free regimen was noninferior to the historical rate with telaprevir plus peginterferon–ribavirin, a noninferiority margin of 10.5 percentage points was used. To establish that the rate with the interferon-free regimen was noninferior to the historical rate, the lower boundary of the 95% confidence interval (based on the normal approximation to the binomial distribution) had to exceed 73% for the genotype 1b study and

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	HCV Genotype 1a		HCV Genotype 1b	
	Antiviral Regimen with Ribavirin (N=100)	Antiviral Regimen without Ribavirin (N=205)	Antiviral Regimen with Ribavirin (N=210)	Antiviral Regimen without Ribavirin (N=209)
Male sex — no. (%)	70 (70.0)	129 (62.9)	106 (50.5)	86 (41.1)
Race — no./total no. (%)†				
White	86/100 (86.0)	171/205 (83.4)	198/210 (94.3)	196/208 (94.2)
Black	10/100 (10.0)	26/205 (12.7)	10/210 (4.8)	10/208 (4.8)
Other	4/100 (4.0)	8/205 (3.9)	2/210 (1.0)	2/208 (1.0)
Hispanic or Latino ethnic group — no. (%)†	10 (10.0)	18 (8.8)	2 (1.0)	5 (2.4)
Age — yr	51.6±11.0	51.4±10.6	48.4±11.9	49.2±12.0
Geographic region — no. (%)				
North America	92 (92.0)	186 (90.7)	48 (22.9)	47 (22.5)
Europe	8 (8.0)	19 (9.3)	162 (77.1)	162 (77.5)
Body-mass index‡	26.9±4.0	26.7±4.3	25.8±3.8	26.1±4.2
Metavir fibrosis score — no./total no. (%)§				
F0 or F1	63/100 (63.0)	132/205 (64.4)	150/210 (71.4)	141/208 (67.8)
F2	21/100 (21.0)	35/205 (17.1)	38/210 (18.1)	47/208 (22.6)
F3¶	16/100 (16.0)	38/205 (18.5)	22/210 (10.5)	20/208 (9.6)
IL28B CC genotype — no. (%)	31 (31.0)	63 (30.7)	44 (21.0)	44 (21.1)
HCV RNA — $\log_{10}$ IU/ml	6.64±0.50	6.53±0.68	6.29±0.77	6.33±0.67
HCV RNA ≥800,000 IU/ml — no. (%)	92 (92.0)	172 (83.9)	159 (75.7)	148 (70.8)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between treatment groups in either study. HCV denotes hepatitis C virus.
† 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 Metavir fibrosis score (on a scale from F0 to F4, with F4 consistent with cirrhosis) was based on liver biopsy or derived from FibroTest or FibroScan results. Biopsy confirmation of the absence of cirrhosis was required for patients with a FibroTest result of F4.
¶ Four patients in the genotype 1a study were enrolled with a FibroTest result of F4. In three of these patients, a biopsy result subsequently ruled out the presence of cirrhosis. No confirmatory liver biopsy or FibroScan data were available for the fourth patient.

65% for the genotype 1a study. Superiority could be established if the lower boundary of the confidence interval for the interferon-free regimen was greater than the upper boundary of the confidence interval for the historical rate: 84% for the genotype 1b study and 75% for the genotype 1a study. The assessment of the noninferiority of the regimen without ribavirin as compared with the regimen with ribavirin was based on a noninferiority margin of 10.5 percentage points.[24] Details of the efficacy analyses, including the fixed-sequence testing plan for the primary and secondary end points, are provided in the Supplementary Appendix.

Safety analyses compared the rate of adverse events and laboratory abnormalities between treatment groups in each study with the use of Fisher's exact test. Sample-size determination is described in the Supplementary Appendix. SAS software for the UNIX operating system (SAS Institute) was used for all analyses. All statistical tests and all confidence intervals were two-sided, with a significance level of 0.05.

RESULTS

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

In the genotype 1a study, 305 of 436 screened patients underwent randomization and received at least one dose of a study drug (Fig. S1 in the Supplementary Appendix). A total of 629 patients were screened for the genotype 1b study, of whom 419 underwent randomization and received at least one dose of a study drug. Baseline demographic and clinical characteristics were well balanced between the two groups in each study (Table 1). The majority of patients in the genotype 1a study were enrolled in North America, whereas the majority of patients in the genotype 1b study were enrolled in Europe. Among patients enrolled in the United States, blacks accounted for 14.2% of patients in the genotype 1a study (35 of 247 patients) and 21.1% of patients in the genotype 1b study (20 of 95 patients).

EFFICACY OUTCOMES

Genotype 1a Study

After 12 weeks of treatment with ABT-450/r–ombitasvir and dasabuvir in the genotype 1a study, 97 of 100 patients who received the antiviral regimen with ribavirin had a sustained virologic response at post-treatment week 12, for a rate of 97.0% (95% CI, 93.7 to 100); 185 of 205 patients who received the regimen without ribavirin had a sustained virologic response, for a rate of 90.2% (95% CI, 86.2 to 94.3) (Fig. 2). Hence, the sustained-virologic-response rates for the regimens with and without ribavirin were both noninferior and superior to the historical rate with telaprevir plus peginterferon–ribavirin in previously untreated adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the confidence interval for the difference (–6.8 percentage points [95% CI, –12.0 to –1.5]) crossed the noninferiority margin of 10.5 percentage points. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups.

A total of 18 patients with genotype 1a infection had virologic failure, 16 of whom received the regimen without ribavirin. Of the 3 patients with genotype 1a infection who received the regimen with ribavirin and did not have a sus-

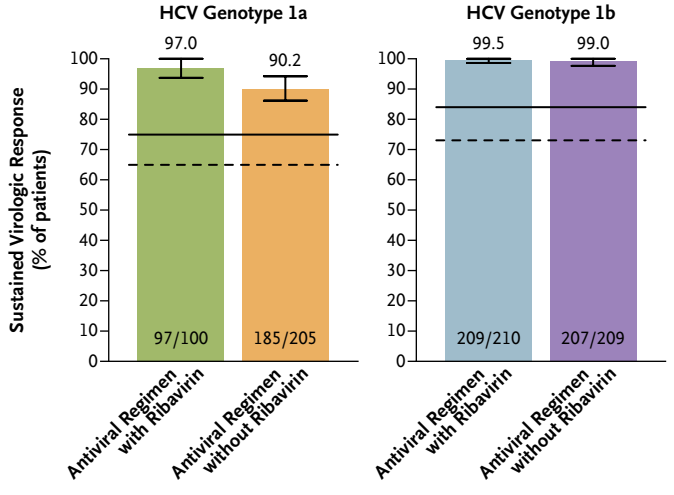

Figure 2. Sustained Virologic Response at 12 Weeks after the End of Treatment.

The dashed horizontal lines indicate noninferiority thresholds, based on the historical rate of sustained virologic response with telaprevir plus peginterferon–ribavirin, for the genotype 1a study (65%) and genotype 1b study (73%). The solid horizontal lines indicate superiority thresholds, based on the historical rate with telaprevir plus peginterferon–ribavirin, for the genotype 1a study (75%) and genotype 1b study (84%). The I bars indicate 95% confidence intervals.

tained virologic response, 2 had virologic failure (1 had a rebound in HCV RNA levels during treatment and 1 had a relapse after treatment), and 1 did not complete follow-up testing at post-treatment week 12. Of the 16 patients with genotype 1a infection who received the regimen without ribavirin and had virologic failure, 6 had a virologic rebound during treatment and 10 had a relapse after treatment. All the patients with a relapse received at least 11 weeks of treatment. Adherence to the dosing regimen for each study drug was greater than 95% for 16 of the 17 patients with virologic failure for whom data were available; 1 patient who received the antiviral regimen without ribavirin and had a virologic rebound took 88.5% of the planned ABT-450/r–ombitasvir doses and 90.8% of the planned dasabuvir doses. On the basis of logistic-regression analyses of baseline demographic and clinical characteristics, only *IL28B* CC genotype, which has historically been associated with increased rates of response to treatment for HCV infection, was associated with an increased rate of sustained virologic response among patients with genotype 1a infection (P=0.03).

At the time of virologic failure, each of the 18 patients with genotype 1a infection and a virologic failure had at least one resistance-associated variant known to be selected by one of the three direct-acting antiviral agents included in the regimen. The most frequently detected variants in patients with virologic failure were D168V in NS3, M28T and Q30R in NS5A, and S556G in NS5B.

Genotype 1b Study

In this study, 209 of the 210 patients who received the antiviral regimen with ribavirin had a sustained virologic response at post-treatment week 12, for a rate of 99.5% (95% CI, 98.6 to 100.0); 207 of the 209 patients who received the regimen without ribavirin had a sustained virologic response, for a rate of 99.0% (95% CI, 97.7 to 100.0). Thus, the sustained-virologic-response rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir plus peginterferon–ribavirin among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the sustained-virologic-response rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, –0.5 percentage points [95% CI, –2.1 to 1.1]).

Only one patient with genotype 1b infection had virologic failure during treatment; this patient, who received the antiviral regimen with ribavirin, had a virologic rebound during treatment. The two patients who received the regimen without ribavirin and did not have a sustained virologic response completed treatment but did not complete follow-up testing at post-treatment week 12 (Table 2). Owing to the high

Table 2. Sustained Virologic Response and Reasons for Nonresponse.

Variable	HCV Genotype 1a		HCV Genotype 1b	
	Antiviral Regimen with Ribavirin (N=100)	Antiviral Regimen without Ribavirin (N=205)	Antiviral Regimen with Ribavirin (N=210)	Antiviral Regimen without Ribavirin (N=209)
Sustained virologic response at post-treatment wk 12 — no. (%)	97 (97.0)	185 (90.2)	209 (99.5)	207 (99.0)
Reasons for nonresponse				
Virologic failure during treatment — no. (%)	1 (1.0)	6 (2.9)	1 (0.5)	0
Relapse — no./total no. (%)*	1/98 (1.0)	10/194 (5.2)	0/208	0/207
Early discontinuation of study treatment — no. (%)	0	3 (1.5)	0	0
Missing data at post-treatment wk 12 — no. (%)	1 (1.0)	1 (0.5)	0	2 (1.0)

* Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per milliliter or more between the final visit during the double-blind treatment period and 12 weeks after the last dose of study drug among patients who completed treatment (duration of study-drug exposure, ≥77 days), had an HCV RNA level of less than 25 IU per milliliter at the final visit during the double-blind treatment period, and had data on HCV RNA levels available after the completion of treatment.

rates of sustained virologic response, there were no significant predictors of virologic failure.

ADVERSE EVENTS

In both studies, adverse events were more frequently reported in the groups receiving antiviral regimens that contained ribavirin than in the groups that received the ribavirin-free regimen (P=0.03 in the genotype 1a study and P=0.003 in the genotype 1b study) (Table 3). The most common adverse events reported in the two studies, headache and fatigue, did not differ significantly in either study between the group that received ribavirin and the group that did not receive it. Among other common adverse events, pruritus, nausea, and insomnia occurred at a higher frequency among patients who received ribavirin than among those who did not in one or both studies. The majority of adverse events in all treatment groups were mild; overall, two patients (both in the genotype 1a study) discontinued the study drugs owing to adverse events.

Serious adverse events occurred in eight patients in the genotype 1b study (four who received ribavirin and four who did not) and in four patients in the genotype 1a study (three who received ribavirin and one who did not). All patients with a serious adverse event had a sustained virologic response. Details of all serious adverse events are provided in Table S5 in the Supplementary Appendix.

Table 3. Adverse Events and Laboratory Abnormalities.*

Event	HCV Genotype 1a			HCV Genotype 1b		
	Antiviral Regimen with Ribavirin (N=100)	Antiviral Regimen without Ribavirin (N=205)	P Value	Antiviral Regimen with Ribavirin (N=210)	Antiviral Regimen without Ribavirin (N=209)	P Value
Any adverse event — no. (%)	92 (92.0)	169 (82.4)	0.03	168 (80.0)	140 (67.0)	0.003
Any severe adverse event — no. (%)†	2 (2.0)	4 (2.0)		2 (1.0)	1 (0.5)	
Any serious adverse event — no. (%)‡	3 (3.0)	1 (0.5)		4 (1.9)	4 (1.9)	
Common adverse events — no. (%)§						
Headache	25 (25.0)	58 (28.3)		51 (24.3)	49 (23.4)	
Fatigue	46 (46.0)	72 (35.1)		45 (21.4)	48 (23.0)	
Pruritus	10 (10.0)	12 (5.9)		25 (11.9)	11 (5.3)	0.02
Nausea	21 (21.0)	28 (13.7)		23 (11.0)	9 (4.3)	0.02
Insomnia	17 (17.0)	16 (7.8)	0.02	19 (9.0)	7 (3.3)	0.02
Diarrhea	14 (14.0)	33 (16.1)		9 (4.3)	13 (6.2)	
Laboratory abnormalities						
Hemoglobin <LLN — no./total no. (%)¶	42/100 (42.0)	8/203 (3.9)	<0.001	106/207 (51.2)	7/205 (3.4)	<0.001
Hemoglobin ≤10 g/dl — no. (%)	4 (4.0)	0	0.01	19 (9.0)	0	<0.001
Total bilirubin >3× ULN — no. (%)	3 (3.0)	1 (0.5)		12 (5.7)	1 (0.5)	0.003
Alanine aminotransferase >5× ULN — no. (%)	1 (1.0)	1 (0.5)		2 (1.0)	0	
Aspartate aminotransferase >5× ULN — no.	0	0		0	0	
Alkaline phosphatase >2.5× ULN — no.	0	0		0	0	

* LLN denotes the lower limit of the normal range, and ULN the upper limit of the normal range.
† A severe adverse event was defined as one that caused considerable interference with the usual activities of the patient and that may have been incapacitating or life-threatening.
‡ A serious adverse event was defined as one that resulted in hospitalization, persistent or clinically significant disability, or death or that was life-threatening or required medical intervention or hospitalization to prevent a serious outcome.
§ All other adverse events occurred in less than 10% of patients in any treatment group.
¶ Patients with a hemoglobin level below the LLN at baseline were not included in the analysis.

DECREASED HEMOGLOBIN LEVELS

Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). A hemoglobin level of less than 10 g per deciliter at any time during treatment occurred in 4.0% of patients with genotype 1a infection who received ribavirin and in 9.0% of patients with genotype 1b infection who received ribavirin but did not occur in any patients who received the ribavirin-free regimen (Table 3). The ribavirin dose was reduced in accordance with the protocol because of a decreased hemoglobin level in 6 patients with genotype 1a infection who received ribavirin (6.0%) and in 16 patients with genotype 1b infection who received ribavirin (7.6%); all these patients had a sustained virologic response. Additional data on hemoglobin levels are provided in the Supplementary Appendix.

OTHER LABORATORY ABNORMALITIES

In both studies, the proportions of patients with elevations in the serum level of bilirubin were higher in the groups that received the ribavirin-containing regimen than in the groups that received the ribavirin-free regimen (Tables S6 and S7 in the Supplementary Appendix). Elevated levels of indirect (unconjugated) bilirubin primarily accounted for the abnormalities in both studies. Mean bilirubin levels peaked 1 week after the start of study-drug treatment and stabilized or normalized thereafter; maximal observed bilirubin levels were 6.5 mg per deciliter (110 μmol per liter) in the genotype 1a study and 9.4 mg per deciliter (160 μmol per liter) in the genotype 1b study. Elevations in the bilirubin level were not associated with elevations in aminotransferase levels. Additional details on laboratory abnormalities are provided in the Supplementary Appendix.

DISCUSSION

In two phase 3 studies (PEARL-III and PEARL-IV), 90.2 to 99.5% of previously untreated patients with HCV genotype 1 infection and no cirrhosis had a sustained virologic response after 12 weeks of treatment with ABT-450/r–ombitasvir and dasabuvir with or without ribavirin. Response rates in all treatment groups were superior to the historical response rate with a peginterferon-containing telaprevir-based regimen.[5] These findings suggest that in previously untreated patients with HCV infection and no cirrhosis, this 12-week regimen of three direct-acting antiviral agents is efficacious both with and without ribavirin.

We also assessed the contribution of ribavirin to the treatment response and safety profile of the regimen. The effect of ribavirin on the treatment response in patients with HCV genotype 1a infection differed from that in patients with genotype 1b infection. The inclusion of ribavirin did not significantly affect the sustained-virologic-response rate among patients with genotype 1b infection, because the rate was 99.0% in the group that did not receive ribavirin and 99.5% in the group that received it. Thus, in this patient population, the 12-week regimen of ABT-450/r–ombitasvir and dasabuvir resulted in similarly high rates of sustained virologic response with and without ribavirin, results that are consistent with those of a phase 2b study[18] and phase 3 studies[25,26] of this regimen. In contrast, although more than 90% of patients in each treatment group in the genotype 1a study had a sustained virologic response, the response rate in the group that that received the ribavirin-free regimen did not meet the criterion for noninferiority to the rate in the group that received the ribavirin-containing regimen owing to a higher rate of virologic failure with the ribavirin-free regimen. A total of 18 patients with genotype 1a infection had virologic failure, and only 2 of these patients received ribavirin. Hence, the use of ribavirin in this population appears to confer an additional benefit.

Regardless of whether the antiviral regimen included ribavirin, the rate of discontinuation of the study drugs owing to adverse events was low (<1%). As compared with the groups that did not receive ribavirin, the groups that did receive it had more adverse events, particularly pruritus, nausea, and insomnia — events that are known to be associated with ribavirin. In addition, laboratory abnormalities that have historically been associated with ribavirin — decreases in the hemoglobin level and increases in the total biliru-

bin level — were more common in the groups that received ribavirin. The pattern of bilirubin elevations across treatment regimens confirmed that the hyperbilirubinemic effect of ABT-450, an inhibitor of the bilirubin transporter OATP1B1, is enhanced by ribavirin-associated hemolysis. However, these abnormalities did not appear to affect the likelihood of treatment success and did not result in treatment discontinuation. Overall, the adverse events observed in these two phase 3 trials were consistent with those observed in past trials with these regimens.

Studies of direct-acting antiviral therapy have shown that these regimens can result in high rates of sustained virologic response. The role of and need for ribavirin in maximizing sustained-virologic-response rates in different patient populations remain incompletely characterized by clinical studies. Exploratory studies have shown sustained-virologic-response rates of 95% or higher when sofosbuvir is combined with other direct-acting antiviral agents (ledipasvir, daclatasvir, or simeprevir) with or without ribavirin, although these findings remain to be confirmed by larger trials.[19,20,27,28] Although these results suggest that sufficiently efficacious ribavirin-free treatments may obviate the need for ribavirin in some patients, larger studies will be needed to determine which patient populations may require ribavirin for the greatest chance of virologic cure.

The PEARL-III and PEARL-IV studies were double-blind, randomized trials with large samples and a broad geographic scope of enrollment. The patient populations were representative of typical North American or European populations with genotype 1a or 1b infection, the two most prevalent subgenotypes in North America, Asia, and Europe. Rates of premature discontinuation and loss to follow-up were low in both trials. A limitation of the studies was the inability to completely conceal the ribavirin and placebo assignments from patients and investigators because of the characteristic adverse events and laboratory abnormalities associated with ribavirin. In addition, the studies did not include previously treated patients or patients with cirrhosis, although this regimen with ribavirin was associated with a high rate of sustained virologic response in these patient populations in recent studies.[25,26]

Although the two studies showed that premature discontinuation and serious adverse events were uncommon with the 12-week course of all-oral therapy that included ribavirin, as well as with the ribavirin-free regimen, some patients may benefit from a ribavirin-free treatment option, including patients with contraindications to ribavirin therapy, such as hemoglobinopathies and severe cardiac or pulmonary disease, and those with severe renal impairment. Given the known teratogenicity of ribavirin, a ribavirin-free regimen would also be preferable for some women of childbearing potential.

In conclusion, previously untreated patients with HCV genotype 1a or 1b infection and no cirrhosis who received ABT-450/r–ombitasvir and dasabuvir with or without ribavirin had high sustained-virologic-response rates that were superior to the historical response rate with peginterferon–ribavirin plus telaprevir. Although ribavirin did not improve the response in patients with genotype 1b infection, our findings suggest that ribavirin confers an additional benefit for patients with genotype 1a infection.

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

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APPENDIX

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REFERENCES

1. Hepatitis C: fact sheet no. 164. Geneva: World Health Organization (http://www.who.int/mediacentre/factsheets/fs164/en).
2. Rosen HR. Chronic hepatitis C infection. N Engl J Med 2011;364:2429-38.
3. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
4. Global Alert and Response (GAR): hepatitis C. Geneva: World Health Organization (http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index2.html).
5. 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.
6. 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.
7. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360:1827-38.
8. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. Hepatology 2013;58:1918-29.
9. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
10. Chung RT. A watershed moment in the treatment of hepatitis C. N Engl J Med 2012;366:273-5.
11. Hézode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009;360:1839-50.
12. Lok AS, Gardiner DF, Hezode C, et al. Randomized trial of daclatasvir and asunaprevir with or without PegIFN/RBV for hepatitis C virus genotype 1 null responders. J Hepatol 2014;60:490-9.
13. Sun SC, Bae A, Qi X, et al. Natural variation in drug susceptibility to HCV polymerase inhibitors in treatment-naïve HCV patient isolates. J Viral Hepat 2011;18:861-70.
14. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. Gastroenterology 2010;138:447-62.
15. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009;50:1709-18.
16. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med 2013;369:630-9.
17. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 2012;366:216-24.
18. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222-32.
19. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44.
20. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515-23. [Erratum, Lancet 2014;383:870.]
21. Jacobson IM, Kowdley KV, Kwo PY. Anemia management in the era of triple combination therapy for chronic HCV. Gastroenterol Hepatol (N Y) 2012;8:Suppl 6:1-16.
22. Menon RM, Klein CE, Lawal AA, et al. Pharmacokinetics and tolerability of the HCV protease inhibitor ABT-450 following single ascending doses in healthy adult volunteers with and without ritonavir. In: Program and abstracts of HepDART 2009, Kohala Coast, HI, December 6–10, 2009.
23. Pilot-Matias T, Koev G, Krishnan P, et al. In vitro combinatory effect of HCV NS3/4A protease inhibitor ABT-450, NS5A inhibitor ABT-267, and non-nucleoside NS5B polymerase inhibitor ABT-333. In: Program and abstracts of the 47th Annual Meeting of the European Association for the Study of the Liver, Barcelona, April 18–22, 2012.
24. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-24. [Erratum, N Engl J Med 2011;365:1551.]
25. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r–ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
26. Poordad F, Hezode C, Trinh R, et al. ABT-450/r–ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. DOI: 10.1056/NEJMoa1402869.
27. Jacobson IM, Ghalib RH, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. In: Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, November 1–5, 2013.
28. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-21.