

ORIGINAL ARTICLE

ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis

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ABSTRACT

BACKGROUND

Interferon-containing regimens for the treatment of hepatitis C virus (HCV) infection are associated with increased toxic effects in patients who also have cirrhosis. We evaluated the interferon-free combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r), the NS5A inhibitor ombitasvir (ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (ABT-333), and ribavirin in an open-label phase 3 trial involving previously untreated and previously treated adults with HCV genotype 1 infection and compensated cirrhosis.

METHODS

We randomly assigned 380 patients with Child–Pugh class A cirrhosis to receive either 12 or 24 weeks of treatment with 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. The primary efficacy end point was a sustained virologic response 12 weeks after the end of treatment. The rate of sustained virologic response in each group was compared with the estimated rate with a telaprevir-based regimen (47%; 95% confidence interval [CI], 41 to 54). A noninferiority margin of 10.5 percentage points established 43% as the noninferiority threshold; the superiority threshold was 54%.

RESULTS

A total of 191 of 208 patients who received 12 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 91.8% (97.5% CI, 87.6 to 96.1). A total of 165 of 172 patients who received 24 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 95.9% (97.5% CI, 92.6 to 99.3). These rates were superior to the historical control rate. The three most common adverse events were fatigue (in 32.7% of patients in the 12-week group and 46.5% of patients in the 24-week group), headache (in 27.9% and 30.8%, respectively), and nausea (in 17.8% and 20.3%, respectively). The hemoglobin level was less than 10 g per deciliter in 7.2% and 11.0% of patients in the respective groups. Overall, 2.1% of patients discontinued treatment owing to adverse events.

CONCLUSIONS

In this phase 3 trial of an oral, interferon-free regimen evaluated exclusively in patients with HCV genotype 1 infection and cirrhosis, multitargeted therapy with the use of three new antiviral agents and ribavirin resulted in high rates of sustained virologic response. Drug discontinuations due to adverse events were infrequent. (Funded by AbbVie; TURQUOISE-II ClinicalTrials.gov number, NCT01704755.)

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AN ESTIMATED 184 MILLION PEOPLE worldwide have hepatitis C virus (HCV) infection,¹ a leading cause of chronic liver disease and the leading indication for liver transplantation globally.^{2,3} Approximately 25% of persons with HCV infection in the United States have cirrhosis, and this number is expected to rise to 37% by 2020.^{4,5} Eradication of HCV with antiviral therapy reduces the risk of hepatic decompensation, hepatocellular carcinoma, and death from a liver-related cause or any cause.⁶⁻¹⁰

Among patients with HCV infection and cirrhosis in whom peginterferon-ribavirin treatment has failed, rates of sustained virologic response to retreatment with interferon-containing regimens are as low as 14%.¹¹⁻¹⁹ In addition, treatment for HCV infection, especially with interferon-containing regimens, in patients with cirrhosis is associated with increased toxic effects.^{20,21} Peginterferon-ribavirin plus telaprevir or boceprevir is not recommended for patients with cirrhosis who have a platelet count of less than 100,000 per cubic millimeter and an albumin level of less than 35 g per liter, owing to the risk of severe complications, including death.²⁰ Interferon-free combinations of direct-acting antiviral agents are therefore needed to improve the efficacy and safety of HCV treatment in patients with cirrhosis.

ABT-450, an inhibitor of the HCV nonstructural 3/4A (NS3/4A) protease, is administered with ritonavir (ABT-450/r).²² As a pharmacoenhancer, ritonavir has no activity against HCV; instead, it inhibits ABT-450 metabolism, increasing peak and trough drug exposures and allowing for a once-daily dose of ABT-450.²³ Ombitasvir (ABT-267) is an HCV NS5A inhibitor, and dasabuvir (ABT-333) is a nonnucleoside HCV NS5B RNA polymerase inhibitor.²² In phase 3 studies involving patients who had chronic HCV genotype 1 infection without cirrhosis, 12 weeks of treatment with the all-oral, interferon-free combination of ABT-450/r-ombitasvir and dasabuvir, administered with ribavirin, resulted in a rate of sustained virologic response of 96% among both previously untreated patients²⁴ and patients in whom prior peginterferon-ribavirin treatment had failed.²⁵

We report the results of TURQUOISE-II, a phase 3, randomized, open-label, international trial that evaluated the safety and efficacy of the

combination of coformulated ABT-450/r-ombitasvir and dasabuvir with ribavirin for 12 or 24 weeks in previously untreated and previously treated adults with chronic HCV genotype 1 infection and compensated cirrhosis.

METHODS

STUDY PATIENTS

Patients were screened from October 24, 2012, through April 30, 2013, at 78 sites in North America and Europe. Patients 18 to 70 years of age were eligible for enrollment if they had previously untreated or previously treated chronic HCV genotype 1 infection and a plasma HCV RNA level of more than 10,000 IU per milliliter. Eligible patients had documentation of cirrhosis by means of liver biopsy (Metavir score >3 or Ishak score >4) or FibroScan result (≥ 14.6 kPa within 6 months before screening or during screening), a Child-Pugh class A score of less than 7 at screening, and no current or past clinical evidence of Child-Pugh class B or C disease. Key eligibility criteria were a platelet count of 60,000 per cubic millimeter or more, a serum albumin level of 2.8 g per deciliter or more, a total bilirubin level of less than 3 mg per deciliter, an international normalized ratio of 2.3 or less, and a serum alpha-fetoprotein level of 100 ng per milliliter or less. Exclusion criteria were prior therapy with direct-acting antiviral agents (e.g., telaprevir and boceprevir) for the treatment of HCV infection and a diagnosis of hepatocellular carcinoma. For detailed eligibility criteria, see the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY DESIGN AND OVERSIGHT

Patients were randomly assigned in a ratio of approximately 1:1 (see the Supplementary Appendix) to the 12-week or 24-week treatment group (Fig. S1 in the Supplementary Appendix), with stratification according to previous peginterferon-ribavirin treatment for HCV infection (no vs. yes). Previously untreated patients were stratified according to HCV subgenotype (1a vs. 1b) and interleukin 28B (*IL28B*) genotype (CC vs. non-CC), a genetic marker associated with treatment outcomes.²⁶ Previously treated patients were stratified according to HCV subgenotype and type of previous treatment failure: null response, partial

response, or relapse (see the Supplementary Appendix). Patients received coformulated 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) with ribavirin (1000 mg or 1200 mg daily, according to body weight, in two doses) for 12 weeks or 24 weeks.

The study was designed by the study investigators and the sponsor (AbbVie) according to Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable regulations, with approval by an institutional review board at each study site. All the patients provided written informed consent. The site investigators gathered the data, and the sponsor conducted the data analysis. The first draft of the manuscript was written by a medical writer employed by the sponsor. All the authors had full access to the data and participated in the development of the manuscript. All the authors confirm that the results presented are complete and accurate and that the study was conducted and reported according to the protocol (available at NEJM.org).

EFFICACY AND SAFETY ASSESSMENTS

The collection of plasma samples and measurement of HCV RNA levels are described in the Supplementary Appendix. Vital signs were monitored, adverse events were assessed, and clinical laboratory testing was performed at each visit during the treatment and post-treatment periods. Adverse events were classified by the site investigator as mild, moderate, or severe, and data on adverse events were collected from the time of the first dose of study medication until 30 days after the last dose. Data on serious adverse events were collected throughout the study.

EFFICACY END POINTS

The primary efficacy end point was a sustained virologic response (an HCV RNA level of <25 IU per milliliter [the lower limit of quantitation]) 12 weeks after the end of study-drug administration. HCV RNA levels were measured with the use of the COBAS TaqMan real-time reverse-transcriptase–polymerase-chain-reaction assay, version 2.0 (Roche). The primary study objectives were to assess the rate of sustained virologic response in the 12-week and 24-week groups for

noninferiority and superiority to a historical rate with telaprevir plus peginterferon–ribavirin among patients with HCV genotype 1 infection and cirrhosis. The key secondary efficacy end point was the percentage of patients with a sustained virologic response in the 24-week group as compared with the 12-week group. Other secondary efficacy end points were the percentage of patients in each group with virologic failure during treatment or relapse after treatment. A gatekeeping multiple-testing procedure (described in the Supplementary Appendix) was used for the primary efficacy end point and the key secondary efficacy end point. Rates of virologic failure during treatment and relapse after treatment were not part of the multiple-testing procedure, because no hypothesis was being tested for those two end points. The rate of sustained virologic response at post-treatment week 12 was also determined for patient subgroups defined according to prespecified baseline demographic or clinical characteristics.

Virologic failure during treatment was defined as two consecutive HCV RNA measurements of more than 1 \log_{10} IU per milliliter above the nadir at any time during treatment, an HCV RNA level of 25 IU per milliliter or more at all assessments during treatment among patients who received at least 6 weeks of treatment, or a confirmed HCV RNA level of 25 IU per milliliter or more after a level of less than 25 IU per milliliter during treatment. Virologic relapse was defined as a confirmed HCV RNA level of 25 IU per milliliter or more between the end of treatment and 12 weeks after the last dose of study drug among patients who completed treatment and had an HCV RNA level of less than 25 IU per milliliter at the final visit during the treatment period.

STATISTICAL ANALYSIS

Analyses were performed on the modified intent-to-treat population (all randomly assigned patients who received at least one dose of study drugs). For efficacy evaluations, the percentage of patients with a sustained virologic response at post-treatment week 12 and a two-sided 97.5% confidence interval (based on the normal approximation to the binomial distribution) were calculated for each treatment group.

Rates of sustained virologic response at post-treatment week 24 that were previously reported

for telaprevir^{11,12} were used to calculate a weighted average of rates of sustained virologic response among previously untreated and previously treated patients, reflective of the population that we expected to enroll in the TURQUOISE-II study (see the Supplementary Appendix). The estimated rate used for comparison was 47% (95% confidence interval [CI], 41 to 54). The noninferiority margin was 10.5 percentage points; for the rate of sustained virologic response with ABT-450/r-ombitasvir, dasabuvir, and ribavirin to be considered noninferior, the lower confidence bound had to exceed 43% (equal to the upper confidence bound of the historical rate with telaprevir plus peginterferon-ribavirin, 54%, minus 10.5 percentage points and rounded). For the rate of sustained virologic response with ABT-450/r-ombitasvir, dasabuvir, and ribavirin to be considered superior, the lower confidence bound had to exceed the upper confidence bound of the historical rate (54%).

The 12-week and 24-week groups were compared with the use of a logistic-regression model, as prespecified in the protocol for the key secondary efficacy end point, with treatment group, baseline log₁₀ HCV RNA level, HCV subtype (1a vs. 1b), *IL28B* genotype (CC vs. non-CC), and previous peginterferon-ribavirin treatment (no vs. yes) as predictors of the rate of sustained virologic response at post-treatment week 12. Rates of sustained virologic response were summarized for each treatment group and randomization stratum to assess responses across stratification variables. For exploratory purposes, a stepwise logistic-regression model was used to assess the association between the rate of sustained virologic response at post-treatment week 12 and continuous and categorical subgroup variables.

Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). A gatekeeping multiple-testing procedure was used to maintain a type I error rate of 0.05 for the analyses of the primary and key secondary efficacy end points (see the Supplementary Appendix, including Fig. S2). All statistical tests and confidence intervals were two-sided, with a significance level of 0.05. The number and percentage of patients with adverse events, abnormalities in laboratory values of grade 3 or 4, or abnormalities in hemoglobin levels were compared between treatment groups with the use of

Fisher's exact test. For additional details, see the Supplementary Appendix.

RESULTS

PATIENTS

Of 671 patients assessed for eligibility, 381 were enrolled in the study and 380 received at least one dose of study drugs. Ineligibility was the most common reason for nonenrollment (Fig. S3 in the Supplementary Appendix). Baseline demographic and clinical characteristics were similar in the two treatment groups (Table 1).

EFFICACY

A total of 191 of 208 patients who received 12 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 91.8% (97.5% CI, 87.6 to 96.1). A total of 165 of 172 patients who received 24 weeks of treatment had a sustained virologic response at post-treatment week 12, for a rate of 95.9% (97.5% CI, 92.6 to 99.3) (Fig. 1). In both treatment groups, the primary efficacy end points met the prespecified criteria for noninferiority and superiority to the historical rate with telaprevir plus peginterferon-ribavirin among patients with HCV genotype 1 infection and cirrhosis. Rates of sustained virologic response in subgroups defined by HCV subtype, status with respect to prior treatment, and type of treatment failure among previously treated patients were superior to the historical rate (Fig. 1). Rates did not differ substantially according to race, body-mass index, *IL28B* genotype, status with respect to a history of diabetes mellitus, status with respect to a history of depression or bipolar disorder, or baseline HCV RNA level, platelet count, or serum albumin level (Table S3 in the Supplementary Appendix).

The difference in the rates of sustained virologic response between the two treatment groups was not significant ($P=0.09$) (Fig. 1). Rates were similar in the two treatment groups across the randomization strata (Table 2). Among patients with HCV genotype 1a infection and a prior null response, 39 of 42 patients in the 24-week group had a sustained virologic response at post-treatment week 12 (92.9% [95% CI, 85.1 to 100]), as compared with 40 of 50 patients in the 12-week group (80.0% [95% CI, 68.9 to 91.1]).

A multivariate logistic-regression analysis showed that a prior null response to peginter-

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

Characteristic	12-Wk Group (N=208)	24-Wk Group (N=172)
Male sex — no. (%)	146 (70.2)	121 (70.3)
Race — no. (%)†		
White	199 (95.7)	161 (93.6)
Black	6 (2.9)	6 (3.5)
Asian	3 (1.4)	5 (2.9)
Hispanic or Latino ethnic group — no. (%)‡	25 (12.0)	20 (11.6)
Age — yr	57.1±7.0	56.5±7.9
Body-mass index‡	27.9±4.1	27.9±4.3
HCV subgenotype — no. (%)		
1a	140 (67.3)	121 (70.3)
1b	68 (32.7)	51 (29.7)
<i>IL28B</i> non-CC genotype — no. (%)	173 (83.2)	138 (80.2)
HCV RNA — log ₁₀ IU/ml	6.41±0.62	6.53±0.52
Prior treatment with peginterferon-ribavirin — no. (%)		
Null response§	75/122 (61.5)	62/98 (63.3)
Partial response¶	18/122 (14.8)	13/98 (13.3)
Relapse	29/122 (23.8)	23/98 (23.5)
Platelet count — ×10 ⁹ /liter		
Median	140.0	142.5
Interquartile range	104.0–188.5	105.0–183.0
Serum albumin — g/liter		
Median	40	39
Interquartile range	37–42	37–42

* Plus-minus values are means ±SD. Differences in baseline characteristics between the treatment groups were evaluated with the use of chi-square tests for categorical data and one-way analysis of variance for continuous data. There were no significant between-group differences in the listed baseline characteristics except for hepatitis C virus (HCV) RNA level ($P=0.04$). Details about randomization can be found in the Supplementary Appendix.

† 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.

§ Patients received at least 12 weeks of peginterferon-ribavirin for the treatment of HCV infection and did not have a reduction in the HCV RNA level of at least 2 log₁₀ IU per milliliter at week 12, or they received at least 4 weeks of peginterferon-ribavirin for the treatment of HCV infection and had a reduction in the HCV RNA level of less than 1 log₁₀ IU per milliliter at week 4 (≥25 days).

¶ Patients received at least 20 weeks of peginterferon-ribavirin for the treatment of HCV infection and had a reduction in the HCV RNA level of 2 log₁₀ IU per milliliter or more at week 12 but had a detectable HCV RNA level at the end of treatment.

|| Patients received at least 36 weeks of peginterferon-ribavirin for the treatment of HCV infection and had an undetectable level of HCV RNA at the end of treatment or thereafter but a detectable level within 52 weeks after treatment.

feron-ribavirin treatment, infection with HCV subgenotype 1a, and former injection-drug use were associated with a lower likelihood of a sustained virologic response at post-treatment week 12 (Table 3). When the self-reported variable of former injection-drug use was excluded from the model, a prior null response and infection with HCV subgenotype 1a were still associ-

ated with a lower likelihood of a sustained virologic response.

Virologic failure during treatment or relapse after treatment occurred in 13 of 208 patients in the 12-week group (6.2%) and 4 of 172 patients in the 24-week group (2.3%). Virologic failure during treatment occurred in 1 of 208 patients in the 12-week group (0.5% [95% CI, 0 to 1.4])

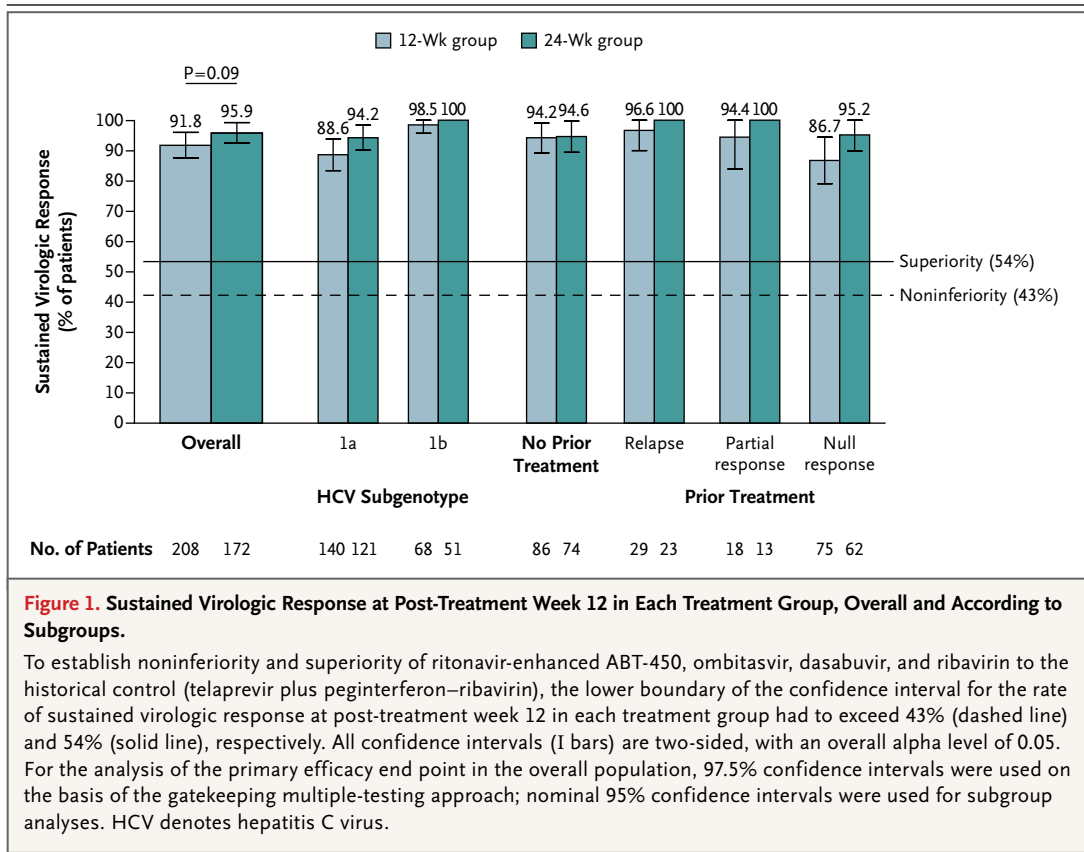


Table 2. Sustained Virologic Response at Post-Treatment Week 12 in Each Treatment Group, According to HCV Subgenotype and Status with Respect to Prior Treatment.*

Variable	12-Wk Group (N=208)	24-Wk Group (N=172)
	no./total no. (%)	
HCV genotype 1a infection		
No prior treatment	59/64 (92.2)	52/56 (92.9)
Prior treatment		
Null response	40/50 (80.0)	39/42 (92.9)
Partial response	11/11 (100)	10/10 (100)
Relapse	14/15 (93.3)	13/13 (100)
HCV genotype 1b infection		
No prior treatment	22/22 (100)	18/18 (100)
Prior treatment		
Null response	25/25 (100)	20/20 (100)
Partial response	6/7 (85.7)	3/3 (100)
Relapse	14/14 (100)	10/10 (100)

* Prior treatment refers to peginterferon–ribavirin for the treatment of HCV infection.

and in 3 of 172 patients in the 24-week group (1.7% [95% CI, 0 to 3.7]) (Table S4 in the Supplementary Appendix). Significantly more patients in the 12-week group than in the 24-week group had a relapse: 12 of 203 patients, for a rate of 5.9% (95% CI, 2.7 to 9.2), versus 1 of 164 patients, for a rate of 0.6% (95% CI, 0 to 1.8). Seven of the 12 patients with a relapse in the 12-week group (58.3%) had HCV genotype 1a infection and a prior null response to peginterferon–ribavirin treatment.

Virologic resistance was assessed by means of population sequencing of samples from the 17 patients who had virologic failure through post-treatment week 12. At the time of virologic failure, 2 patients had no resistance-associated variants detected in NS3, NS5A, or NS5B. The remaining 15 patients had resistance-associated variants in two or more of the drug targets, with variants D168V (NS3) and Q30R (NS5A) observed most frequently in patients with HCV genotype 1a infection and D168V (NS3), Y93H (NS5A), and C316Y and M414I (NS5B) observed in the single patient with HCV genotype 1b infection.

Table 3. Logistic-Regression Analysis of Association of Subgroup Variables with a Sustained Virologic Response at Post-Treatment Week 12.*

Variable	Estimated Odds Ratio (95% CI)	P Value
Model including former injection-drug use		
Previous peginterferon–ribavirin treatment (null response vs. partial response, relapse, or no prior treatment)	0.39 (0.16–0.94)	0.04
HCV subtype (1a vs. 1b)	0.12 (0.02–0.90)	0.04
Former injection-drug use (yes vs. no)	0.35 (0.14–0.86)	0.02
Model excluding former injection-drug use		
Previous peginterferon–ribavirin treatment (null response vs. partial response, relapse, or no prior treatment)	0.33 (0.13–0.80)	0.02
HCV subtype (1a vs. 1b)	0.10 (0.01–0.80)	0.03

* The model including former injection-drug use also adjusted for baseline Child–Pugh score and ethnic group; the model excluding former injection-drug use also adjusted for geographic region and treatment duration ($P > 0.05$). Candidate continuous variables considered were age, body-mass index, platelet count, serum albumin level, serum alpha-fetoprotein level, and HCV RNA level. Candidate categorical variables considered were treatment duration (12 weeks vs. 24 weeks), HCV subtype (1a vs. 1b), *IL28B* genotype (CC vs. non-CC), previous peginterferon–ribavirin treatment (null response vs. partial response, relapse, or no prior treatment), sex (female vs. male), race (black vs. nonblack), geographic region (Europe vs. North America), Child–Pugh score (5 vs. >5), history of diabetes (yes vs. no), history of depression or bipolar disorder (yes vs. no), former injection-drug use (yes vs. no), and ethnic group (Hispanic or Latino vs. not Hispanic or Latino). The significance level for entering predictors into and removing predictors from the model was 0.10. P values are based on the Wald test. CI denotes confidence interval.

SAFETY

Adverse events were common in both groups, although few occurred more commonly in the 24-week group than in the 12-week group (Table 4). Two percent of patients in either group discontinued the study drug owing to an adverse event. No specific adverse event led to premature discontinuation by more than one patient, and no pattern in the types of adverse events leading to discontinuation was observed (Table S5 in the Supplementary Appendix).

The most frequent grade 3 or 4 laboratory abnormalities observed during the treatment period were elevations in total bilirubin levels (in 37 of 380 patients [9.7%]), which predominantly reflected elevated indirect bilirubin values; patients with such elevations did not have concomitant abnormalities in aminotransferase levels of grade 3 or 4. No grade 4 elevations in the total bilirubin level (i.e., >10 times the upper limit of the normal range) were observed. Peak values generally occurred after week 1 or 2 of treatment and declined to baseline levels by the end of the treatment period. Six patients (1.6%) had clinical jaundice, and 2 patients reported scleral icterus. No patient discontinued treatment owing to hyperbilirubinemia.

Six patients (1.6%) had post-baseline elevations in the alanine aminotransferase level of at

least grade 3 during treatment or within 30 days after the end of treatment. Four of these patients completed the study treatment, with normal or grade 1 alanine aminotransferase levels in the post-treatment period; all four had a sustained virologic response by post-treatment week 12. In one of the two patients who prematurely discontinued the study treatment, the elevated alanine aminotransferase level was due to acute hepatitis; in the other patient, the elevation occurred after discontinuation of the study drug.

Grade 1 reductions in the hemoglobin level were common (Table 4). A total of 15 patients in the 12-week group (7.2%) and 19 patients in the 24-week group (11.0%) had a hemoglobin value of grade 2 or higher during the treatment period. In total, 34 patients required a reduction in the ribavirin dose because of anemia-related adverse events, and all 34 had a sustained virologic response at post-treatment week 12.

One patient had severe lactic acidosis in the context of metformin use and a subsequent ischemic liver injury requiring liver transplantation. Pathological examination of the liver revealed advanced cirrhosis with recent coagulative necrosis of most of the cirrhotic nodules, findings that are characteristic of severe ischemic or hypoxic injury. There was no evidence of diffuse microvesicular steatosis (characteristic of mito-

Table 4. Adverse Events and Laboratory Abnormalities.

Variable	12-Wk Group (N=208)	24-Wk Group (N=172)	Total (N=380)
Any adverse event	191 (91.8)	156 (90.7)	347 (91.3)
Adverse event leading to treatment discontinuation*	4 (1.9)	4 (2.3)	8 (2.1)
Serious adverse event†‡	13 (6.2)	8 (4.7)	21 (5.5)
Common adverse events‡‡			
Fatigue	68 (32.7)	80 (46.5)§	148 (38.9)
Headache	58 (27.9)	53 (30.8)	111 (29.2)
Nausea	37 (17.8)	35 (20.3)	72 (18.9)
Pruritus	38 (18.3)	33 (19.2)	71 (18.7)
Insomnia	32 (15.4)	31 (18.0)	63 (16.6)
Diarrhea	30 (14.4)	29 (16.9)	59 (15.5)
Asthenia	29 (13.9)	22 (12.8)	51 (13.4)
Rash	23 (11.1)	25 (14.5)	48 (12.6)
Irritability	15 (7.2)	21 (12.2)	36 (9.5)
Anemia	16 (7.7)	18 (10.5)	34 (8.9)
Dyspnea	12 (5.8)	21 (12.2)¶	33 (8.7)
Death	1 (0.5)	0	1 (0.3)
Laboratory abnormalities			
Alanine aminotransferase, grade 3 or 4	6 (2.9)	0¶	6 (1.6)
Aspartate aminotransferase, grade 3 or 4	1 (0.5)	0	1 (0.3)
Alkaline phosphatase, grade 3 or 4	0	0	0
Total bilirubin, grade 3 or 4	28 (13.5)	9 (5.2)§	37 (9.7)
Hemoglobin			
Grade 1	103 (49.5)	97 (56.4)	200 (52.6)
Grade 2	12 (5.8)	18 (10.5)	30 (7.9)
Grade 3	2 (1.0)	1 (0.6)	3 (0.8)
Grade 4	1 (0.5)	0	1 (0.3)

* Adverse events leading to the discontinuation of treatment are listed in Table S5 in the Supplementary Appendix.

† Serious adverse events that occurred during the treatment period are listed in Table S6 in the Supplementary Appendix. An adverse event was classified as serious if it resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, or was an important medical event requiring medical or surgical intervention to prevent a serious outcome.

‡ Common adverse events were those that occurred in more than 10% of patients in either group during the treatment period. Events that occurred in more than 5% of patients in either group are shown in Table S7 in the Supplementary Appendix.

§ P<0.01 by Fisher's exact test.

¶ P<0.05 by Fisher's exact test.

|| The abnormalities listed here reflect postbaseline laboratory values, regardless of baseline values. For alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, a level of grade 3 was defined as a value that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a value that was more than 20 times the upper limit of the normal range. A total bilirubin level of grade 3 was defined as a value that was more than 3 to 10 times the upper limit of the normal range, and grade 4 as a value that was more than 10 times the upper limit of the normal range. For hemoglobin, a level of grade 1 was defined as 10 g per deciliter to less than the lower limit of the normal range, grade 2 as 8 to less than 10 g per deciliter, grade 3 as 6.5 to less than 8 g per deciliter, and grade 4 as less than 6.5 g per deciliter.

chondrial toxic effects) or drug-induced liver injury. The patient died from complications after liver transplantation, including multiorgan failure and septic shock that began 80 days after the last dose of the study drug.

DISCUSSION

This phase 3 clinical trial examined an interferon-free, all-oral, direct-acting antiviral regimen exclusively in patients with HCV genotype 1 infection and cirrhosis. Twelve weeks or 24 weeks of treatment with coformulated ABT-450/r-ombitasvir and dasabuvir, administered with ribavirin, resulted in high rates of sustained virologic response at post-treatment week 12. Patients who have historically not been eligible for clinical trials, such as those with thrombocytopenia, hypoalbuminemia, or major depression, were included in this trial. Notably, approximately 15% of the study population had platelet counts that were clinically suggestive of portal hypertension. Thus, the patients in this study are more broadly representative of the population of patients with cirrhosis than patients in previous studies have been.

The overall efficacy of 12-week and 24-week treatment did not differ significantly (91.8% and 95.9%, respectively). This study included previously untreated patients and those who had previously been treated with peginterferon-ribavirin. A clinically meaningful difference in the rates of sustained virologic response between the 12-week and 24-week treatment groups was observed among patients with HCV genotype 1a infection and a null response to prior peginterferon-ribavirin treatment. Patients with cirrhosis and a prior null response, a group with rates of sustained virologic response as low as 14% after retreatment with a protease inhibitor plus peginterferon-ribavirin,^{11,18} accounted for approximately 62% of the previously treated patients enrolled in this trial and had rates of sustained virologic response of 86.7% and 95.2% in the 12-week and 24-week groups, respectively. Specifically, patients with HCV genotype 1a infection and a prior null response had a rate of 80.0% with 12 weeks of treatment and 92.9% with 24 weeks of treatment. All other subgroups with HCV genotype 1a infection, including previously untreated patients, those with a prior partial response, and those

with a prior relapse, had rates of sustained virologic response of 92 to 100% with 12 weeks or 24 weeks of treatment, and patients with HCV genotype 1b infection and a prior null response had a rate of 100% with either treatment duration.

In this study, a 12-week treatment duration with the regimen of coformulated ABT-450/r-ombitasvir and dasabuvir with ribavirin resulted in a high rate of sustained virologic response. Although the between-group differences among patients with HCV genotype 1a infection and a prior null response were not definitive, the numerically higher rate of sustained virologic response with the 24-week regimen suggests that the longer treatment duration is more effective in this subgroup of patients.

Declines in the hemoglobin level of grade 2 or higher occurred in 7.2% of patients in the 12-week group and in 11.0% of patients in the 24-week group. A 5 to 6% rate of hemoglobin decline of at least grade 2 has been reported among patients without cirrhosis who received the same regimen in phase 3 trials.^{24,25} For patients in both treatment groups, declines in the hemoglobin level were successfully managed with modifications in the ribavirin dose, without a negative effect on the rate of sustained virologic response.

Elevations in the total bilirubin level occurred at a higher frequency in this population of patients with cirrhosis than has been observed in clinical trials of the same regimen for the treatment of patients without cirrhosis.^{24,25} Elevations in indirect bilirubin with this regimen are probably related to ribavirin-associated hemolysis, along with inhibition of the bilirubin transporter OATP1B1 by ABT-450, as has been reported for other NS3 protease inhibitors.²⁷ Elevated bilirubin levels did not lead to treatment discontinuation, typically peaked at about 2 weeks of treatment, were not associated with elevations in the alanine aminotransferase level, and resolved to baseline levels during the post-treatment period.

The majority of adverse events were mild or moderate in severity, with few events occurring more frequently in the 24-week group than in the 12-week group. Serious adverse events occurred in 5.5% of all patients, with similar rates in each group, and few patients discontinued the study treatment because of adverse events (2.1% overall). By contrast, in patients with cirrhosis,

interferon-containing protease-inhibitor regimens have been associated with a high rate of serious adverse events, including death, severe infection, hepatic decompensation, and difficult-to-treat anemia.²⁰

Our study was not placebo-controlled, a design limitation that was justified because of the risk of hepatic decompensation among untreated patients. Similarly, there was no active-comparator group owing to the toxic effects of standard interferon-containing regimens. Finally, the study population did not include patients who had virologic failure with other direct-acting antiviral therapy.

In conclusion, this multitargeted approach combining ritonavir-enhanced ABT-450 with ombitasvir, dasabuvir, and ribavirin resulted in rates

of sustained virologic response at post-treatment week 12 of 92% with a 12-week regimen and 96% with a 24-week regimen, with a low rate of treatment discontinuation, among both previously untreated and previously treated patients with HCV genotype 1 infection and compensated cirrhosis, a group at risk for liver-related illness and death.

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