ORIGINAL ARTICLE

Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin

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ABSTRACT

BACKGROUND

In this phase 3 trial we evaluated the efficacy and safety of the interferon-free combination of ABT-450 with ritonavir (ABT-450/r), ombitasvir (also known as ABT-267), dasabuvir (also known as ABT-333), and ribavirin for the retreatment of HCV in patients who were previously treated with peginterferon–ribavirin.

METHODS

We enrolled patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with peginterferon–ribavirin and had a relapse, a partial response, or a null response. Patients were randomly assigned in a 3:1 ratio to receive 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 or 1200 mg daily) or matching placebos during the 12-week double-blind period. The primary end point was the rate of sustained virologic response 12 weeks after the end of study treatment. The primary efficacy analysis compared this rate among patients assigned to the active regimen with a historical response rate (65%) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and peginterferon–ribavirin.

RESULTS

A total of 394 patients received at least one study-drug dose. In the active-regimen group, 286 of 297 patients had a sustained virologic response at post-treatment week 12, for an overall rate of 96.3% (95% confidence interval, 94.2 to 98.4). This rate was noninferior and superior to the historical control rate. Rates were 95.3% among patients with a prior relapse (82 of 86 patients), 100% among patients with a prior partial response (65 of 65 patients), and 95.2% among patients with a prior null response (139 of 146 patients). Pruritus occurred more frequently with the active regimen (in 13.8% of patients) than with placebo (5.2%, P=0.03). Three patients in the active-regimen group (1.0%) discontinued the study drugs owing to adverse events. Hemoglobin values of grade 2 (8.0 to <10.0 g per deciliter) and grade 3 (6.5 to <8.0 g per deciliter) occurred in 4.7% and 0.3% of patients in the active-regimen group, respectively.

CONCLUSIONS

Rates of response to a 12-week interferon-free combination regimen were more than 95% among previously treated patients with HCV genotype 1 infection, including patients with a prior null response. (Funded by AbbVie; SAPPHIRE-II ClinicalTrials.gov number, NCT01715415.)

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Patients with chronic hepatitis C virus (HCV) infection are at risk for progressive liver fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma, and decompensated liver disease. HCV infection can be cured with antiviral therapy, reducing the risk of illness and death associated with end-stage liver disease.[1-3]

For more than a decade, patients with HCV genotype 1 infection have been treated with peginterferon–ribavirin dual therapy, resulting in rates of sustained virologic response of approximately 40 to 50%.[4-6] Response rates among previously untreated patients have been shown to increase to 68 to 75% with peginterferon–ribavirin plus a protease inhibitor (telaprevir or boceprevir, both introduced in 2011).[7,8] However, rates of response to this triple therapy among patients previously treated with peginterferon–ribavirin dual therapy vary according to the prior treatment response, with rates of 69 to 88% among patients with a prior relapse (an undetectable level of HCV RNA during treatment but a detectable level after the end of treatment), 40 to 59% among patients with a partial response (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU per milliliter at treatment week 12 but with a detectable level), and 29 to 33% among patients with a null response (a decrease in the HCV RNA level of <2 $\log_{10}$ IU per milliliter at treatment week 12).[9,10] Furthermore, peginterferon–ribavirin therapy is associated with clinically significant and frequent side effects, including influenza-like symptoms, neuropsychiatric disorders, and cytopenias. Side effects of telaprevir and boceprevir include rash and anemia.[7-10]

ABT-450 is an inhibitor of the HCV nonstructural 3/4A (NS3/4A) protease, which is administered with ritonavir (ABT-450/r). Ritonavir is a pharmacoenhancer that inhibits ABT-450 metabolism. Administration of ritonavir with ABT-450 increases peak and trough drug exposures, allowing for once-daily dosing.[11] Ombitasvir (also known as ABT-267) is an HCV NS5A inhibitor; dasabuvir (also known as ABT-333) is a nonnucleoside HCV NS5B RNA polymerase inhibitor.[12,13]

A phase 2b study involving patients with HCV genotype 1 infection who had a null response to prior therapy with peginterferon–ribavirin showed that the rate of sustained virologic response to 12 weeks of treatment with ABT-450/r, ombitasvir, dasabuvir, and ribavirin was 93% 24 weeks after the end of treatment.[14] We report the results of SAPPHIRE-II, an international, randomized, placebo-controlled, double-blind, phase 3 trial assessing the efficacy and safety of 12 weeks of the all-oral regimen of ABT-450/r–ombitasvir and dasabuvir with ribavirin in patients with HCV genotype 1 infection and no cirrhosis who had received previous treatment with peginterferon–ribavirin.

Methods

Patients

Patients 18 to 70 years of age were eligible for enrollment if they had chronic HCV genotype 1 infection and a plasma HCV RNA level of more than 10,000 IU per milliliter, without cirrhosis. Eligible patients had documentation of prior peginterferon–ribavirin dual therapy with a relapse (an undetectable level of HCV RNA at the end of treatment but a detectable level within 52 weeks after treatment), a partial response (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU per milliliter at treatment week 12 but a detectable level at the end of treatment), or a null response (a decrease in the HCV RNA level of <2 $\log_{10}$ IU per milliliter at week 12 or <1 $\log_{10}$ IU per milliliter at week 4). (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients were excluded if they did not have a response to prior triple therapy with peginterferon–ribavirin and a protease inhibitor. Additional exclusion criteria were a positive screening result for hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies, a recent history of drug or alcohol abuse or a positive screening result for drugs or alcohol, and use of specified concomitant medications, including those contraindicated for use with ribavirin and ritonavir. Patients with an advanced stage of fibrosis (Metavir score >3, Ishak score >4, aspartate aminotransferase:platelet ratio index >2, and FibroTest score >0.72 or FibroScan result ≥9.6 kPa without a qualifying liver biopsy) were also excluded. (For details, see the Supplementary Appendix.)

Study Design and Conduct

The SAPPHIRE-II study was performed at 76 sites in Australia, North America, and Europe. Patients were randomly assigned in a 3:1 ratio to receive an active regimen or placebo (Fig. S1 in the Supplementary Appendix). The randomization schedule was stratified according to the type of response to previous peginterferon–ribavirin treatment (re-

lapse, partial response, or null response) and HCV genotype (1a or non-1a). During the double-blind period, patients assigned to the active regimen received 12 weeks of treatment with oral 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 administered 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). Patients assigned to placebo received matching placebo pills during this period. After the double-blind period, patients in the placebo group received the active regimen on an open-label basis for 12 weeks.

The study sponsor (AbbVie), investigators, and patients were unaware of the study-group assignments during the double-blind period. Laboratory results for levels of HCV RNA, hemoglobin, hematocrit, alanine aminotransferase, aspartate aminotransferase, and bilirubin (indirect and total) were not disclosed to these parties in order to prevent implicit unblinding. The study is ongoing, and all patients who received the active regimen will be followed for 48 weeks after the end of treatment.

All patients provided written informed consent. The study was conducted in accordance with International Conference on Harmonisation guidelines, other guidelines governing clinical-study conduct, applicable regulations, and ethical principles enumerated in the Declaration of Helsinki. An independent ethics committee or institutional review board at each participating site approved the study.

The study was designed jointly by the investigators and the sponsor. The investigators gathered the data. The sponsor conducted the data analyses. All the authors had full access to the data and signed confidentiality agreements with the sponsor regarding the data. The first draft of the manuscript was written by a sponsor-employed medical writer with input from all the authors. All the authors reviewed and provided feedback on all versions of the manuscript and made the final decision to submit it for publication. All the authors assume responsibility for the completeness and accuracy of the data and analyses presented and for the fidelity of the study to the protocol, available at NEJM.org.

EFFICACY ASSESSMENTS

HCV genotype and subtype were evaluated from plasma samples with the use of the Versant HCV Genotype Inno-LiPA Assay, version 2.0 (Siemens Healthcare Diagnostics). Plasma HCV RNA levels were measured by a central laboratory with the use of the COBAS TaqMan real-time reverse-transcriptase–polymerase-chain-reaction assay, version 2.0 (Roche), with a lower limit of detection of 15 IU per milliliter and a lower limit of quantification of 25 IU per milliliter. Details of the collection of plasma samples, protocol-specified criteria for virologic failure, and resistance testing are provided in the Supplementary Appendix.

SAFETY ASSESSMENTS

Adverse events were assessed at each study visit. The site investigator classified events as mild, moderate, or severe. Data on all adverse events were collected from the start of study-drug administration until 30 days after the last dose. Data on serious adverse events were collected throughout the entire study period. Adverse events and serious adverse events occurring during the double-blind period plus 30 days after the last dose of active study drugs are reported. Clinical laboratory testing occurred at visits during the double-blind treatment period and at post-treatment weeks 4 and 48.

EFFICACY END POINTS

The primary efficacy end point was a sustained virologic response (i.e., an HCV RNA level of <25 IU per milliliter 12 weeks after the end of study treatment). Secondary efficacy end points were normalization of the alanine aminotransferase level, sustained virologic response at post-treatment week 12 according to HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse. Analyses were performed in the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of the study drug during the double-blind treatment period.

Virologic failure during study treatment was defined as a confirmed HCV RNA level of 25 IU per milliliter or more after an HCV RNA level of less than 25 IU per milliliter during treatment, a confirmed increase in the HCV RNA level of more than 1 $\log_{10}$ IU per milliliter above the nadir during treatment, or 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. 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. Normalization of the alanine aminotransferase level was defined as a final value that did not exceed the upper limit of the normal range (as defined by the processing laboratory) during the double-blind period among patients with a baseline level above the upper limit of the normal range.

STATISTICAL ANALYSIS

The primary efficacy analyses assessed the noninferiority and superiority of the rate of sustained virologic response at post-treatment week 12 with ABT-450/r–ombitasvir, dasabuvir, and ribavirin, as compared with a calculated historical control rate of 65% (95% confidence interval [CI], 60 to 70). This control rate was based on response rates among patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with peginterferon–ribavirin and who received retreatment with telaprevir and peginterferon–ribavirin.[15,16] The control rate was weighted for the proportions of patients with a prior relapse, partial response, or null response that were expected in the current study (details in the Supplementary Appendix).

To establish that the rate of sustained virologic response with ABT-450/r–ombitasvir, dasabuvir, and ribavirin was noninferior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper confidence boundary of the control rate minus 10.5 percentage points (60%). To establish that the rate of sustained virologic response with ABT-450/r–ombitasvir, dasabuvir, and ribavirin was superior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper confidence boundary of the historical rate (70%). We calculated that a sample of 400 patients (300 recipients of the active regimen during the double-blind period) would provide more than 90% power to show noninferiority and superiority of the active regimen with a rate of sustained virologic response at post-treatment week 12 of 85%. A fixed-sequence testing procedure was used to maintain a type I error rate of 0.05 for the analyses of the primary and secondary efficacy end points. Details of the noninferiority and superiority analyses, sample-size determination, fixed-sequence testing procedure, and all secondary efficacy end points are provided in the Supplementary Appendix.

The primary analysis was performed after all patients receiving the active regimen during the double-blind period reached post-treatment week 12 and all patients receiving placebo reached week 12 of open-label treatment. Data regarding the primary analysis are reported.

SAS software, version 9.3, for the UNIX operating system (SAS Institute) was used for all analyses. All statistical tests and 95% confidence intervals were two-sided with a significance level of 0.05. For analysis of efficacy, normal approximation to binomial distribution was used to calculate 95% confidence intervals. For analyses of adverse events, abnormal laboratory values, and rates of normalization of the alanine aminotransferase level during the double-blind period, the active-regimen group and the placebo group were compared with the use of Fisher's exact test.

RESULTS

PATIENTS

A total of 562 patients were screened, 395 underwent randomization, and 394 received at least one dose of study drug (Fig. S2 in the Supplementary Appendix). Patients were screened from November 2012 through May 2013. The final date for data collection regarding the analysis of the rate of sustained virologic response at post-treatment week 12 among patients receiving the active regimen during the double-blind period was December 3, 2013. Baseline demographic and clinical characteristics of the study patients are shown in Table 1.

EFFICACY

Among 297 patients receiving the active regimen during the double-blind period, 98.7% had an HCV RNA level of less than 25 IU per milliliter at treatment week 4 (95% CI, 97.3 to 100); 99.0% had an HCV RNA level of less than 25 IU per milliliter at treatment week 12 (95% CI, 97.9 to 100). A total of 286 patients in the active-regimen group had a sustained virologic response at post-treatment week 12, for an overall rate of 96.3% (95% CI, 94.2 to 98.4) (Fig. 1); this was

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

Characteristic	Active Regimen (N=297)†	Placebo (N=97)
Male sex — no. (%)	167 (56.2)	60 (61.9)
Race — no. (%)‡§		
White	269 (90.6)	86 (88.7)
Black	22 (7.4)	10 (10.3)
Asian	6 (2.0)	0
Hispanic or Latino ethnic group — no. (%)‡		
Hispanic or Latino	22 (7.4)	3 (3.1)
Not Hispanic or Latino	275 (92.6)	94 (96.9)
Geographic region — no. (%)		
North America	136 (45.8)	33 (34.0)
Europe	150 (50.5)	61 (62.9)
Australia or New Zealand	11 (3.7)	3 (3.1)
Age — yr		
Mean	51.7	54.9
Range	19.0–71.0	30.0–69.0
Body-mass index¶		
Mean	26.3	26.4
Range	18.1–38.1	18.5–36.7
Fibrosis score of F2 or F3 — no. (%)‖	95 (32.0)	32 (33.0)
IL28B genotype CC — no. (%)	34 (11.4)	7 (7.2)
IP-10 — no./total no. (%)**		
<600 ng/liter	199/276 (72.1)	70/95 (73.7)
≥600 ng/liter	77/276 (27.9)	25/95 (26.3)
HCV genotype — no. (%)††		
1a	173 (58.2)	57 (58.8)
1b	123 (41.4)	40 (41.2)
HCV RNA — $\log_{10}$ IU/ml		
Mean	6.55	6.52
Range	4.61–7.70	5.20–7.55
Type of prior response — no. (%)		
Relapse	86 (29.0)	29 (29.9)
Partial response	65 (21.9)	21 (21.6)
Null response	146 (49.2)	47 (48.5)

* Differences in baseline characteristics between the study groups were evaluated with the use of chi-square tests for categorical data and a one-way analysis of variance for continuous data. There were no significant between-group differences in the listed baseline characteristics except for age (P=0.005). HCV denotes hepatitis C virus.

† The active regimen consisted of ABT-450 with ritonavir (ABT-450/r), ombitasvir, dasabuvir, and ribavirin.

‡ Race and ethnic group were self-reported.

§ One patient in the placebo group reported more than one race.

¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

‖ The fibrosis score was determined by means of liver biopsy (Metavir, Batts–Ludwig, Knodell, International Association for the Study of the Liver [IASL], Scheuer, Laennec, or Ishak score), FibroScan, or FibroTest. A score of F2 or higher was defined as a Metavir, Batts–Ludwig, Knodell, IASL, Scheuer, or Laennec score of 2 or higher, an Ishak score of 3 or higher, a FibroScan result of 8.8 kPa or higher, or a FibroTest score of 0.49 or higher. Patients with an advanced stage of fibrosis (Metavir score >3, Ishak score >4, aspartate aminotransferase:platelet ratio index >2, and FibroTest score >0.72 or FibroScan result ≥9.6 kPa without a qualifying liver biopsy) were excluded. Additional details of scoring are provided in Table S2 in the Supplementary Appendix. The fibrosis score ranges from F0 (no fibrosis) to F4 (cirrhosis).

** Baseline plasma IP-10 (interferon-γ–inducible protein 10) levels of at least 600 ng per liter predict a poor response to peginterferon–ribavirin therapy.[17]

†† The HCV subtype could not be determined in one patient in the active-regimen group.

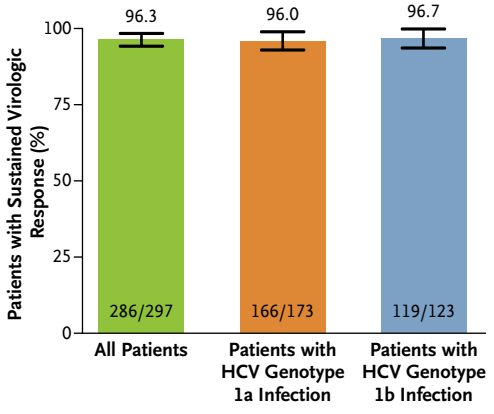

Figure 1. Sustained Virologic Response in the Entire Active-Regimen Group and According to Hepatitis C Virus (HCV) Genotype.

Shown is the rate of sustained virologic response at post-treatment week 12 among all patients receiving the active regimen (ABT-450 with ritonavir [ABT-450/r], ombitasvir, dasabuvir, and ribavirin) during the double-blind period, as well as the rates among patients with HCV genotype 1a infection and those with HCV genotype 1b infection. The numbers at the bottom of each bar are the number of patients with a sustained response and the total number of patients. The I bars indicate 95% confidence intervals.

noninferior and superior to the historical control rate with telaprevir and peginterferon–ribavirin. A total of 166 of 173 patients with HCV genotype 1a infection had a sustained virologic response, for a rate of 96.0% (95% CI, 93.0 to 98.9); 119 of 123 patients with HCV genotype 1b had a sustained virologic response, for a rate of 96.7% (95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for 1 patient, who had a sustained virologic response.

The rates of sustained virologic response were 95.3% among patients with a prior relapse (82 of 86 patients), 100% among patients with a prior partial response (65 of 65 patients), and 95.2% among patients with a prior null response (139 of 146 patients) (Table 2). Rates of sustained virologic response were high across subgroups defined by race, age, fibrosis score, and *IL28B* genotype (Fig. 2). No patient had virologic failure during treatment; all patients completing treatment (≥77 days of study-drug exposure) had an HCV RNA level of less than 25 IU per milliliter at the end of treatment.

Seven of 293 patients who completed therapy (2.4%) had a post-treatment viral relapse (Table 2). All patients with a relapse reported high adherence to study drugs. At the time of relapse, 4 of the 5 patients with HCV genotype 1a infection and 1 of the 2 patients with HCV genotype 1b infection had at least one amino acid variant known to confer resistance to one of the three direct-acting antiviral agents included in the regimen. The most frequently detected variants in the 4 patients with HCV genotype 1a infection who had variants at the time of relapse were D168V in NS3 (2 patients), M28V (3 patients) and Q30R (2 patients) in NS5A, and S556G in NS5B (2 patients). The patient with HCV genotype 1b infection who had resistance-associated variants present at the time of relapse had Y56H and D168A in NS3, Y93H in NS5A, and C316N and S556G in NS5B. The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9% [217 of 224 patients] vs. 12.8% [10 of 78 patients], P<0.001).

SAFETY

During the double-blind treatment period, 91.2% of patients in the active-regimen group and 82.5% of patients in the placebo group had an adverse event (Table 3). In both groups, the two most common adverse events were headache (in 36.4% of patients in the active-regimen group and in 35.1% of those in the placebo group, P=0.90) and fatigue (33.3% and 22.7%, respectively; P=0.06). Among adverse events occurring in more than 10% of patients in either group, only pruritus had a higher frequency in the active-regimen group than in the placebo group (13.8% vs. 5.2%, P=0.03). Among adverse events occurring in less than 10% of patients in both groups, those with a higher frequency in the active-regimen group were anemia (P=0.01), a decrease in the hemoglobin level (P=0.04), and vomiting (P=0.006), and those with a higher frequency in the placebo group were constipation (P=0.02), erythema (P=0.05), neck pain (P=0.05), and neutropenia (P=0.01).

There were no moderate or severe adverse events that occurred more frequently with the active regimen than with placebo (P>0.10 for all comparisons). Six patients in the active-regimen group (2.0%) and one patient in the placebo group (1.0%) had at least one serious adverse event (Table S5 in the Supplementary Appendix). Three patients in the active-regimen group (1.0%) and no patients in the placebo group discontinued the study drug owing to adverse events. Discontinuation was due to elevated aminotransferase

Table 2. Virologic Response in Patients Receiving the Active Regimen during the Double-Blind Period.

Variable	Sustained Virologic Response at Post-Treatment Wk 12	Virologic Failure		Premature Treatment Discontinuation*
		During Treatment†	Relapse‡	
		no. of patients/total no. (%)		
All patients	286/297 (96.3)	0	7/293 (2.4)	4/297 (1.3)
Type of prior response				
Relapse	82/86 (95.3)	0	1/83 (1.2)§	3/86 (3.5)
Partial response	65/65 (100)	0	0	0
Null response	139/146 (95.2)	0	6/145 (4.1)¶	1/146 (0.7)

* Data are for patients who did not have virologic failure during treatment.
† Virologic failure during treatment was defined as a confirmed HCV RNA level of 25 IU per milliliter or more after an HCV RNA level of less than 25 IU per milliliter during treatment, a confirmed increase in the HCV RNA level of more than 1 $\log_{10}$ IU per milliliter above the nadir during treatment, or 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.
‡ 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.
§ This patient had HCV genotype 1a infection. Of patients with a prior relapse, those with HCV genotype 1a infection had a rate of sustained virologic response of 94.0% (47 of 50 patients), and those with HCV genotype 1b infection had a rate of 97.2% (35 of 36 patients) (Table S3 in the Supplementary Appendix).
¶ Four of these six patients had HCV genotype 1a infection, and two patients had HCV genotype 1b infection. Of patients with a prior null response, those with HCV genotype 1a infection had a rate of sustained virologic response of 95.4% (83 of 87 patients), and those with HCV genotype 1b infection had a rate of 94.9% (56 of 59 patients) (Table S3 in the Supplementary Appendix).

levels (grade 3), diarrhea, and acute renal failure in one patient each. The case of acute renal failure was a serious adverse event; the site investigator deemed this event to be unrelated to direct-acting antiviral treatment (details in Table S5 in the Supplementary Appendix).

Abnormalities in laboratory values of grade 3 or 4 that occurred during the double-blind period are shown in Table 3. The most common abnormality of grade 3 or 4 in patients in the active-regimen group was an elevated total bilirubin level, occurring in seven patients (2.4%) (maximum total bilirubin level, 173 μmol per liter [10.1 mg per deciliter]); in six of the patients, these elevations were classified as grade 3. None of these patients had concomitant grade 3 or 4 elevations in the alanine aminotransferase or aspartate aminotransferase level. Elevations in the total bilirubin level were predominantly due to indirect bilirubin and resolved in all patients by post-treatment week 4. Four patients with hyperbilirubinemia of grade 3 or 4 had jaundice or ocular icterus. No patient discontinued treatment owing to hyperbilirubinemia.

During the double-blind period, elevations in the alanine aminotransferase level of grade 3 or 4 occurred in 1.7% of patients in the active-regimen group and in 3.1% of patients in the placebo group. Elevations in the aspartate aminotransferase level of grade 3 or 4 occurred in 1.0% of patients in each group.

During the double-blind period, abnormalities in the hemoglobin value of grade 1 (below the lower limit of the normal range to 10.0 g per deciliter) and grade 2 (8 to <10.0 g per deciliter) occurred in 52.0% and 4.7% of patients in the active-regimen group, respectively. One patient in the active-regimen group (0.3%) had a hemoglobin value of grade 3 (6.5 to <8.0 g per deciliter). No patient had a hemoglobin value of grade 4 (<6.5 g per deciliter) (Table S6 in the Supplementary Appendix). No patient discontinued the study drug owing to anemia. In 6.4% of patients in the active-regimen group, the ribavirin dose was modified owing to adverse events. No patient received erythropoietin or a transfusion. There were no deaths from any cause in the active-regimen group or the placebo group.

DISCUSSION

In this large, multicenter, phase 3 trial involving patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with peginterferon–ribavirin, 96.3% of patients who received retreatment with ABT-450/r–ombitasvir and dasabuvir with ribavirin had a sustained virologic response at post-treatment week 12. According to a modified intention-to-treat analysis, the rate of sustained virologic response with this combination regimen was noninferior and superior to the historical control rate with telaprevir plus peginterferon–ribavirin in a similar patient population. This rate of sustained virologic response also exceeds reported response rates of 59 to 80% in retreatment studies involving patients with HCV genotype 1 infection who received boceprevir or simeprevir with peginterferon–ribavirin.[9,18]

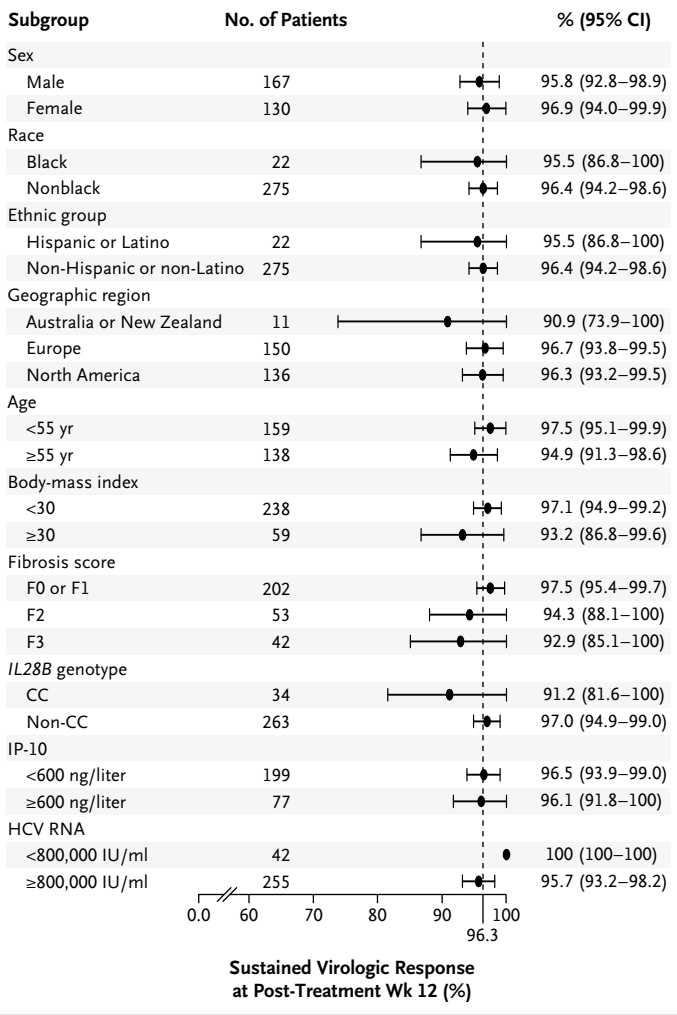

Figure 2. Sustained Virologic Response According to Subgroups.

Shown are the rates of sustained virologic response at post-treatment week 12 among patients receiving the active regimen during the double-blind period. The position of the circle indicates the rate, and the horizontal lines indicate 95% confidence intervals. The dotted vertical line indicates the overall rate. 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. IP-10 denotes interferon-γ–inducible protein 10.

The results of our study confirm previous data suggesting that this 12-week regimen combining antiviral drugs with multiple mechanisms of action is effective regardless of the prior response to peginterferon–ribavirin.[14] The rates of sustained virologic response in this study were high even among patients with a null response to prior treatment, who made up nearly half the study population; such patients have been the least likely to have a response to retreatment regimens comprising peginterferon–ribavirin plus a protease inhibitor.[10,18] In patients with a prior null response, 12 weeks of telaprevir with 48 weeks of peginterferon–ribavirin resulted in rates of sustained virologic response of 29 to 33%, whereas the use of simeprevir with peginterferon–ribavirin for similar durations resulted in rates of 38 to 53%.[10,18] In contrast, in this study the 12-week regimen resulted in a 95.2% rate of sustained virologic response among patients with a prior null response.

Data from trials of peginterferon-containing and peginterferon-free regimens have suggested that the HCV genotype (1a or 1b) affects the efficacy of some regimens.[19-21] However, in this trial, high rates of sustained virologic response were observed among patients with HCV genotype 1a and among those with HCV genotype 1b (96.0% and 96.7%, respectively), with few true virologic failures.

The double-blind design of this trial allowed a comparison of adverse events in patients receiving the active regimen with events in those receiving placebo. One percent of patients discontinued active therapy owing to an adverse event. Pruritus was the only adverse event occurring in more than 10% of patients in either study group that was significantly more frequent with the active regimen than with placebo. Although there were three adverse events occurring in less

Table 3. Adverse Events and Abnormalities in Laboratory Values of Grade 3 or 4 during the Double-Blind Treatment Period.*

Variable	Active Regimen (N=297)	Placebo (N=97)
Any adverse event — no. of patients (%)	271 (91.2)	80 (82.5)
Any adverse event leading to discontinuation of study drug — no. of patients (%)†	3 (1.0)	0
Any serious adverse event — no. of patients (%)‡	6 (2.0)	1 (1.0)
Common adverse events — no. of patients (%)§		
Headache	108 (36.4)	34 (35.1)
Fatigue	99 (33.3)	22 (22.7)
Nausea	60 (20.2)	17 (17.5)
Asthenia	47 (15.8)	11 (11.3)
Insomnia	42 (14.1)	7 (7.2)
Pruritus	41 (13.8)	5 (5.2)
Diarrhea	39 (13.1)	12 (12.4)
Dyspnea	37 (12.5)	10 (10.3)
Cough	32 (10.8)	5 (5.2)
Myalgia	23 (7.7)	10 (10.3)
Abnormalities in laboratory values of grade 3 or 4 — no. of patients/total no. (%)¶		
Alanine aminotransferase	5/296 (1.7)	3/96 (3.1)
Aspartate aminotransferase	3/296 (1.0)	1/96 (1.0)
Alkaline phosphatase	0	0
Creatinine	2/297 (0.7)	0
Total bilirubin	7/296 (2.4)	0
Hemoglobin	1/296 (0.3)	0

* For comparisons between groups, a P value of less than 0.05 was considered to indicate statistical significance. The frequency of any adverse event was significantly greater in the active-regimen group than in the placebo group (P=0.02), as was the frequency of pruritus (P=0.03). Fatigue and insomnia were more frequent in the active-regimen group than in the placebo group, but these differences did not reach statistical significance (P=0.06 and P=0.08, respectively). P values were greater than 0.10 for all other comparisons between groups.

† Adverse events leading to study-drug discontinuation were elevated aminotransferase levels, diarrhea, and acute renal failure (in one patient each).

‡ Serious adverse events that occurred in patients in the active-regimen group were chronic obstructive pulmonary disease, acute transient stroke (cerebrovascular accident), pneumonia, acute renal failure, and intestinal obstruction (in one patient each) and dizziness, nausea, vomiting, and bradycardia in one patient. Atrial fibrillation occurred in one patient in the placebo group.

§ Common adverse events were those that occurred in more than 10% of patients in either group during study treatment. Adverse events that occurred in more than 5% of patients in either group are shown in Table S4 in the Supplementary Appendix.

¶ An alanine aminotransferase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as more than 20 times the upper limit of the normal range. An aspartate aminotransferase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. An alkaline phosphatase level of grade 3 was defined as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range. A creatinine level of grade 3 was defined as a level of at least 2.1 to 2.5 mg per deciliter (186 to 221 μmol per liter), and grade 4 as a level that was more than 2.5 mg per deciliter. A total bilirubin level of grade 3 was defined as a level that was more than 3 to 10 times the upper limit of the normal range, and grade 4 as a level that was more than 10 times the upper limit of the normal range. A hemoglobin level of grade 3 was defined as a level of 6.5 to less than 8.0 g per deciliter, and grade 4 as a level that was less than 6.5 g per deciliter. Additional information about changes in hemoglobin levels is available in Table S6 in the Supplementary Appendix.

than 10% of patients in each group that were significantly more frequent with the active regimen (anemia, a decrease in the hemoglobin level, and vomiting), four adverse events occurring in less than 10% of patients in each group were significantly more frequent with placebo (constipation, erythema, neck pain, and neutropenia).

The most common laboratory abnormality in the active-regimen group was a transient elevation in the total bilirubin level, occurring in 2.4% of patients. These elevations are consistent with the known role of ABT-450 as an inhibitor of the OATP1B1 transporter.[22,23] Hemoglobin values of 8.0 to less than 10.0 g per deciliter (grade 2), 6.5 to less than 8.0 g per deciliter (grade 3), and less than 6.5 g per deciliter (grade 4) occurred in 4.7%, 0.3%, and 0% of patients in the active-regimen group, respectively. No patient discontinued the study treatment owing to anemia.

Patients who did not have a response to triple therapy with an approved protease inhibitor and peginterferon–ribavirin were excluded from this study. Thus, the results cannot be extrapolated to that population. Although this study did not include previously untreated patients, Feld et al. now report in the *Journal* that treatment with the same regimen of new antiviral agents and ribavirin in such patients was associated with a high rate of sustained virologic response at post-treatment week 12.[24]

In conclusion, an all-oral combination regimen of ABT-450/r, ombitasvir, and dasabuvir with ribavirin resulted in rates of sustained virologic response at post-treatment week 12 of more than 95%, regardless of HCV genotype (1a or 1b) and with low rates of treatment discontinuation, in previously treated patients with HCV genotype 1 infection and no cirrhosis, including those with a prior null response. The similarity of safety and efficacy data in the previous phase 2 trial and this phase 3 trial supports further exploration of this all-oral regimen in other difficult-to-cure populations, such as patients with HCV and HIV coinfection and liver-transplant recipients.

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