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

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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 NSSA 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.)
A

n 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 trans-
plantation globally.2,3 Approximately 25% of per-
sons 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 de-
compensation, hepatocellular carcinoma, and
death from a liver-related cause or any cause.6-10

Among patients with HCV infection and cir-
rhosis in whom peginterferon–ribavirin treatment
has failed, rates of sustained virologic response
to retreatment with interferon-containing regi-
enms are as low as 14%.11-19 In addition, treat-
ment 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 bocepre-
vir is not recommended for patients with cir-
rhosis 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 Inter-
feron-free combinations of direct-acting antiviral
agents are therefore needed to improve the effi-
cacy and safety of HCV treatment in patients
with cirrhosis.

ABT-450, an inhibitor of the HCV nonstruc-
tural 3/4A (NS3/4A) protease, is administered
with ritonavir (ABT-450/r.)22 As a pharmacoen-
hancer, ritonavir has no activity against HCV;
instead, it inhibits ABT-450 metabolism, increas-
ing peak and trough drug exposures and allow-
ing for a once-daily dose of ABT-450.23 Ombitas-
vir (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 dasa-
buvir, administered with ribavirin, resulted in a
rate of sustained virologic response of 96% amon-
g 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–ombi-
tasvir and dasabuvir with ribavirin for 12 or 24
weeks in previously untreated and previously
treated adults with chronic HCV genotype 1 infe-
c tion 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 previ-
ously untreated or previously treated chronic HCV
genotype 1 infection and a plasma HCV RNA
level of more than 10,000 IU per milliliter. Eligi-
ble 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 evi-
dence of Child–Pugh class B or C disease. Key eligi-
ability 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 biliru-
bin level of less than 3 mg per deciliter, an inter-
national normalized ratio of 2.3 or less, and a
serum alpha-fetoprotein level of 100 ng per milli-
liter or less. Exclusion criteria were prior therapy
with direct-acting antiviral agents (e.g., telaprevir
and boceprevir) for the treatment of HCV infec-
tion and a diagnosis of hepatocellular carcinoma.
For detailed eligibility criteria, see the Supple-
mental Appendix, available with the full text of
this article at NEJM.org.

STUDY DESIGN AND OVERSIGHT

Patients were randomly assigned in a ratio of ap-
proximately 1:1 (see the Supplementary Appen-
dix) 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 ac-
cording to HCV subgenotype (1a vs. 1b) and inter-
leukin 28B (IL28B) genotype (CC vs. non-CC), a
genetic marker associated with treatment out-
comes.26 Previously treated patients were strat-
fied 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/ombratavir (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) 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\textsuperscript{11,12} were used to calculate a weight-
ed average of rates of sustained virologic response among previously untreated and previously treat-
ed 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\textsubscript{r}–ombitasvir, dasabuvir, and ribavirin to be con-
sidered noninferior, the lower confidence bound had to exceed 43\% (equal to the upper confi-
dence bound of the historical rate with telaprevir plus peginterferon–ribavirin, 54\%, minus 10.5 per-
centage points and rounded). For the rate of sus-
tained virologic response with ABT-450\textsubscript{r}–ombi-
tasvir, dasabuvir, and ribavirin to be considered superior, the lower confidence bound had to exceed the upper confidence bound of the his-
torical rate (54\%).

The 12-week and 24-week groups were com-
pared with the use of a logistic-regression model, as prespecified in the protocol for the key sec-
condary efficacy end point, with treatment group, baseline \log_{10} HCV RNA level, HCV subgenotype (1a vs. 1b), \textit{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 sum-
marized for each treatment group and random-
ization stratum to assess responses across strat-
ification variables. For exploratory purposes, a stepwise logistic-regression model was used to assess the association between the rate of sus-
tained 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 Ap-
pendix, including Fig. S2). All statistical tests and confidence intervals were two-sided, with a significance level of 0.05. The number and per-
centage of patients with adverse events, abnor-
malities in laboratory values of grade 3 or 4, or abnormalities in hemoglobin levels were com-
pared 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 pa-
tients 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 pri-
mary efficacy end points met the prespecified criteria for noninferiority and superiority to the his-
torical rate with telaprevir plus peginterferon–ri-
avirin among patients with HCV genotype 1 infection and cirrhosis. Rates of sustained viro-
logic response in subgroups defined by HCV sub-
genotype, 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, \textit{IL28B} geno-
type, status with respect to a history of diabetes melitus, status with respect to a history of de-
pression 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 viro-
logic 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-
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 associated 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 (0.5% [95% CI, 0 to 1.4])
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.

Figure 1. Sustained Virologic Response at Post-Treatment Week 12 in Each Treatment Group, Overall and According to Subgroups.

To establish noninferiority and superiority of ritonavir-enhanced ABT-450, ombitasvir, dasabuvir, and ribavirin to the historical control (telaprevir plus peginterferon–ribavirin), the lower boundary of the confidence interval for the rate of sustained virologic response at post-treatment week 12 in each treatment group had to exceed 43% (dashed line) and 54% (solid line), respectively. All confidence intervals (I bars) are two-sided, with an overall alpha level of 0.05. For the analysis of the primary efficacy end point in the overall population, 97.5% confidence intervals were used on the basis of the gatekeeping multiple-testing approach; nominal 95% confidence intervals were used for subgroup analyses. HCV denotes hepatitis C virus.

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.*

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

* Prior treatment refers to peginterferon–ribavirin for the treatment of HCV infection.
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 predominately 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 3. Logistic-Regression Analysis of Association of Subgroup Variables with a Sustained Virologic Response at Post-Treatment Week 12.*

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

* 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 subgenotype (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.
### Table 4. Adverse Events and Laboratory Abnormalities.

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

*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.
with 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.25 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 omibitasvir, 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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES


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