ORIGINAL ARTICLE

Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1

Kris V. Kowdley, M.D., Eric Lawitz, M.D., Fred Poordad, M.D., Daniel E. Cohen, M.D., David R. Nelson, M.D., Stefan Zeuzem, M.D., Gregory T. Everson, M.D., Paul Kwo, M.D., Graham R. Foster, F.C.R.P., Mark S. Sulkowski, M.D., Wangang Xie, Ph.D., Tami Pilot-Matias, Ph.D., George Liossis, B.A., Lois Larsen, Ph.D., Amit Khatri, Ph.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.

From the Digestive Disease Institute, Virginia Mason Medical Center, Seattle (K.V.K.); Texas Liver Institute, University of Texas Health Science Center, San Antonio (E.L., F.P.); AbbVie, North Chicago (D.E.C., W.X., T.P.-M., G.L., L.L., A.K., T.P., B.B.); University of Florida College of Medicine, Gainesville (D.R.N.); J.W. Goethe University, Frankfurt, Germany (S.Z.); University of Colorado Denver, Aurora (G.T.E.); Indiana University, Indianapolis (P.K.); Queen Mary, University of London, Barts Health, London (G.R.F.); and Johns Hopkins University, Baltimore (M.S.S.). Address reprint requests to Dr. Kowdley at the Digestive Disease Institute, Virginia Mason Medical Center, Mailstop C3-GAS, 1100 Ninth Ave., Seattle, WA 98111, or at kris.kowdley@vmmc.org.

N Engl J Med 2014;370:222-32.
DOI: 10.1056/NEJMoa1306227
Copyright © 2014 Massachusetts Medical Society.

ABSTRACT

BACKGROUND

An interferon-free combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r), the nonnucleoside polymerase inhibitor ABT-333, and ribavirin showed efficacy against the hepatitis C virus (HCV) in a pilot study involving patients with HCV genotype 1 infection. The addition of another potent agent, the NS5A inhibitor ABT-267, may improve efficacy, especially in difficult-to-treat patients. This study was designed to evaluate multiple regimens of direct-acting antiviral agents and ribavirin in patients with HCV genotype 1 infection who had not received therapy previously or who had no response to prior therapy with pegylated interferon and ribavirin.

METHODS

In this phase 2b, open-label study with 14 treatment subgroups, 571 patients without cirrhosis who had not received treatment previously or who had not had a response to prior therapy were randomly assigned to a regimen of ABT-450/r, combined with ABT-267 or ABT-333 or both, for 8, 12, or 24 weeks and received at least one dose of therapy. All the subgroups but 1 also received ribavirin (dose determined according to body weight). The primary end point was sustained virologic response at 24 weeks after the end of treatment. The primary efficacy analysis compared rates between previously untreated patients who received three direct-acting antiviral agents and ribavirin for 8 weeks and those who received the same therapy for 12 weeks.

RESULTS

Among previously untreated patients who received three direct-acting antiviral agents (with the ABT-450/r dose administered as 150 mg of ABT-450 and 100 mg of ritonavir) plus ribavirin, the rate of sustained virologic response at 24 weeks after treatment was 88% among those who received the therapy for 8 weeks and 95% among those who received the therapy for 12 weeks (difference, –7 percentage points; 95% confidence interval, –19 to 5; P=0.24). The rates of sustained virologic response across all treatment subgroups ranged from 83 to 100%. The most frequent adverse events were fatigue, headache, nausea, and insomnia. Eight patients (1%) discontinued treatment owing to adverse events.

CONCLUSIONS

In this phase 2b study, all-oral regimens of antiviral agents and ribavirin were effective both in patients with HCV genotype 1 infection who had not received therapy previously and in those who had not had a response to prior therapy. (Funded by AbbVie; ClinicalTrials.gov number, NCT01464827.)

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

Chronic hepatitis C virus (HCV) infection is a leading cause of cirrhosis, liver cancer, and end-stage liver disease.[1] The current standard of care for chronic HCV genotype 1 infection is pegylated interferon (peginterferon) and ribavirin, with a protease inhibitor (boceprevir or telaprevir).[2] Although the addition of a protease inhibitor has been associated with a significant increase in response rates, only approximately one third of patients who had not had a response to prior therapy with peginterferon and ribavirin had a sustained virologic response when re-treated with the addition of a protease inhibitor.[3,4] Furthermore, these therapies are associated with adverse effects that can lead to early discontinuation of treatment.[5-7] Patient characteristics, such as host genetic factors (e.g., *IL28B* rs12979860 CT or TT genotype), HCV subtype 1a, black race, and high baseline viral load, are also associated with poor response rates.[6-8] New interferon-free therapies with greater activity in difficult-to-treat patients with HCV infection are needed.

ABT-450, a potent inhibitor of the HCV NS3/4A protease, is coadministered with 100 mg of ritonavir (ABT-450/r) to increase ABT-450 plasma levels and half-life, permitting once-daily dosing.[9] ABT-333 is a nonnucleoside NS5B polymerase inhibitor. A recent pilot study involving patients with HCV genotype 1 infection who received 12 weeks of treatment with ABT-450/r, ABT-333, and ribavirin showed rates of sustained virologic response 12 weeks after treatment of 93 to 95% among previously untreated patients and 47% among patients who had not had a response or who had had only a partial response to prior therapy with peginterferon and ribavirin.[10]

The addition of a potent third direct-acting antiviral agent, the NS5A inhibitor ABT-267, may improve efficacy in patients for whom a poor response is predicted, including those who have not had a response to prior therapy. ABT-267 monotherapy for 3 days in previously untreated patients resulted in a mean decrease in the HCV RNA level of 3.10 $\log_{10}$ IU per milliliter.[11] Because patients who have not had a response to prior therapy have historically had the lowest levels of response to retreatment, a favorable therapeutic outcome in this population would be likely to extend to other patient populations that have received therapy previously.

In this article, we present the results of a phase 2b, open-label, multiple-group study that was designed to determine the safety and efficacy of various combinations of ABT-450/r, ABT-333, ABT-267, and ribavirin in patients with HCV genotype 1 infection who had not received therapy previously and in those who had not had a response to prior therapy. The study design enabled multiple comparisons between treatment groups, allowing preliminary comparisons of treatment durations, antiviral-drug combinations, and ABT-450 doses in a single study.

Methods

Study Population

Eligible patients were 18 to 70 years of age with a plasma HCV RNA level of more than 50,000 IU per milliliter at screening and no evidence of cirrhosis. Previously untreated patients and those who had not had a response to prior therapy (patients who had received peginterferon and ribavirin for at least 12 weeks and did not have a decline in the HCV RNA level of at least 2 $\log_{10}$ IU per milliliter) were eligible. Detailed eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design

This study was designed as an open-label trial with respect to treatment durations, drug combinations, and doses for each of 14 treatment subgroups (Fig. 1). Details of the randomization procedure are provided in the Supplementary Appendix.

ABT-450/r was administered in doses of 100 mg, 150 mg, or 200 mg of ABT-450 with 100 mg of ritonavir daily. The ABT-267 dose was 25 mg daily. The ABT-333 dose was 400 mg twice daily. The daily dose of ribavirin was 1000 mg (divided into doses of 400 mg and 600 mg) if the body weight was less than 75 kg or 1200 mg (600 mg twice daily) if the body weight was 75 kg or more. The treatment duration was 8, 12, or 24 weeks.

Study Oversight

All the patients provided written informed consent. The study was performed in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and the study protocol was approved by the relevant institutional review boards and regulatory agencies.

The study was designed jointly by the study investigators and the sponsor (AbbVie). The investigators gathered the data, and the sponsor

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

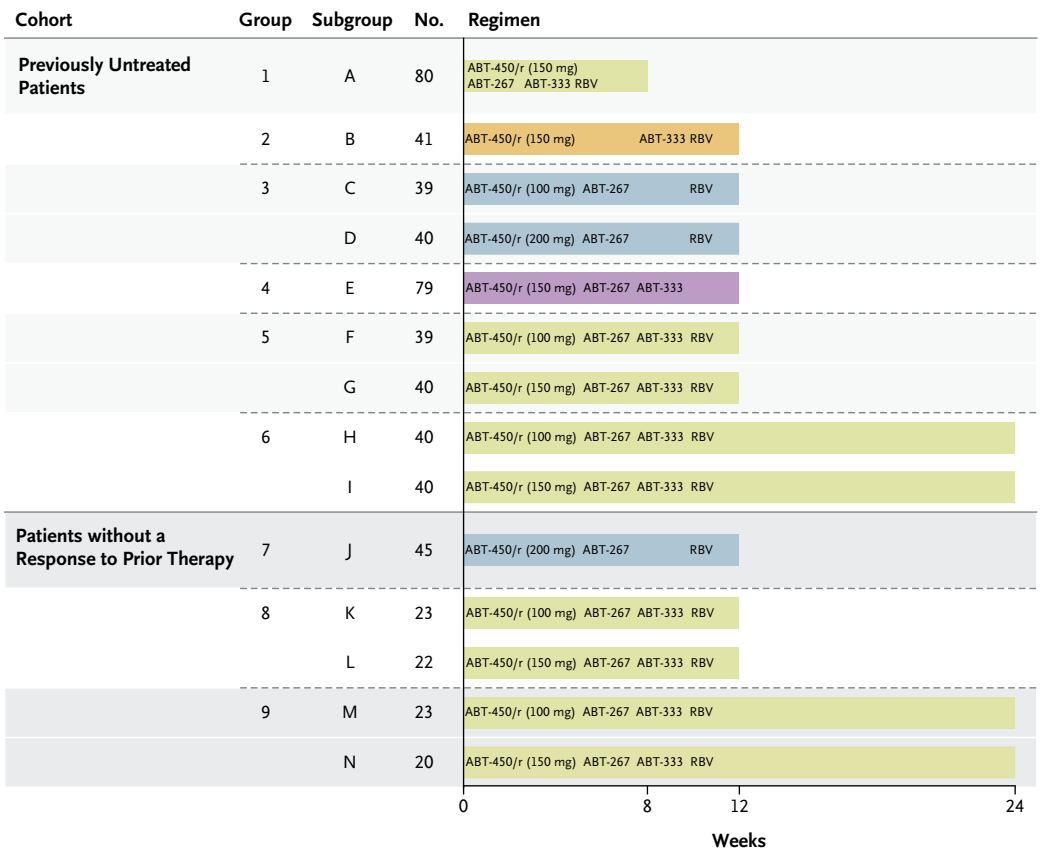

Figure 1. Treatment Regimens.

The drugs administered to each treatment subgroup are listed in the bars. The daily dose of ABT-450 plus ritonavir (ABT-450/r) included 100 mg of ritonavir and 100 mg, 150 mg, or 200 mg of ABT-450; the ABT-450 dose in each subgroup is shown in parentheses. The ABT-333 dose was 400 mg twice daily. The ABT-267 dose was 25 mg once daily. The total daily dose of ribavirin (RBV) was 1000 mg (divided into doses of 400 mg and 600 mg) if the body weight was less than 75 kg or 1200 mg (600 mg twice daily) if the body weight was 75 kg or more. Patients were followed through 48 weeks after the end of treatment.

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 medical writer employed by the sponsor and was edited and revised by the first author, with input from all the authors. All the authors reviewed and provided feedback on all subsequent versions of the manuscript. All the authors vouch for the completeness and accuracy of the data and analyses presented and confirm that the study was conducted and reported with fidelity to the protocol, which is available at NEJM.org.

VIROLOGIC AND SAFETY ASSESSMENTS

Details on the collection of plasma samples, HCV RNA measurement, resistance testing, and criteria for virologic failure are provided in the Supplementary Appendix. Assessments of adverse events and clinical laboratory testing were performed at each study visit. Events were classified as mild, moderate, or severe by the investigator.

Data on all adverse events were collected from the start of study-drug administration until 30 days after the last dose was administered. Data on serious adverse events were collected throughout the study.

EFFICACY ANALYSES

The primary efficacy end point was sustained virologic response (HCV RNA level below the lower limit of quantitation [25 IU per milliliter]) at 24 weeks after the end of treatment. Analyses

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

were performed on the modified intention-to-treat population, which included patients who had undergone randomization and received at least one dose of study drug. The primary analysis was a comparison of the rate of sustained virologic response at 24 weeks after treatment between previously untreated patients who received three direct-acting antiviral agents (including ABT-450/r administered in daily doses of 150 mg of ABT-450 and 100 mg of ritonavir) with ribavirin for 8 weeks (subgroup A) and those who received the same therapy for 12 weeks (subgroup G). Secondary analyses compared the rate of sustained virologic response at 24 weeks after treatment among other treatment groups and subgroups.

Virologic breakthrough during treatment was defined as two consecutive HCV RNA measurements of more than 1 $\log_{10}$ IU per milliliter above the nadir HCV RNA level or two consecutive HCV RNA measurements that were higher than the lower limit of quantitation at any time after the HCV RNA level had been less than the lower limit of quantitation. Virologic relapse was defined as a confirmed quantifiable HCV RNA level in a patient who had had an HCV RNA level that was less than the lower limit of quantitation at the end of treatment.

STATISTICAL ANALYSIS

SAS software, version 9.2, for the UNIX operating system (SAS Institute) was used for all analyses. Details of the sample-size determination and interim analysis are provided in the Supplementary Appendix. All statistical tests and confidence intervals were two-sided, with a significance level of 0.05. The stratum-adjusted Mantel–Haenszel method, with adjustment for the stratification variables at baseline (*IL28B* genotype [CC vs. non-CC] and HCV subgenotype [1a vs. non-1a]), was used to calculate between-group differences in the rates of sustained virologic response at 24 weeks after treatment and the two-sided 95% confidence intervals of the differences.

RESULTS

STUDY POPULATION

A total of 1013 patients with chronic HCV genotype 1 infection were screened at 97 sites in nine countries, including the United States. From October 2011 through April 2012, a total of 571 patients (438 previously untreated patients and 133 patients who had not had a response to prior therapy) underwent randomization and received at least one dose of study drug (Fig. S1 and Table S1 in the Supplementary Appendix). The final data collection for the analysis of the rate of sustained virologic response at 24 weeks after treatment occurred in August 2013. Demographic and clinical characteristics of the patients at baseline are shown in Table 1.

EFFICACY

Primary Analysis

Across all treatment subgroups, the rates of sustained virologic response at 24 weeks after treatment ranged from 83 to 100% (Table S5 in the Supplementary Appendix). With respect to the primary analysis, among previously untreated patients who received treatment with three direct-acting agents plus ribavirin, with ABT-450/r administered as 150 mg of ABT-450 and 100 mg of ritonavir, the rate of sustained virologic response at 24 weeks after treatment was 88% in the subgroup that received 8 weeks of therapy and 95% in the subgroup that received 12 weeks of therapy (difference between 8-week and 12-week subgroups, –7 percentage points; 95% confidence interval, –19 to 5; P=0.24). Secondary analyses of the rates of sustained virologic response at 24 weeks after treatment are shown in Table S6 in the Supplementary Appendix.

Analysis According to ABT-450/r Dose

In a prespecified analysis comparing subgroups that received ABT-450/r administered as 100 mg of ABT-450 and 100 mg of ritonavir with those that received ABT-450/r administered as 150 mg of ABT-450 and 100 mg of ritonavir in otherwise identical regimens, the rates of sustained virologic response at 24 weeks were similar (93.6% and 94.3%, respectively; P=0.91). Therefore, the subgroups differing only in the dose of ABT-450 were combined, which resulted in nine groups for further analysis. With these groups combined, the rates of sustained virologic response at 24 weeks after treatment ranged from 83 to 96% among previously untreated patients and from 89 to 95% among patients who had not had a response to prior therapy (Fig. 2).

Analysis According to Regimen

Across all treatment groups, the rates of sustained virologic response at 24 weeks after treatment were high regardless of host *IL28B*

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

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

Characteristic	Previously Untreated Patients (N=438)	Patients without a Response to Prior Therapy (N=133)
Male sex — no. (%)	232 (53)	82 (62)
Age — yr	50.1±10.2	51.1±11.4
Black race — no. (%)†	60 (14)	18 (14)
Hispanic ethnic group — no. (%)†	33 (8)	13 (10)
HCV subtype 1a — no. (%)	297 (68)	81 (61)
Non-CC *IL28B* genotype — no. (%)	314 (72)	129 (97)
HOMA-IR ≥3 — no./total no. (%)‡	98/385 (25)	34/112 (30)
IP-10 ≥600 ng/ml — no./total no. (%)§	101/428 (24)	53/128 (41)
Fibrosis score ≥F2 — no. (%)¶	127 (29)	66 (50)
HCV RNA — $\log_{10}$ IU/ml	6.53±0.55	6.64±0.45

* Plus–minus values are means ±SD. Differences in baseline characteristics between the cohort of previously untreated patients and the cohort of patients who had not had a response to prior therapy were assessed with the use of chi-square tests for categorical data and one-way analysis of variance for continuous data. The *IL28B* genotype, interferon-γ–inducible protein 10 (IP-10 level), fibrosis score, and hepatitis C virus (HCV) RNA level differed significantly between the group that had not received prior treatment and the group that had not had a response to prior treatment (P<0.001, P<0.001, P<0.001, and P=0.03, respectively). No other significant between-group differences were identified. The baseline characteristics for each treatment subgroup are shown in Tables S2 and S3 in the Supplementary Appendix.

† Race and ethnic group were self-reported.

‡ A score on the homeostasis model assessment of insulin resistance (HOMA-IR) of more than 3 indicates insulin resistance, and a score of more than 5 indicates severe insulin resistance. A baseline HOMA-IR score of at least 2 is a predictor of poor response to therapy with peginterferon and ribavirin.[12]

§ A baseline plasma level of IP-10 of at least 600 ng per milliliter is a predictor of poor response to therapy with peginterferon and ribavirin.[13]

¶ The fibrosis score was determined by means of liver biopsy (Metavir or Ishak score), FibroScan (Echosens), or FibroTest (BioPredictive). Details of scoring are provided in Table S4 in the Supplementary Appendix. Scores for fibrosis range from 0 (no fibrosis) to 4 (cirrhosis).

rs12979860 haplotype, HCV subtype, race, or HCV RNA level at baseline (Table S7 and S8 in the Supplementary Appendix). The rates of sustained virologic response were highest in the groups that received regimens that included three direct-acting agents plus ribavirin, but comparisons of the group that received three direct-acting agents plus ribavirin for 12 weeks with groups that received two direct-acting agents plus ribavirin did not show significant differences (Fig. 3). Among patients administered three direct-acting antiviral agents with ribavirin for 12 weeks, the rates of sustained virologic response at 24 weeks after treatment were 96% among previously untreated patients and 93% among those who had not had a response to prior therapy.

Analysis According to Duration of Therapy

The rate of sustained virologic response at 24 weeks after treatment was higher among previously untreated patients who received three direct-acting agents plus ribavirin for 12 weeks than among those who received the same therapy for 8 weeks (96% and 88%, respectively) (Fig. 3), but the difference was not significant. Among previously untreated patients who received three direct-acting agents with ribavirin, relapse after treatment occurred in 12%, 1%, and 2% of patients randomly assigned to 8 weeks, 12 weeks, and 24 weeks of therapy, respectively. None of these patients had virologic breakthrough. Among patients who had not had a response to prior therapy and who received this regimen, there were no relapses among patients treated for 12 weeks or for 24 weeks; 7% and 2% of the patients, respectively, had virologic breakthrough. A 24-week duration of therapy, as compared with a 12-week duration, was not associated with an increase in the rate of sustained virologic response, among either previously untreated patients or patients who had not had a response to prior therapy (P=0.24 and P=0.71, respectively). Information on virologic failure in each group is provided in Tables S9 and S10 in the Supplementary Appendix.

Among 166 patients with HCV genotype 1b infection who were previously untreated or who had not had a response to prior therapy and who received 12 or 24 weeks of any treatment regimen in this study, none had virologic failure. Relapse occurred in 1 patient with HCV genotype 1b infection who received 8 weeks of treatment.

No resistance-associated variants emerging during the treatment period were detected in 7 of the 10 samples from patients with relapse in the 8-week treatment group. In the 12-week and 24-week treatment groups, all but 1 of the samples obtained at breakthrough or relapse showed the emergence of variants known to confer resistance to ABT-450, ABT-267, or ABT-333. The most frequently detected variants that developed during the treatment period were at amino acid positions 168 in NS3, 28 and 30 in NS5A, and 556 in NS5B.

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

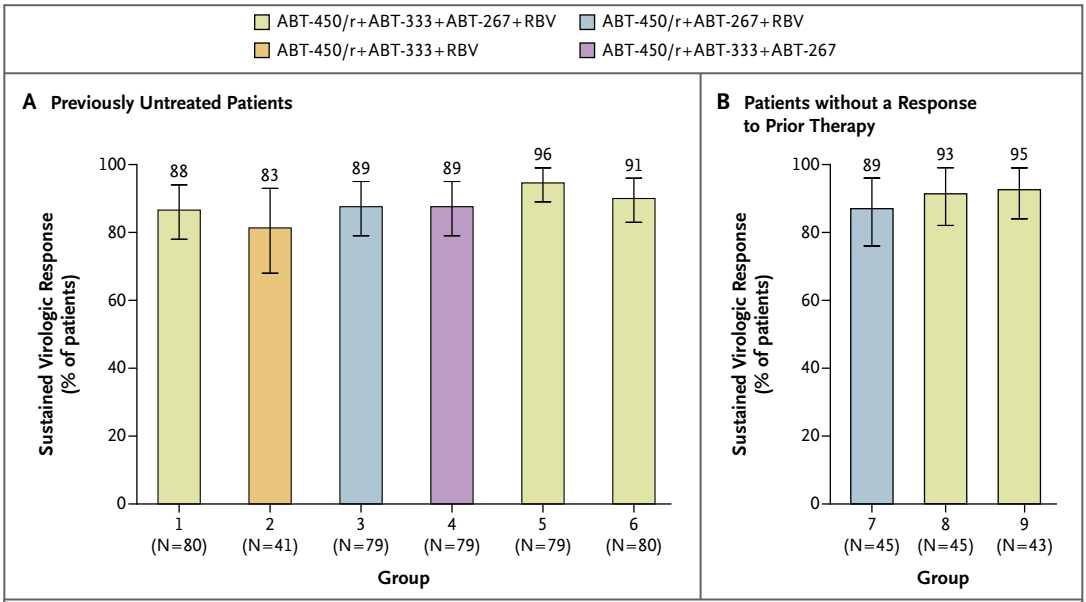

Figure 2. Rates of Sustained Virologic Response at 24 Weeks after the End of Treatment.

The rates of sustained virologic response at 24 weeks after treatment were calculated in the modified intention-to-treat population. Panel A shows the results in the cohort of previously untreated patients (groups 1 through 6), and Panel B the results in the cohort of patients who had not had a response to prior therapy (groups 7, 8, and 9). The duration of treatment was 8 weeks in group 1; 12 weeks in groups 2, 3, 4, 5, 7, and 8; and 24 weeks in groups 6 and 9. I bars indicate 95% confidence intervals.

Comparison	Rate of Sustained Virologic Response	P Value
Group 1 vs. Group 5 8-Wk vs. 12-wk duration	88% vs. 96%	0.08
Group 2 vs. Group 5 Contribution of ABT-267	83% vs. 96%	0.06
Group 3 vs. Group 5 Contribution of ABT-333	89% vs. 96%	0.09
Group 4 vs. Group 5 Contribution of RBV	89% vs. 96%	0.09
Group 6 vs. Group 5 24-Wk vs. 12-wk duration	91% vs. 96%	0.24

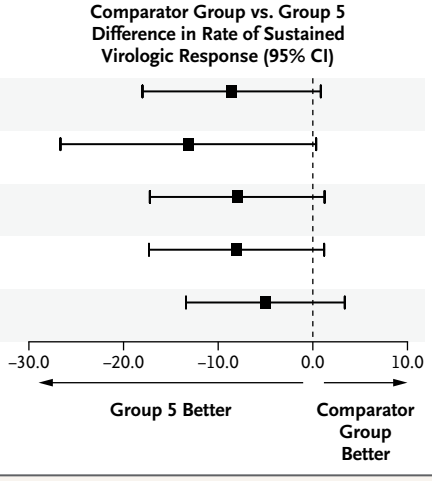

Figure 3. Comparison of Rates of Sustained Virologic Response at 24 Weeks after Treatment among Previously Untreated Patients, According to Treatment Regimen.

Boxes show the differences in the rates of sustained virologic response at 24 weeks after treatment between the group of previously untreated patients who received the three direct-acting antiviral agents (ABT-450/r, ABT-333, ABT-267) and ribavirin for 12 weeks (group 5; 79 patients) and groups of previously untreated patients who received other regimens or durations of treatment. Group 1 (80 patients) received 8 weeks of the three direct-acting antiviral agents and ribavirin; group 2 (41 patients) received 12 weeks of ABT-450/r, ABT-333, and ribavirin; group 3 (79 patients) received 12 weeks of ABT-450/r, ABT-267, and ribavirin; group 4 (79 patients) received 12 weeks of ABT-450/r, ABT-333, and ABT-267; and group 6 (80 patients) received 24 weeks of the three direct-acting antiviral agents and ribavirin. Horizontal bars show the 95% confidence intervals of the differences in the rates of sustained virologic response at 24 weeks after treatment.

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

Table 2. Adverse Events and Chemical and Hematologic Abnormalities of Grade 3 and 4 Occurring during the Treatment Period.*

Variable	Previously Untreated Patients						Patients without a Response to Prior Therapy		
	Group 1 (N=80)	Group 2 (N=41)	Group 3 (N=79)	Group 4 (N=79)	Group 5 (N=79)	Group 6 (N=80)	Group 7 (N=45)	Group 8 (N=45)	Group 9 (N=43)
	8 wk of ABT-450/r, ABT-267, ABT-333, and ribavirin	12 wk of ABT-450/r, ABT-333, and ribavirin	12 wk of ABT-450/r, ABT-267, and ribavirin	12 wk of ABT-450/r, ABT-267, and ABT-333	12 wk of ABT-450/r, ABT-267, ABT-333, and ribavirin	24 wk of ABT-450/r, ABT-267, ABT-333, and ribavirin	12 wk of ABT-450/r, ABT-267, and ribavirin	12 wk of ABT-450/r, ABT-267, ABT-333, and ribavirin	24 wk of ABT-450/r, ABT-267, ABT-333, and ribavirin
	number of patients (percent)								
Discontinuation due to adverse event†	1 (1)	0	0	0	2 (3)	3 (4)	1 (2)	0	1 (2)
Serious adverse event‡	0	0	2 (3)	2 (3)	1 (1)	1 (1)	0	0	2 (5)
Common adverse event									
Fatigue	29 (36)	13 (32)	22 (28)	16 (20)	22 (28)	30 (38)	12 (27)	12 (27)	9 (21)
Headache	28 (35)	13 (32)	23 (29)	15 (19)	21 (27)	29 (36)	15 (33)	13 (29)	14 (33)
Nausea	12 (15)	7 (17)	16 (20)	11 (14)	19 (24)	20 (25)	6 (13)	9 (20)	8 (19)
Insomnia	10 (12)	8 (20)	9 (11)	6 (8)	16 (20)	20 (25)	8 (18)	6 (13)	7 (16)
Diarrhea	8 (10)	10 (24)	8 (10)	13 (16)	10 (13)	11 (14)	7 (16)	8 (18)	8 (19)
Asthenia	7 (9)	1 (2)	8 (10)	5 (6)	3 (4)	12 (15)	10 (22)	4 (9)	4 (9)
Cough	12 (15)	5 (12)	11 (14)	2 (3)	8 (10)	12 (15)	7 (16)	3 (7)	9 (21)
Chemical abnormality of grade 3 or 4									
High total bilirubin§¶	0	0	3 (4)	0	4 (5)	0	2 (4)	0	2 (5)
High alanine aminotransferase¶	0	0	3 (4)	0	1 (1)	0	1 (2)	0	0
High glucose	0	0	2 (3)	0	1 (1)	0	1 (2)	0	1 (2)
Low sodium	0	0	2 (3)	0	1 (1)	1 (1)	0	0	0
High triglycerides	0	0	3 (4)	0	1 (1)	1 (1)	1 (2)	0	1 (2)
Hematologic abnormality of grade 3 or 4									
Increased white-cell count	1 (1)	0	0	2 (3)	1 (1)	0	1 (2)	0	0
Low lymphocyte count	1 (1)	0	0	2 (3)	1 (1)	1 (1)	0	0	0

Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
The New England Journal of Medicine
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

* Common adverse events listed here are events occurring during the treatment period in more than 20% of patients in any group. Events occurring in more than 5% of patients in any subgroup are shown in Table S12 in the Supplementary Appendix. Chemical and hematologic abnormalities of grade 3 or 4 occurring in more than one patient in any group are listed. A total bilirubin level of grade 3 was defined as a level of more than 3 times the upper limit of the normal range to 10 times the upper limit of the normal range, and grade 4 as a level of more than 10 times the upper limit of the normal range. An alanine aminotransferase level of grade 3 was defined as a level of more than 5 times the upper limit of the normal range to 20 times the upper limit of the normal range, and grade 4 as a level of more than 20 times the upper limit of the normal range. A high glucose level of grade 3 was defined as a level of more than 250 mg per deciliter (14 mmol per liter) to 500 mg per deciliter (28 mmol per liter), and grade 4 as a level of more than 500 mg per deciliter. A low sodium level of grade 3 was defined as a level of less than 130 mmol per liter to 120 mmol per liter, and grade 4 as a level of less than 120 mmol per liter. A triglyceride level of grade 3 was defined as a level of more than 500 mg per deciliter (6 mmol per liter) to 1000 mg per deciliter (12 mmol per liter), and grade 4 as a level of more than 1000 mg per deciliter. An increased white-cell count of grade 3 was defined as a count of more than 20×10^9 per liter to 25×10^9 per liter, and grade 4 as a count of more than 25×10^9 per liter. A lymphocyte count of grade 3 was defined as a count of less than 0.5×10^9 per liter to 0.2×10^9 per liter, and grade 4 as less than 0.2×10^9 per liter. Values of grade 3 and 4 also had to be more extreme than the baseline values.

† Adverse events leading to the discontinuation of treatment were decreased creatinine clearance, affective disorder, homicidal ideation, convulsion, cholestatic hepatitis, and anxiety (occurring in one patient each); asthenia, jitteriness, and confusional state occurring in the same patient; and headache, constipation, nausea, diarrhea, aphthous stomatitis, generalized pruritus, and burning sensation occurring in the same patient.

‡ Serious adverse events that occurred during the treatment period were affective disorder, animal bite, arthralgia, acute cholecystitis, and facial paresis (occurring in one patient each); increased blood creatinine level and bronchitis occurring in the same patient; the cervicobrachial syndrome, neck pain, and osteoarthritis of the spine occurring in the same patient; and lung disorder and pneumonia occurring in the same patient.

§ The measurement was of predominantly indirect bilirubin.

¶ Bilirubin elevations of grade 3 were not concurrent with aminotransferase elevations of grade 3.

SAFETY

A total of eight patients (1%) discontinued study-drug therapy owing to adverse events, including six previously untreated patients and two who had not had a response to prior therapy (Table 2). The reasons for discontinuation included affective disorder, homicidal ideation, convulsion, jitteriness, and confusional state. Six of these patients had a sustained virologic response at 24 weeks after treatment, including both patients who had not had a response to prior therapy. Serious adverse events occurred in eight patients (1%) during the study treatment period or the following 30 days (Table 2). One event (arthralgia) was considered by the investigator to be possibly related to a study drug.

Adverse events that occurred during treatment in more than 20% of patients in any group are shown in Table 2. The most common adverse events were fatigue, headache, nausea, and insomnia. The nature and frequency of adverse events were similar across treatment groups. Adverse events that occurred during treatment in more than 5% of patients in any subgroup are listed in the Table S12 in the Supplementary Appendix.

Laboratory abnormalities of grade 3 or 4 that occurred in more than 1 patient in any group are shown in Table 2. A total of 11 patients (2%) had grade 3 elevations in the bilirubin concentration (predominantly indirect bilirubin), which normalized during or immediately after treatment. No patient had a grade 4 elevation. These elevations were not associated with elevations in aminotransferase levels. A total of 5 patients (1%) had a grade 3 elevation in the alanine aminotransferase level, with a maximum alanine aminotransferase level of 408 U per liter; there were no grade 4 elevations. Alanine aminotransferase levels normalized in each case without interruption of the study drug. Triglyceride values of grade 3 or 4 were observed in 7 patients (1%); in 4 patients, the samples were not obtained while the patient was fasting. Anemia developed during the treatment period in 5% of previously untreated patients, in 6% of patients who had not had a response to prior therapy, and in 1% of patients who did not receive ribavirin. No grade 3 or 4 decreases in the hemoglobin level were observed. Additional details regarding patients with laboratory abnormalities of grade 3 or 4 are provided in the Supplementary Appendix.

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

DISCUSSION

In this phase 2b study of interferon-free antiviral regimens for the treatment of chronic HCV genotype 1 infection without cirrhosis, the treatment regimens were associated with rates of sustained virologic response at 24 weeks after treatment that ranged from 83 to 100%. Among previously untreated patients, the rate of treatment failure was lower among those receiving three direct-acting agents plus ribavirin for 12 weeks than among those who received the same regimen for only 8 weeks and among those who received fewer agents; extending the treatment to 24 weeks offered no further benefit. However, no differences in the rates of sustained virologic response reached statistical significance. The higher number of relapses among patients in the 8-week treatment group (in 10 of 80 patients, vs. in 1 of 79 patients in the 12-week treatment group) and the absence of resistance-associated variants in most patients who had a relapse in the 8-week treatment group suggest that 8 weeks of treatment might not be sufficient to eradicate the susceptible HCV population in these patients. Treatment durations longer than 8 weeks were not associated with a less favorable safety profile.

The 12-week regimen was also associated with a 93% rate of sustained virologic response at 24 weeks after treatment among patients who had not had a response to prior therapy, with a similar rate among patients treated for 24 weeks, which suggests that 12 weeks may be the preferred duration in this population as well. Previous studies have shown that patients who have not had a response to prior therapy with peginterferon and ribavirin have a poorer response to retreatment than do previously untreated patients, regardless of whether the treatments are interferon-based regimens or interferon-free combinations.[10,14-16] In the current study, the rates of sustained virologic response at 24 weeks after treatment were similar among previously treated patients and patients who had not had a response to prior therapy. In addition, the rates in this study were consistently high, even in the presence of baseline characteristics that have been associated historically with poor rates of response to treatment, such as host *IL28B* non-CC genotype, HCV genotype 1a infection, black race, and high baseline HCV RNA levels.

Response rates to interferon-free, protease inhibitor–containing combination therapy have been reported to be higher among patients with HCV genotype 1b infection than among those with HCV genotype 1a infection.[17,18] In this study, among 166 patients with HCV genotype 1b infection who received any 12-week or 24-week regimen and had not received treatment previously or had not had a response to prior therapy, there were no treatment failures, and only 1 of 24 patients who received an 8-week regimen had a relapse. These results suggest that a regimen containing fewer agents (e.g., without ribavirin) may be effective in treating this population, but this possibility would need to be explored in larger studies.

The results of other studies of interferon-free therapies currently in development have recently been published. Various regimens consisting of the investigational protease inhibitor faldaprevir and the nonnucleoside polymerase inhibitor deleobuvir with ribavirin, with treatment duration of 16 to 40 weeks, were associated with rates of sustained virologic response at 12 weeks after treatment of 52 to 69% among previously untreated patients with HCV genotype 1 infection, with low response rates among patients with HCV genotype 1a infection or an *IL28B* non-CC genotype.[19] A 12-week regimen of the nucleotide polymerase inhibitor sofosbuvir with ribavirin was associated with rates of sustained virologic response at 24 weeks after treatment of 84% among 25 previously untreated patients with HCV genotype 1 infection and 10% among 10 patients who had not had a response to prior therapy.[16]

Preliminary data suggest that the addition of the NS5A inhibitor ledipasvir to sofosbuvir and ribavirin can improve the rates of sustained virologic response among patients who have not had a response to prior therapy.[20] That finding is consistent with the similar rates we observed among previously untreated patients and those who had not had a response to prior therapy, suggesting that a regimen that is active against multiple viral targets may provide additional benefit in patients who have not had a response to prior therapy.

In this study, 1% of the patients had a serious adverse event during the study treatment period and the following 30 days; 1% of patients discontinued the study drug owing to an adverse

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

event. Larger studies are needed, but this preliminary assessment of adverse events compares favorably with the findings in studies of treatment with telaprevir or boceprevir plus peginterferon and ribavirin, in which serious adverse events occurred in 9 to 14% of patients, and 10 to 16% of patients discontinued therapy owing to adverse events.[5-7,15] The most common laboratory abnormality of grade 3 or 4 in this study, observed in 2% of patients, was a grade 3 elevation in the total bilirubin level. This finding appears to be related to the known inhibitory effect of protease inhibitors on the organic anion–transporting polypeptide 1B1.[21,22]

This study had several limitations. First, the open-label design could bias the assessment of adverse events. However, the use of objective, laboratory-based efficacy end points and laboratory assessments for safety mitigate this limitation. Second, the small number of patients in each study group limits the power to detect differences between groups. Third, patients with cirrhosis, who are less likely than those without cirrhosis to have a response to peginterferon and ribavirin,[5,15] were excluded from this study. Finally, the fibrosis stage at baseline was assessed by means of serum biomarkers, transient elastography, or biopsy. The use of various methods limits the ability to assess the effect of the disease stage at baseline on treatment response.

In conclusion, in this phase 2b study, interferon-free combinations of ABT-450/r, ABT-267, ABT-333, and ribavirin were associated with high rates of sustained virologic response at 24 weeks after treatment among previously untreated patients with chronic HCV genotype 1 infection and among patients who had not had a response to prior therapy. These preliminary data suggest that a 12-week regimen of three direct-acting agents plus ribavirin is efficacious in patients without cirrhosis who either had not received treatment previously or had not had a response to prior therapy.

Supported by AbbVie.

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

We thank the trial participants and coordinators who made this study possible; Christine Ratajczak and Rebecca Maag (AbbVie) for medical-writing services; and Christine Collins, Rakesh Tripathi, Preethi Krishnan, Michelle Irvin, Jill Beyer, Thomas Reisch, Hsiao-Ming Sharon Sun, Mary Knauss-Townsend, Christal Marincic, Manal Abunimeh, Jim Watson, Lorena Gomez, and Gaby Swerts (AbbVie) for their contributions to the study.

REFERENCES

1. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. Hepatology 2002;36:Suppl 1:S1-S2.
2. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-44.
3. Incivek (telaprevir) film coated tablets: prescribing information. Cambridge, MA: Vertex Pharmaceuticals, 2013 (http://pi.vrtx.com/files/uspi_telaprevir.pdf).
4. Victrelis (boceprevir) capsules: prescribing information. Whitehouse Station, NJ: Merck, 2013 (http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf).
5. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-17.
6. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.
7. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.
8. Poordad F, Bronowicki JP, Gordon SC, et al. Factors that predict response of patients with hepatitis C virus infection to boceprevir. Gastroenterology 2012;143:608-18.
9. Menon R, Klein C, Lawal A, et al. Pharmacokinetics and tolerability of the HCV protease inhibitor ABT-450 following single ascending doses in healthy adult volunteers with and without ritonavir. Global Antiviral J 2009;5:Suppl:53. abstract.
10. Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53.
11. Lawitz E, Marbury T, Campbell A, et al. Safety and antiviral activity of ABT-267, a novel NS5A inhibitor, during 3-day monotherapy: first study in HCV genotype-1 (GT1)-infected treatment-naive subjects. J Hepatol 2012;56:Suppl 2:S469-S470. abstract.
12. Romero-Gómez M, Del Mar Viloria M, Andrade RJ, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterology 2005;128:636-41.
13. Romero AI, Lagging M, Westin J, et al. Interferon (IFN)-gamma-inducible protein-10: association with histological results, viral kinetics, and outcome during treatment with pegylated IFN-alpha 2a and ribavirin for chronic hepatitis C virus infection. J Infect Dis 2006;194:895-903.
14. Bacon BR, Gordon SC, Lawitz E, et al. HCV RESPOND-2 final results: high sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus PegIntron (peginterferon alfa-2b)/ribavirin. Hepatology 2010;52:Suppl:430A. abstract.
15. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.
16. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44.
17. Sulkowski M, Rodriguez-Torres M, Lawitz E, et al. High sustained virologic response rate in treatment-naive HCV genotype 1A and 1B patients treated for 12 weeks with an interferon-free all-oral quad regimen: interim results. J Hepatol 2012;56:Suppl:S560. abstract.
18. Zeuzem S, Soriano V, Asselah T, et al. SVR4 and SVR12 with an interferon-free regimen of BI201335 and BI207127, +/– ribavirin, in treatment-naive patients with chronic genotype-1 HCV infection: interim

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

results of SOUND-C2. J Hepatol 2012;56: Suppl:S45. abstract.
19. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med 2013;369: 630-9.
20. Gane E, Hyland R, Ding X, et al. ELECTRON: 100% suppression of viral load through 4 weeks' post-treatment for sofosbuvir + ledipasvir (GS-5885) + ribavirin for 12 weeks in treatment-naive and -experienced hepatitis C virus GT 1 patients. In: Programs and abstracts of the 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, March 3–6, 2013. abstract.
21. Manns MP, Bourlière M, Benhamou Y, et al. Potency, safety, and pharmacokinetics of the NS3/4A protease inhibitor BI201335 in patients with chronic HCV genotype-1 infection. J Hepatol 2011;54: 1114-22.
22. Zeuzem S, Buggisch P, Agarwal K, et al. The protease inhibitor, GS-9256, and non-nucleoside polymerase inhibitor tegobuvir alone, with ribavirin, or pegylated interferon plus ribavirin in hepatitis C. Hepatology 2012;55:749-58.
Copyright © 2014 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org by JULES LEVIN on January 16, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.