ORIGINAL ARTICLE

Exploratory Study of Oral Combination Antiviral Therapy for Hepatitis C

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ABSTRACT

BACKGROUND

There is a need for interferon-free treatment regimens for hepatitis C virus (HCV) infection. The goal of this study was to evaluate ABT-450, a potent HCV NS3 protease inhibitor, combined with low-dose ritonavir (ABT-450/r), in addition to ABT-333, a nonnucleoside NS5B polymerase inhibitor, and ribavirin, for the treatment of HCV infection.

METHODS

We conducted a 12-week, phase 2a, open-label study involving patients who had HCV genotype 1 infection without cirrhosis. All patients received ABT-333 (400 mg twice daily) and ribavirin (1000 to 1200 mg per day) and one of two daily doses of ABT-450/r. Groups 1 and 2 included previously untreated patients; group 1 received 250 mg of ABT-450 and 100 mg of ritonavir, and group 2 received 150 mg and 100 mg, respectively. Group 3, which included patients who had had a null or partial response to previous therapy with peginterferon and ribavirin, received daily doses of 150 mg of ABT-450 and 100 mg of ritonavir. The primary end point was an undetectable level of HCV RNA from week 4 through week 12 (extended rapid virologic response).

RESULTS

A total of 17 of the 19 patients in group 1 (89%) and 11 of the 14 in group 2 (79%) had an extended rapid virologic response; a sustained virologic response 12 weeks after the end of treatment was achieved in 95% and 93% of the patients, respectively. In group 3, 10 of 17 patients (59%) had an extended rapid virologic response, and 8 (47%) had a sustained virologic response 12 weeks after therapy; 6 patients had virologic breakthrough, and 3 had a relapse. Adverse events included abnormalities in liver-function tests, fatigue, nausea, headache, dizziness, insomnia, pruritus, rash, and vomiting.

CONCLUSIONS

This preliminary study suggests that 12 weeks of therapy with a combination of a protease inhibitor, a nonnucleoside polymerase inhibitor, and ribavirin may be effective for treatment of HCV genotype 1 infection. (Funded by Abbott; ClinicalTrials.gov number, NCT01306617.)

HEPATITIS C VIRUS (HCV) INFECTION IS A leading cause of cirrhosis, liver cancer, and liver transplantation. Peginterferon-free regimens of direct-acting antiviral agents have the potential to improve both the safety and efficacy of HCV therapy, as compared with the current standard treatment of peginterferon and ribavirin with telaprevir or boceprevir.[1,2] Interferon is associated with substantial toxicity, and many patients with HCV infection are not eligible for interferon therapy owing to coexisting medical or psychiatric conditions or adverse events related to interferon, or they decline such therapy.[3,4] There is also a large population of HCV-infected patients in whom interferon treatment has failed; the options for subsequent treatment in this population have limited success rates.

ABT-450, a potent inhibitor of the HCV NS3 protease, has been combined with ritonavir (ABT-450/r) to increase the ABT-450 plasma concentration and half-life, permitting once-daily dosing.[5] When ABT-450/r was administered alone for 3 days in patients with HCV infection, higher levels of exposure were associated with a decreased emergence of resistance in the NS3 gene.[6] ABT-333, a nonnucleoside NS5B polymerase inhibitor, is administered twice daily. In previously untreated patients with HCV genotype 1 infection, treatment with peginterferon and ribavirin plus ABT-450/r or ABT-333 resulted in higher rates of sustained virologic response than treatment with peginterferon and ribavirin alone.[7,8] The present study assessed the safety and efficacy of the combination of ABT-450/r and ABT-333 with ribavirin in previously untreated patients with HCV genotype 1 infection and in patients with a null or partial response to previous treatment with peginterferon and ribavirin.

METHODS

STUDY POPULATION

We screened patients with chronic HCV genotype 1 infection from February 2011 through June 2011 at 11 sites in the United States. Eligible patients were 18 to 65 years of age, with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18 to 35, a detectable level of HCV RNA, and histologic findings on liver biopsy within the previous 3 years that were consistent with HCV-induced liver damage but with no evidence of cirrhosis or advanced bridging fibrosis. Exclusion criteria were a positive test result for hepatitis B surface antigen or anti–human immunodeficiency virus (HIV) antibodies, an alanine aminotransferase or aspartate aminotransferase level of more than 5 times the upper limit of the normal range, a calculated creatinine clearance of less than 50 ml per minute (according to the Cockcroft–Gault formula), an albumin level below the lower limit of the normal range, a prothrombin-time international normalized ratio of more than 1.5, a hemoglobin level below the lower limit of the normal range, a platelet count of less than 120,000 per cubic millimeter, a neutrophil count of less than 1500 per cubic millimeter, and a total bilirubin level above the upper limit of the normal range.

Patients were classified as having had a null or partial response to previous therapy if they met any of the following criteria: receipt of peginterferon and ribavirin for 12 weeks or more, without a decline in the HCV RNA level of at least $2 \log_{10}$ IU per milliliter by week 12 (null response); receipt of peginterferon and ribavirin, without a decline in the HCV RNA level of at least $1 \log_{10}$ IU per milliliter by week 4 (null response); or receipt of peginterferon and ribavirin for 12 weeks or more, with an HCV RNA level that was not below the limit of detection at the end of treatment (partial response).

STUDY DESIGN AND CONDUCT

In this sequentially enrolled, phase 2a, multicenter, open-label, three-group study, groups 1 and 2 included previously untreated patients, and group 3 included patients with a null or partial response to previous therapy. In group 1, patients received ABT-450/r at doses of 250 mg of ABT-450 and 100 mg of ritonavir once daily, ABT-333 (at a dose of 400 mg twice daily), and ribavirin (at a total daily dose of 1000 mg [divided into doses of 400 mg and 600 mg] if the body weight was <75 kg or 1200 mg [at twice-daily doses of 600 mg] if the body weight was ≥75 kg). In groups 2 and 3, patients received ABT-450/r (at doses of 150 mg of ABT-450 and 100 mg of ritonavir), as well as ABT-333 and ribavirin, at the same doses as those administered in group 1. The treatment duration for all groups was 12 weeks. Patients were followed for 48 weeks after treatment.

All patients provided written informed consent. The study was conducted in accordance with the principles of Good Clinical Practice and was ap-

proved by the appropriate institutional review boards and regulatory agencies.

Abbott sponsored the study, which was designed jointly by the study investigators and the sponsor. The sponsor conducted the data analyses, and all the authors had full access to the data; the first author vouches for the completeness and accuracy of the data presented and the analyses. The first draft of the manuscript was written by a medical writer employed by the sponsor, with input from all the authors. All the authors reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit it for publication. All the authors signed confidentiality agreements with the sponsor regarding the data. All the authors vouch that the study was conducted and reported with fidelity to the protocol, which is available with the full text of this article at NEJM.org.

EFFICACY ASSESSMENTS

Plasma samples for HCV RNA measurements were obtained at screening, at days 1 and 3, and weekly through week 12. After the last dose of study drugs, samples for assessment of the HCV RNA level were collected at post-treatment weeks 2, 4, 8, 12, 24, 36, and 48. Samples were processed by a central laboratory with the use of the COBAS TaqMan HCV Test, version 2.0 (Roche Molecular Systems), which is a real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay with a lower limit of quantitation of 25 IU per milliliter and a lower limit of detection of 15 IU per milliliter. Patients were required to stop treatment with the study drug if they met any of the following criteria: an HCV RNA level that was not decreased by at least 2 $\log_{10}$ IU per milliliter at week 1, a confirmed increase in the HCV RNA level from a nadir of more than 0.5 $\log_{10}$ IU per milliliter at any time, a detectable level of HCV RNA at week 6, or a confirmed detectable level of HCV RNA at any point after documentation of an undetectable level. Further details are provided in the Supplementary Appendix, available at NEJM.org.

RESISTANCE TESTING

Viral RNA was isolated from plasma with the use of an automated method (m2000 RealTime System, Abbott Molecular). RT-PCR assay of extracted RNA with the use of sense and antisense primers located outside the coding region for NS3–NS4A

or NS5B was performed with the Superscript III One-Step RT-PCR System with Platinum Taq High Fidelity (Invitrogen, Life Technologies), according to the manufacturer's recommendations. Nested PCR analysis was performed with sense and antisense primers specific for the region encoding NS3 protease or NS5B polymerase with the use of Platinum Pfx DNA Polymerase (Invitrogen, Life Technologies). The NS3 protease or NS5B polymerase nested PCR product was cloned into an *Escherichia coli* plasmid, and at least 74 clones were sequenced from each sample.

SAFETY ASSESSMENTS

Adverse-event assessment, clinical laboratory testing, and 12-lead electrocardiography were performed at each study visit. 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 during the entire study. Events were classified by the investigator as mild, moderate, or severe.

END POINTS

The primary end point was the percentage of patients with an undetectable level of HCV RNA from week 4 through week 12 (extended rapid virologic response). Secondary end points included the percentage of patients with an HCV RNA level below the lower limit of quantitation (25 IU per milliliter) at week 4 (rapid virologic response), at week 12, and 12 weeks after the end of treatment (sustained virologic response). Virologic breakthrough during treatment was defined as a confirmed increase of 0.5 $\log_{10}$ IU per milliliter or more above the nadir or a confirmed detectable level of HCV RNA in patients who previously had an undetectable level of HCV RNA. Relapse was defined as a confirmed level of HCV RNA at or above the lower limit of quantitation for patients with an HCV RNA level below the lower limit of quantitation at the end of treatment. Analyses of virologic end points were performed for all patients who received at least one dose of the study drug.

STATISTICAL ANALYSIS

All analyses were performed with the use of SAS software, version 9.2, for the UNIX operating system (SAS Institute). For the virologic end points of the percentages of patients with a rapid virologic response, an extended rapid virologic

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

Characteristic	Group 1 (N=19)	Group 2 (N=14)	Group 3 (N=17)
Male sex — no. (%)	10 (53)	14 (100)	11 (65)
Race and ethnic group — no. (%)†			
White	15 (79)	12 (86)	13 (76)
Nonwhite	4 (21)	2 (14)	4 (24)
Hispanic	3 (16)	0	4 (24)
Non-Hispanic	16 (84)	14 (100)	13 (76)
Age — yr	53.6±9.8	50.9±10.4	52.3±9.0
Body-mass index‡	27.3±3.8	24.6±3.1	27.6±4.7
IL28 genotype — no. (%)			
CC	10 (53)	5 (36)	0
CT	7 (37)	7 (50)	12 (71)
TT	2 (11)	2 (14)	5 (29)
HCV genotype — no. (%)			
1a	17 (89)	11 (79)	16 (94)
1b	2 (11)	3 (21)	1 (6)
HCV RNA			
Mean $\log_{10}$ level — IU/ml	6.25±0.80	6.44±1.15	6.91±0.48
>800,000 IU/ml — no. (%)	14 (74)	11 (79)	17 (100)
Response to previous therapy§			
Partial	—	—	10 (59)
Null	—	—	7 (41)

* Plus–minus values are means ±SD. Differences among treatment groups were calculated with the use of chi-square tests for the categorical data and one-way ANOVA for the continuous data. Sex and IL28B genotype differed significantly among treatment groups (P=0.01 and P=0.02, respectively). Groups 1 and 2 included previously untreated patients, whereas group 3 included patients with a null or partial response to previous therapy. All patients received ABT-333 and ribavirin. In addition, those in group 1 received ABT-450/r at a daily dose of 250 mg of ABT-450 and 100 mg of ritonavir, and those in groups 2 and 3 received ABT-450/r at a daily dose of 150 mg of ABT-450 and 100 mg of ritonavir. HCV denotes hepatitis C virus.
† Race and ethnic group were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ A partial response to previous therapy was defined as the receipt of peginterferon and ribavirin for 12 weeks or more, with an HCV RNA level that was not below the limit of detection at the end of treatment. A null response to previous therapy was defined as either the receipt of peginterferon and ribavirin for 12 weeks or more, without a decline in the HCV RNA level of at least 2 $\log_{10}$ IU per milliliter by week 12, or the receipt of peginterferon and ribavirin, without a decline in the HCV RNA level of at least 1 $\log_{10}$ IU per milliliter by week 4.

response, a response at week 12, and a sustained virologic response at 12 weeks after the end of treatment, the two-sided 95% confidence intervals were calculated with the use of the binomial exact method.

RESULTS

STUDY PATIENTS

We enrolled a total of 19 previously untreated patients in group 1, a total of 14 previously untreated patients in group 2, and a total of 17 pa-

tients with a null or partial response to previous therapy in group 3 (Fig. S1A in the Supplementary Appendix). Demographic and baseline clinical characteristics of the three groups are shown in Table 1.

EFFICACY IN PREVIOUSLY UNTREATED PATIENTS

In previously untreated patients, the HCV RNA level declined rapidly after the initiation of treatment. After 1 week, all patients had HCV RNA levels of less than 1000 IU per milliliter (Fig. 1A and 1B, and Fig. S1B and S1C in the Supplemen-

tary Appendix). One patient in group 1 discontinued the study treatment during week 3 owing to an adverse event (elevated levels of alanine aminotransferase and aspartate aminotransferase), and 1 patient in group 2 discontinued the study treatment during week 1 owing to noncompliance with the study procedures.

With respect to the primary end point, 17 of the 19 patients in group 1 (89%; 95% confidence interval [CI], 67 to 99) and 11 of the 14 in group 2 (79%; 95% CI, 49 to 95) had an extended rapid virologic response (Table 2). None of the patients in group 1 or group 2 had virologic breakthrough and none who completed treatment had a relapse; all patients who completed treatment had a sustained virologic response at 12 weeks after treatment (18 of the 19 patients in group 1 [95%; 95% CI, 74 to 100] and 13 of the 14 in group 2 [93%; 95% CI, 66 to 100]). All 18 patients who completed treatment in group 1 had an undetectable level of HCV RNA at 48 weeks after treatment. Two of the 13 patients who completed treatment in group 2 discontinued the study after week 12 of follow-up; the other 11 patients had an undetectable level of HCV RNA 48 weeks after treatment.

EFFICACY IN PATIENTS WITH A NULL OR PARTIAL RESPONSE TO PREVIOUS THERAPY

The HCV RNA level initially declined in all patients in group 3 (Fig. 1C, and Fig. S1D in the Supplementary Appendix). Six patients had virologic breakthrough during treatment, including 1 who mistakenly took only 50 mg of ABT-450 daily for the first 3 weeks and who never had an HCV RNA level of less than 25 IU per milliliter. A total of 10 patients (59%; 95% CI, 33 to 82) had an extended rapid virologic response. A total of 3 patients had a relapse 2 weeks after treatment, and 8 had a sustained virologic response 12 weeks after treatment (47%; 95% CI, 23 to 72). A total of 3 of 7 patients (43%; 95% CI, 10 to 82) with a null response to previous treatment and 5 of 10 (50%; 95% CI, 19 to 81) with a partial response to previous treatment had a sustained virologic response 12 weeks after the study treatment. Among patients with IL28B CT and TT genotypes, a sustained virologic response 12 weeks after treatment was achieved in 6 of 12 patients (50%; 95% CI, 21 to 79) and in 2 of 5 (40%; 95% CI, 5 to 85), respectively. All 8 patients who had a sustained virologic response 12 weeks after treatment had an undetectable level
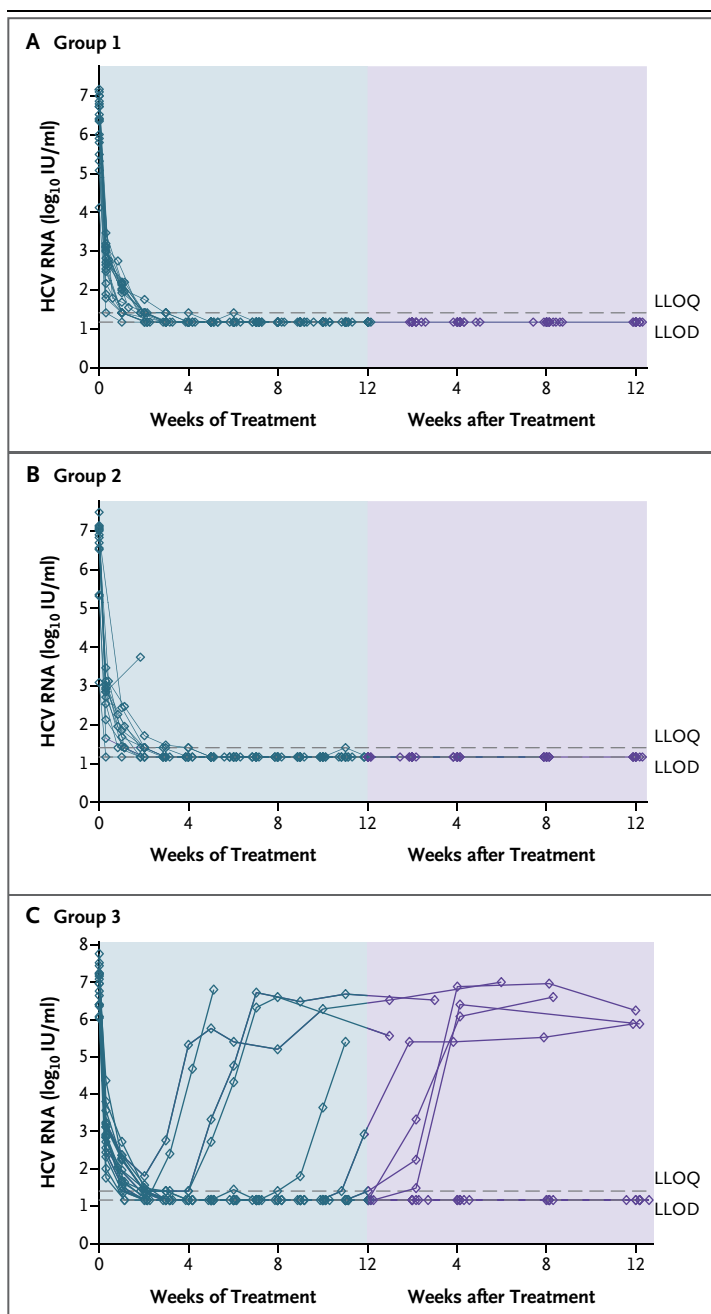

Figure 1. Hepatitis C Virus (HCV) RNA Values through 12 Weeks of Treatment and 12 Weeks of Follow-up in Previously Untreated Patients and in Patients with a Null or Partial Response to Previous Therapy.

The HCV RNA level declined rapidly in the previously untreated patients. Panels A and B show the values for the previously untreated patients in groups 1 and 2, respectively. Panel C shows the values for the patients with a null or partial response to previous therapy. All patients received ABT-333 and ribavirin; in addition, those in group 1 received ABT-450/r at daily doses of 250 mg of ABT-450 and 100 mg of ritonavir, and those in groups 2 and 3 received ABT-450/r at daily doses of 150 mg of ABT-450 and 100 mg of ritonavir. LLOD denotes lower limit of detection, and LLOQ lower limit of quantitation.

Table 2. Virologic Response Rates.

Response	Group 1 (N=19)		Group 2 (N=14)		Group 3 (N=17)	
	no./total no.	% (95% CI)	no./total no.	% (95% CI)	no./total no.	% (95% CI)
Rapid virologic response*	19/19†	100 (82–100)	13/14	93 (66–100)	15/17	88 (64–99)
Extended rapid virologic response‡	17/19	89 (67–99)	11/14	79 (49–95)	10/17	59 (33–82)
Response at week 12 of treatment	19/19†	100 (82–100)	13/14	93 (66–100)	11/17	65 (38–86)
Sustained viral response 12 wk after treatment§	18/19	95 (74–100)	13/14	93 (66–100)	8/17	47 (23–72)
Response to previous therapy						
Partial	—	—	—	—	5/10	50 (19–81)
Null	—	—	—	—	3/7	43 (10–82)
IL28 genotype						
CC	9/10	90 (56–100)	4/5	80 (28–99)	0/0	—
CT	7/7	100 (59–100)	7/7	100 (59–100)	6/12	50 (21–79)
TT	2/2	100 (16–100)	2/2	100 (16–100)	2/5	40 (5–85)

* Rapid virologic response was defined as an HCV RNA level of less than 25 IU per milliliter at week 4.
† One patient who discontinued the study treatment early had a suppressed level of HCV RNA 1 week after treatment. We therefore imputed HCV RNA values for this patient that represented a rapid virologic response and a response at week 12. If this patient were counted as having had a treatment failure, the rates for rapid virologic response and response at week 12 would both be 95% (18 of 19 patients).
‡ Extended rapid virologic response was defined as an undetectable level of HCV RNA from week 4 through week 12.
§ Sustained virologic response 12 weeks after treatment was defined as an HCV RNA level of less than 25 IU per milliliter 12 weeks after treatment.

of HCV RNA at their last follow-up visit, 36 weeks after treatment.

RESISTANCE

HCV RNA was analyzed for the presence of resistance-associated variants in all patients in group 3 who had virologic failure (breakthrough or relapse). Variants at NS3 position 168 were detected at baseline in the one patient with HCV genotype 1b infection in whom previous treatment had failed, meaning that a single subsequent nucleotide substitution conferred resistance to ABT-450/r (Table 3). Resistant variants in NS3 and NS5B were detected in eight patients who had virologic failure; one patient with a relapse had no variants at any signature position.

SAFETY

No deaths or serious adverse events occurred during the study. One patient in group 1 discontinued the study drugs owing to elevated levels of aspartate aminotransferase and alanine aminotransferase at week 2. The patient was asymptomatic, and the highest level of alanine aminotransferase recorded for this patient was 308 U per liter. The elevated aminotransferase levels were not associated with an increased bilirubin level and improved promptly after discontinuation of the study drugs.

The most frequent adverse events that occurred during treatment are shown in Table 4. Overall, the most frequent events were fatigue, nausea, headache, dizziness, insomnia, pruritus, rash, and vomiting. Most events were mild. Four adverse events, occurring in four patients, were classified as severe: fatigue, pain, vomiting, and hyperbilirubinemia (highest recorded total bilirubin level, 6.2 mg per deciliter [106 μmol per liter]; predominantly indirect bilirubin). None of these events led to an interruption or discontinuation of the study treatment; the event of hyperbilirubinemia led to a reduction in the dose of ribavirin only. There were no other modifications of the study drugs.

Laboratory abnormalities of note that occurred during treatment are shown in Table 4. Of the six patients with a total bilirubin level that was more than 2 times the upper limit of the normal range, 3 had this elevation at a single study visit. In all six patients, indirect bilirubin predominated and the abnormality resolved during treatment without adjustment of study-drug doses. Two patients had serum creatinine levels of more than 1.5 mg per deciliter (133 μmol per liter), with an

Table 3. Resistant Variants Present at Baseline and at the Time of Virologic Failure in Patients with a Null or Partial Response to Previous Therapy.*

Patient No.	Virologic Failure	HCV Genotype	NS3 Protease		NS5B Polymerase	
			Baseline	At Time of Failure	Baseline	At Time of Failure
1	Breakthrough during treatment	1a	None	R155K > D168A > D168V	None	G554S
2	Breakthrough during treatment	1a	None	D168A	None	M414T
3	Breakthrough during treatment	1a	None	D168V	None	C316Y > D559G
4	Breakthrough during treatment	1a	None	D168E > D168Y	None	G554S > S556G > M414V and G554S†
5	Breakthrough during treatment	1a	None	D168V	None	S556G
6	Breakthrough during treatment	1b	D168E > D168T‡	D168K	None	C316Y
7	Relapse after treatment	1a	None	D168Y > D168V > D168A	None	S556G > M414T
8	Relapse after treatment	1a	None	None	None	None
9	Relapse after treatment	1a	None	D168V	None	S556G

* Where a resistance-associated variant is indicated, it was present in 5% or more of clones from that sample. If a sample contained multiple variants, they are shown in order of prevalence from highest to lowest percentage of clones containing that variant, as indicated by the greater-than (>) sign. None denotes that no variants were found at amino acid positions known to be associated with resistance to ABT-333 or ABT-450.
† Individual clones contained both amino acid variants.
‡ The conversion of D168E or D168T to D168K in HCV genotype 1b requires only a single nucleotide change.

associated calculated creatinine clearance of less than 50 ml per minute. In both patients, the creatinine elevations occurred at isolated time points and resolved without dose modifications of the study drugs.

DISCUSSION

The primary end point in this exploratory study was the percentage of patients with virologic suppression by week 4 of treatment and sustained suppression through week 12. That end point was met in 28 of the 33 previously untreated patients and in 10 of the 17 patients who had undergone previous treatment. Among the previously untreated patients, there were no virologic failures during treatment or during 48 weeks of follow-up for those who completed treatment. In contrast, 9 of the 17 patients with a null or partial response to previous therapy either had virologic breakthrough or had a relapse by the date of their first follow-up visit after treatment. In most cases, virologic failure was associated with the emergence of variants with substitutions in both NS3 and NS5B, at positions known to confer resistance in vitro to ABT-450 and ABT-333, respectively.

One patient discontinued the study treatment owing to asymptomatic elevations in amino-transferase levels. In previous studies of ABT-450/r, 1 healthy volunteer had a grade 3 elevation in the level of alanine aminotransferase while receiving ABT-450/r (at a daily dose of 250 mg of ABT-450 and 100 mg of ritonavir) with two other investigational direct-acting antiviral agents. That elevation, which was also asymptomatic, was not associated with an increase in the bilirubin level and resolved promptly on discontinuation of the study drug. Similar grade 3 elevations were not seen in participants receiving ABT-450/r monotherapy or in those receiving ABT-450/r at daily doses of less than 250 mg of ABT-450 and 100 mg of ritonavir. For this reason, as well as the similar response rates observed in this study at both dose levels in previously untreated patients, the patients in group 3 received the lower ABT-450/r doses of 150 mg of ABT-450 and 100 mg of ritonavir. The indirect bilirubin level increased transiently in 6 of 50 patients (12%). This finding is consistent with the effect of protease inhibitors on the organic anion–transporting polypeptide 1B1.[9,10]

Other trials of interferon-free, protease-inhibitor–containing combination therapy in previously untreated patients have shown reduced activity against HCV genotype 1a as compared with HCV genotype 1b.[11,12] Although this study was too small for us to draw definitive conclu-

Table 4. Adverse Events and Potentially Clinically Significant Laboratory Abnormalities.*

Event or Abnormality	Group 1 (N=19)	Group 2 (N=14)	Group 3 (N=17)
	number of patients (percent)		
Adverse event			
Fatigue	9 (47)	6 (43)	6 (35)
Nausea	4 (21)	3 (21)	4 (24)
Headache	5 (26)	2 (14)	3 (18)
Dizziness	1 (5)	4 (29)	4 (24)
Insomnia	5 (26)	3 (21)	0
Pruritus	4 (21)	0	2 (12)
Rash	4 (21)	1 (7)	1 (6)
Vomiting	1 (5)	3 (21)	0
Laboratory abnormality			
Total bilirubin ≥2× ULN	3 (16)	3 (21)	0
Creatinine ≥1.5 mg/dl (133 μmol/liter)	2 (11)	0	0
Calculated creatinine clearance <50 ml/min	2 (11)	0	0
Alanine aminotransferase ≥5× ULN	1 (5)	0	0
Sodium <130 mmol/liter	0	1 (7)	0

* Adverse events listed here are those that occurred in more than 20% of patients in any group. All laboratory abnormalities that occurred are listed. ULN denotes upper limit of the normal range.

sions regarding the effect of genotype on treatment response, no virologic failures occurred among the 31 previously untreated patients who completed treatment, including 26 patients with HCV genotype 1a infection. Previous studies have suggested that the IL28B genotype can affect the response to interferon-free regimens.[11,12] In the present study, more than half the previously untreated patients who completed the study treatment had a CT or TT IL28B genotype, and all had a sustained virologic response. Only 1 patient who had undergone treatment previously had HCV genotype 1b infection, and none had the CC IL28B genotype. Thus, no conclusions can be drawn regarding the effect of these factors on the response to therapy in previously treated patients.

Other studies of combinations of direct-acting antiviral agents have also shown the potential for sustained virologic response in some patients without the use of interferon. In a study of the NS3 inhibitor asunaprevir and the NS5A inhibitor daclatasvir, administered for 24 weeks in

patients with HCV genotype 1 infection and a null response to previous therapy, 4 of 11 patients had a sustained virologic response 24 weeks after treatment, including 2 of 9 patients with HCV genotype 1a infection and 2 of 2 with HCV genotype 1b infection.[13] In a Japanese study of patients with HCV genotype 1b infection, this regimen was associated with a sustained virologic response 24 weeks after treatment in 91% of 21 patients with a null response to previous therapy and in 64% of 22 patients who either were ineligible for treatment with peginterferon or had adverse events associated with previous peginterferon therapy.[14] Combination treatment with daclatasvir and sofosbuvir administered for 24 weeks with or without ribavirin was associated with an undetectable level of HCV RNA 4 weeks after treatment in more than 95% of previously untreated subjects who had HCV genotype 1, 2, or 3 infection.[15]

Finally, the combination of ribavirin with the nucleotide-analogue NS5B inhibitor sofosbuvir was associated with an undetectable level of HCV RNA 4 weeks after treatment in 22 of 25 previously untreated patients (88%) with HCV genotype 1 infection, and in 1 of 9 patients (11%) with HCV genotype 1 infection and a null response to previous therapy.[16] Among patients with HCV genotype 2 or 3 infection, the same regimen was associated with a sustained virologic response in all 10 previously untreated patients (100%).[17] Of 15 previously treated patients, 12 (80%) had an undetectable level of HCV RNA 4 weeks after treatment; at least 1 patient had a relapse 8 weeks after treatment.[16] The current study examined response rates to an oral regimen among both previously untreated and previously treated patients who had HCV genotype 1a or 1b infection, allowing comparison of response rates with respect to both previous-treatment status and HCV genotype.

The sustained-virologic-response rate of 47% among patients with a null or partial response to previous treatment with peginterferon and ribavirin, which is markedly lower than the rate among previously untreated patients, suggests that treatments including direct-acting antiviral agents are less effective in patients with a null or partial response to previous treatment than in previously untreated patients, even in the absence of interferon therapy. More-potent regimens will be

needed to achieve similar rates of sustained virologic response in this population, possibly with the addition of a third direct-acting antiviral agent that has a complementary mechanism of action. Although longer durations of therapy could be considered, we found that most of the virologic failures in the patients with a null or partial response to previous therapy occurred during treatment. Extending the treatment duration beyond 12 weeks would not have prevented the virologic failures in these patients.

In conclusion, this preliminary study suggests that the all-oral combination of ABT-450/r, ABT-333, and ribavirin for 12 weeks is associated with a sustained virologic response in a high proportion of previously untreated patients with HCV genotype 1 infection. Larger studies of this and similar regimens will be needed to confirm these findings in subgroups based on HCV genotype, race, sex, and age. This regimen is less effective in patients who have HCV genotype 1 infection with a null or partial response to previous therapy. ABT-450/r–based regimens that include additional or more-potent agents may have applicability across a broader range of patients with HCV infection, and studies are needed to assess safety and efficacy in patients with a null or partial response to previous therapy, those with cirrhosis, and those who also have HIV type 1 infection.

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