ORIGINAL ARTICLE

# Telaprevir for Retreatment of HCV Infection

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## ABSTRACT

### BACKGROUND

Up to 60% of patients with hepatitis C virus (HCV) genotype 1 infection do not have a sustained virologic response to therapy with peginterferon alfa plus ribavirin.

### METHODS

In this randomized, phase 3 trial, we evaluated the addition of telaprevir to peginterferon alfa-2a plus ribavirin in patients with HCV genotype 1 infection who had no response or a partial response to previous therapy or who had a relapse after an initial response. A total of 663 patients were assigned to one of three groups: the T12PR48 group, which received telaprevir for 12 weeks and peginterferon plus ribavirin for a total of 48 weeks; the lead-in T12PR48 group, which received 4 weeks of peginterferon plus ribavirin followed by 12 weeks of telaprevir and peginterferon plus ribavirin for a total of 48 weeks; and the control group (PR48), which received peginterferon plus ribavirin for 48 weeks. The primary end point was the rate of sustained virologic response, which was defined as undetectable HCV RNA 24 weeks after the last planned dose of a study drug.

### RESULTS

Rates of sustained virologic response were significantly higher in the two telaprevir groups than in the control group among patients who had a previous relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group, and 24% in the PR48 group), a partial response (59%, 54%, and 15%, respectively), and no response (29%, 33%, and 5%, respectively) ($P<0.001$ for all comparisons). Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) were more frequent in the telaprevir groups than in the control group (37% vs. 22%).

### CONCLUSIONS

Telaprevir combined with peginterferon plus ribavirin significantly improved rates of sustained virologic response in patients with previously treated HCV infection, regardless of whether there was a lead-in phase. (Funded by Tibotec and Vertex Pharmaceuticals; REALIZE ClinicalTrials.gov number, NCT00703118.)

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Approximately 60% of patients who are infected with hepatitis C virus (HCV) genotype 1 are not cured by 48 weeks of peginterferon alfa combined with ribavirin.[1] Such patients fall into one of three categories: those who have no response to therapy, which is defined as a reduction of less than 2 $\log_{10}$ in HCV RNA levels after 12 weeks of therapy[2]; those who have a partial response, which is defined as a reduction of at least 2 $\log_{10}$ in a patient who has always had detectable serum HCV RNA during therapy; and those who have a relapse, which is defined as undetectable serum HCV RNA at the end of treatment but with subsequent virologic relapse.

In two recent phase 2 trials, telaprevir, an orally bioavailable inhibitor of the nonstructural 3/4A HCV protease,[3] substantially enhanced rates of sustained virologic response when it was combined with peginterferon plus ribavirin in patients who had received previous therapy.[4,5] In this randomized, double-blind, placebo-controlled, phase 3 study, we assessed the efficacy and safety of the addition of telaprevir to a regimen of peginterferon plus ribavirin in patients with chronic HCV genotype 1 infection who did not have a sustained virologic response to previous treatment.

## Methods

### Patients

From September 2008 through July 2010, we enrolled patients at study centers in 17 countries in Europe, South America, and North America, as well as in Israel, and Australia. All patients were between the ages of 18 and 70 years, had chronic HCV genotype 1 infection, did not have a sustained virologic response to one previous course of peginterferon plus ribavirin despite receiving at least 80% of the intended dose, and had well-characterized data on the previous treatment. Eligible patients had detectable HCV RNA, had undergone liver biopsy within 18 months before screening, and had an absolute neutrophil count of at least 1200 per cubic millimeter, a platelet count of at least 90,000 per cubic millimeter, and a hemoglobin level of at least 12 g per deciliter for women and 13 g per deciliter for men. Patients were excluded if they had decompensated liver disease, other causes of significant liver disease, or active cancer.

The protocol (which is available with the full text of this article at NEJM.org) was approved by the independent ethics committee at each participating study center (for a complete list, see the Supplementary Appendix, available at NEJM.org). The study was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

### Study Design

Patients were stratified according to their baseline viral load (HCV RNA, <800,000 or ≥800,000 IU per milliliter) and type of previous response to peginterferon plus ribavirin (no response, partial response, or relapse). No response was defined as a reduction of less than 2 $\log_{10}$ in HCV RNA after 12 weeks of therapy. Partial response was defined as a reduction of 2 $\log_{10}$ or more in HCV RNA after 12 weeks of therapy but with detectable HCV RNA. Relapse was defined as undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter.

Telaprevir (Tibotec) was administered orally at a dose of 750 mg every 8 hours; peginterferon alfa-2a (Pegasys, Roche) was administered subcutaneously at a dose of 180 $\mu$g per week; and ribavirin (Copegus, Roche) was administered orally at a dose of 1000 to 1200 mg per day.

Patients were randomly assigned to one of two groups receiving telaprevir (with or without a lead-in period of therapy with peginterferon alfa-2a plus ribavirin) or a control group that received placebo along with peginterferon alfa-2a plus ribavirin in a 2:2:1 ratio. Randomization was performed with the use of a centralized system according to a predefined randomization list, constructed through random permuted blocks. In the T12PR48 group, 266 patients were assigned to receive telaprevir, peginterferon, and ribavirin for 12 weeks, followed by placebo plus peginterferon and ribavirin for 4 weeks, and then peginterferon plus ribavirin alone for 32 weeks. In the lead-in T12PR48 group, 264 patients were assigned to receive placebo, peginterferon, and ribavirin for 4 weeks, followed by telaprevir plus peginterferon plus ribavirin for 12 weeks, and then peginterferon plus ribavirin alone for 32 weeks. In the PR48 (control) group, 132 patients were assigned to receive placebo, peginterferon, and ribavirin for 16 weeks, followed by peginterferon plus ribavirin for 32 weeks. In all the groups, study drugs were administered for 48 weeks.

All study investigators, patients, and the sponsors were unaware of study-group assignments until all patients had reached week 72, unless unblinding was necessary for medical reasons. Re-

sults of HCV RNA tests up to week 24 were masked and were monitored by an independent reviewer to assess whether patients had met a predefined stopping rule. Telaprevir was stopped if HCV RNA levels were greater than 100 IU per milliliter at weeks 4, 6, and 8 after the start of telaprevir treatment; in such cases, patients were able to continue receiving peginterferon plus ribavirin. All treatment had to be discontinued if patients had less than a 2 $\log_{10}$ decrease in HCV RNA at week 12 in the T12PR48 group and the control group or at week 16 in the lead-in T12PR48 group or in cases of detectable HCV RNA at week 24 or 36. Patients who discontinued telaprevir because of the stopping rule were considered to have had virologic failure.

#### STUDY OVERSIGHT

The first author participated in the development of the study design and protocol development with the study sponsors. The first author also wrote the first draft of the manuscript and vouches for the completeness and veracity of the data and data analyses, as well as the fidelity of the report to the trial protocol. Editorial assistance in the preparation of the manuscript was funded by Janssen Pharmaceuticals, the parent company of Tibotec. Peginterferon and ribavirin were purchased from the manufacturers. All authors reviewed and approved the final form of the manuscript and made the decision to submit it for publication.

#### EFFICACY ASSESSMENTS

We performed plasma HCV RNA quantification using the COBAS TaqMan assay (Roche), version 2.0, which has a lower limit of quantification of 25 IU per milliliter and a limit of detection of 10 IU per milliliter. HCV RNA levels were measured at screening, at baseline, on day 3, and during weeks 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, and 48, as well as at the time of early discontinuation, at follow-up visits 4, 12, and 24 weeks after end of treatment, and at week 72, even in patients who discontinued early.

#### VIROLOGIC ASSESSMENTS

To analyze for resistant variants, HCV RNA was isolated from plasma, and the nonstructural 3/4A protease domains were amplified by reverse-transcriptase polymerase-chain-reaction assay and sequenced. Analyses were performed on baseline samples and in cases of virologic failure (i.e., in cases of viral breakthrough or cases in which patients met a virologic stopping rule) or relapse. Viral breakthrough was defined as an increase of at least 1 $\log_{10}$ in HCV RNA from the nadir reached during treatment or an HCV RNA level of more than 100 IU per milliliter in patients whose viral load had previously been less than 25 IU per milliliter during treatment. Telaprevir-resistant variants included V36A/M, T54A/S, R155I/K/M/T, and A156S/T/V.[6]

#### SAFETY ASSESSMENTS

Data on all adverse events were collected throughout the treatment period and at the safety follow-up assessment 4 weeks after the administration of the last dose of a study drug. Serious adverse events continued to be monitored throughout the follow-up period. Laboratory assessments were performed at the same time points as efficacy assessments.

Guidance for the management and grading of rash was included according to the following criteria: grade 1 (mild, localized to one or several sites), grade 2 (moderate, with a diffuse skin eruption involving up to 50% of body surface), and grade 3 (severe, involving more than 50% of body surface or rash with the appearance of major systemic signs or symptoms). For patients with grade 1 or 2 rash, medical management was performed at the discretion of the investigator. For patients with grade 2 rash that progressed or did not improve or any grade 3 rash, telaprevir was discontinued while the patient continued to receive peginterferon plus ribavirin. The discontinuation of ribavirin (with or without peginterferon) was then suggested if the rash did not improve within 7 days after the discontinuation of telaprevir.

For the management of anemia, reductions in the ribavirin dose were made in accordance with drug labeling. Reductions in the telaprevir dose were prohibited, as was the use of erythropoietin-stimulating agents. If reductions in the ribavirin dose or discontinuation did not result in improvement in anemia, then telaprevir therapy was stopped. An independent data and safety monitoring board analyzed safety data at predefined time points during the study.

#### PRIMARY AND SECONDARY END POINTS

The primary end point was the proportion of patients with either a previous relapse or lack of a previous response who had a sustained virologic response (i.e., undetectable plasma HCV RNA 24 weeks after the last planned administration of a

study drug). Secondary end points included the effect of lead-in treatment with peginterferon plus ribavirin on sustained virologic response, the proportion of patients who had undetectable HCV RNA at 4 and 8 weeks, the proportion of patients who had a relapse, and the change from baseline in $\log_{10}$ HCV RNA.

### STATISTICAL ANALYSIS

All analyses were performed on the intention-to-treat principle in all patients who underwent randomization and received at least one dose of a study drug. The analysis of the primary end point was based on a logistic-regression model that included study group, the type of previous response (no response, partial response, or relapse), and their interaction as factors and the baseline viral RNA as a covariate. We used the Hochberg procedure to adjust for multiple comparisons. The primary objective was to show superior rates of sustained virologic response in each of the two telaprevir study groups, as compared with the control group, separately in patients who had a previous relapse or did not have a virologic response (either no response or a partial response) to therapy.

The estimated study sample size of 650 patients was calculated on the basis of the primary objective to provide a power of 90%. The calculation was performed with the use of a two-sided continuity-corrected chi-square test. A P value of 0.05 was considered to indicate statistical significance. On the basis of the results of the Protease Inhibition for Viral Evaluation 3 (PROVE3) trial (ClinicalTrials.gov number, NCT00420784),[4] it was estimated that virologic response rates with telaprevir would be 55%, as compared with 29% in the control group, in patients who had a relapse and 30% versus 8% in patients who had no response or a partial response to previous therapy.

One of the secondary end points, the change from baseline in $\log_{10}$ HCV RNA levels, was displayed over time descriptively and explored with the use of a longitudinal statistical model. Subgroup analyses of sustained virologic response according to the stage of liver fibrosis and the baseline viral load were conducted to determine the robustness of the primary analysis.

## RESULTS

### PATIENTS

Of 833 patients who were screened, 663 underwent randomization, and 662 received at least one dose of a study drug (intention-to-treat population) (Fig. 1). The baseline characteristics of the patients and their disease level were similar in the three study groups (Table 1). A total of 26% of the patients had cirrhosis. Overall, 53% of the patients had a previous relapse, 19% had a partial response, and 28% had no response. Baseline telaprevir-resistant variants were uncommon (in 12 patients with T54S, 4 with R155K, and 2 with V36M).

### EFFICACY

Changes in $\log_{10}$ HCV RNA levels during treatment are shown in Figure 2. The proportion of patients who had a sustained virologic response was significantly higher in the two telaprevir groups than in the control group for patients who had a previous relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group, and 24% in the control group) and for those who did not have a previous virologic response (41%, 41%, and 9%, respectively), including those who had a partial response (59%, 54%, and 15%, respectively) and those who had no response (29%, 33%, and 5%, respectively) (P<0.001 for all comparisons) (Table 2). Rates of sustained virologic response were similar in the T12PR48 group and the lead-in T12PR48 group for patients who had a relapse or no response or a partial response to previous therapy. The rate of sustained virologic response was also significantly higher for the pooled subgroup of patients who had either a relapse or a partial response in the telaprevir groups than in the control group (78% vs. 21%, P<0.001).

Overall, the rates of sustained virologic response were 64% in the T12PR48 group, 66% in the lead-in T12PR48 group, and 17% in the control group. The differences in the rates of sustained virologic response were 47 percentage points between the T12PR48 group and the control group (95% confidence interval [CI], 37 to 57; P<0.001) and 50 percentage points between lead-in T12PR48 group and the control group (95% CI, 40 to 60; P<0.001).

Subgroup analyses according to the stage of liver fibrosis (Table 2) or baseline viral load (Table 1 in the Supplementary Appendix) showed higher rates of sustained virologic response among patients receiving telaprevir than among those receiving peginterferon plus ribavirin alone.

Relapse rates were lower in the two telaprevir groups than in the control group among patients who had a previous relapse or no response or a partial response to previous therapy (Table 2).

Among patients who had a relapse, virologic failure during treatment was observed in 3 patients (1%) in the two telaprevir groups and in 18 patients (26%) in the control group. Among patients who had a previous partial response to therapy, virologic failure was observed in 9 patients (18%) in the T12PR48 group, 9 (19%) in the lead-in T12PR48 group, and 19 (70%) in the control group. For patients who had no previous response to therapy, virologic failure was observed in 41 patients (57%) in the T12PR48 group, 35 (47%) in the lead-in T12PR48 group, and 31 (84%) in the control group during the overall treatment phase (Table 2).

Among all virologic failures and relapses, 73% were associated with the emergence of variants with a reduced sensitivity to telaprevir. There were no differences in the number or type of emerging viral variants between the two telaprevir groups. Resistant variants were consistent with those that have been reported previously.[6] In 60 of 104 patients (58%) with variants that had a reduced sensitivity to telaprevir (primarily in those with

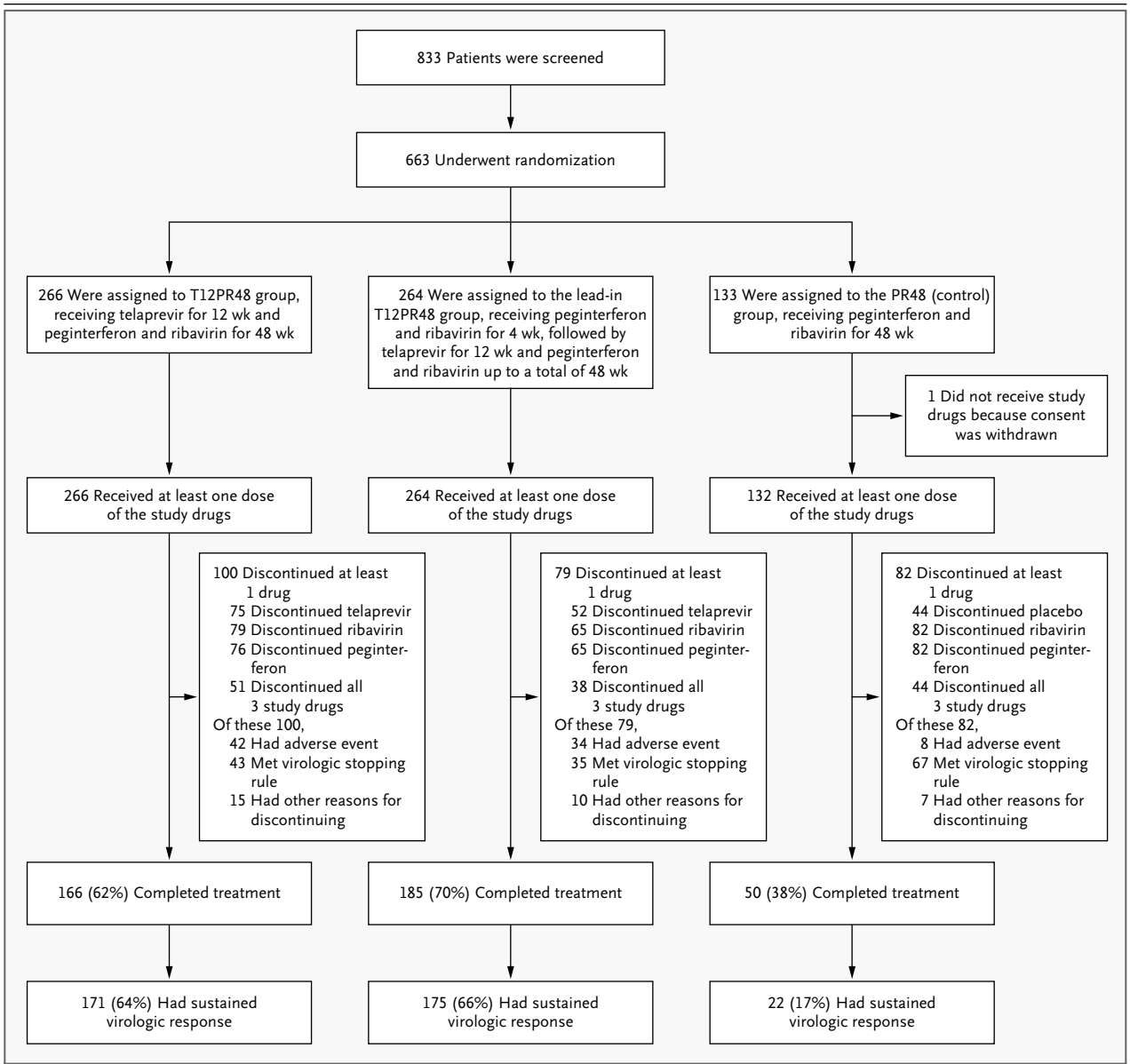



**Figure 1. Enrollment and Outcomes.**

Patients who completed all three study drugs were classified as having completed treatment.

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | T12PR48 (N=266) | Lead-in T12PR48 (N=264) | PR48 (Control) (N=132) |
|---|---|---|---|
| Age in years — mean (range) | 51 (23–69) | 51 (24–70) | 50 (21–69) |
| Body-mass index† | 28±5.0 | 27±4.8 | 27±4.6 |
| Male sex — no. (%) | 183 (69) | 189 (72) | 88 (67) |
| Race or ethnic group — no. (%)‡ | | | |
| White | 246 (92) | 252 (95) | 117 (89) |
| Black | 11 (4) | 8 (3) | 11 (8) |
| Asian or other | 9 (3) | 4 (2) | 4 (3) |
| Hispanic | 25 (9) | 27 (10) | 20 (15) |
| Alanine aminotransferase — IU/liter | 88±63 | 80±56 | 82±58 |
| Total bilirubin — μmol/liter | 12±6 | 12±5 | 12±5 |
| Serum albumin — g/liter | 41±3 | 42±3 | 42±3 |
| Platelet count — per mm³ | 217,000±67,000 | 219,000±74,000 | 221,000±71,000 |
| HCV genotype 1 subtype — no. (%)§ | | | |
| 1a | 118 (44) | 121 (46) | 59 (45) |
| 1b | 121 (45) | 115 (44) | 59 (45) |
| 1c | 0 | 0 | 1 (1) |
| Unknown | 27 (10) | 28 (11) | 13 (10) |
| HCV RNA $\log_{10}$ — IU/ml¶‖ | 6.6±0.03 | 6.6±0.04 | 6.6±0.05 |
| HCV RNA ≥800,000 IU/ml — no. (%)¶ | 238 (89) | 234 (89) | 114 (86) |
| Stage of fibrosis or cirrhosis — no. (%)** | | | |
| No or minimal fibrosis | 51 (19) | 68 (26) | 35 (27) |
| Portal fibrosis | 83 (31) | 71 (27) | 38 (29) |
| Bridging fibrosis | 60 (23) | 58 (22) | 29 (22) |
| Cirrhosis | 72 (27) | 67 (25) | 30 (23) |
| Previous type of response — no. (%) | | | |
| No response | 72 (27) | 75 (28) | 37 (28) |
| Partial response | 49 (18) | 48 (18) | 27 (20) |
| Relapse | 145 (55) | 141 (53) | 68 (52) |

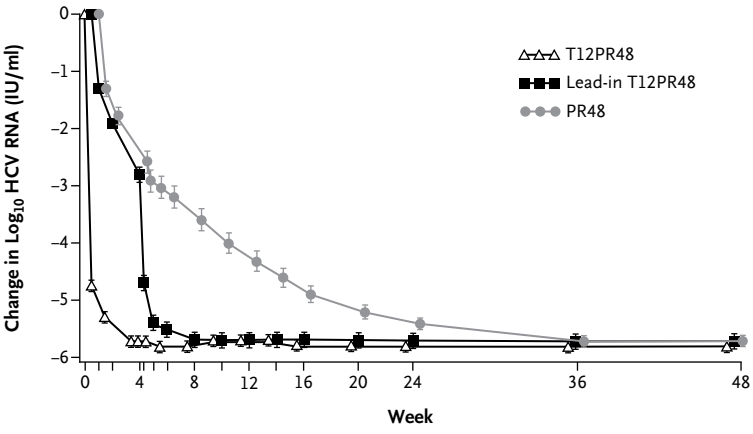
* Plus–minus values are means ±SD unless otherwise indicated. There were no significant differences among the study groups for any characteristic. Percentages may not total 100 because of rounding.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported. Patients of any race could also identify themselves as Hispanic.
§ The HCV genotype and subtype were determined with the use of the Trugene HCV genotyping assay (Siemens) except for one patient in the lead-in T12PR48 group, in whom the subtype was determined with the use of an NS3 assay.
¶ HCV RNA levels were measured with the use of the COBAS TaqMan HCV assay, version 2.0 (Roche).
‖ $\log_{10}$ values for HCV RNA are means ±SE.
** Patients were grouped into four categories of fibrosis, according to the following Metavir and Ishak fibrosis scores: minimal or no fibrosis (Metavir, F0–F1; Ishak, 0–2), portal fibrosis (Metavir, F2; Ishak, 3), bridging fibrosis (Metavir, F3; Ishak, 4), and cirrhosis (Metavir, F4; Ishak, 5–6).

virologic failure), resistant variants were no longer detected by population sequencing at the end of the study (median follow-up, 46.4 weeks).

### ADVERSE EVENTS

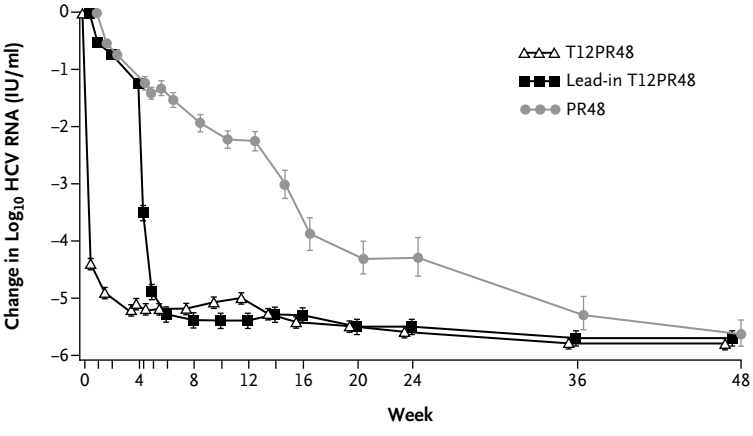
The most frequently reported adverse events (occurring in more than 25% of patients) in the two telaprevir groups were fatigue, pruritus, rash, nausea, influenza-like illness, anemia, and diarrhea (Table 2 in the Supplementary Appendix). Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) were reported more frequently in the two telaprevir groups than in the control group during the overall study period (with a rate of 37%

**A Previous Relapse**




| No. of Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| T12PR48 | 145 | 133 | 135 | 132 | 129 | 128 | 126 | 122 | 121 |
| Lead-in T12PR48 | 141 | 126 | 136 | 136 | 133 | 131 | 131 | 129 | 127 |
| PR48 | 68 | 61 | 64 | 63 | 62 | 61 | 59 | 44 | 41 |

**B No Response or Partial Response to Previous Therapy**




| No. of Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| T12PR48 | 121 | 112 | 114 | 108 | 96 | 92 | 87 | 71 | 67 |
| Lead-in T12PR48 | 123 | 114 | 120 | 118 | 112 | 101 | 97 | 80 | 72 |
| PR48 | 64 | 61 | 61 | 60 | 28 | 27 | 27 | 9 | 8 |

**Figure 2. Changes in HCV RNA Levels in Patients with a Previous Relapse or No Response or a Partial Response.**
Shown are changes in mean $\log_{10}$ HCV RNA levels over the 48-week study period in patients who had a previous relapse (Panel A) or no response or a partial response to previous therapy (Panel B). After the initiation of telaprevir (at baseline in the T12PR48 group and after 4 weeks in the lead-in T12PR48 group), reductions in levels of HCV RNA were greater in the two telaprevir groups than in the PR48 (control) group at all time points except during weeks 36 and 48 in patients with a previous relapse in the two telaprevir groups and during week 4 in the lead-in T12PR48 group. The I bars indicate standard errors.

vs. 22%). Serious adverse events and adverse events leading to permanent discontinuation of a study drug (mainly anemia in both cases) were also more frequent in the two telaprevir groups than in the control group. In the two telaprevir groups, the rate of serious adverse events was 12% and the rate of adverse events leading to permanent discontinuation of a study drug was 13%, as compared with rates of 5% and 3%, respectively, in the control group (Table 3).

In the two telaprevir groups, the rate of grade 3 rash was 3%, and the rate of grade 3 pruritus was 1%, as compared with no patients in the control group. Rash as an adverse event of special interest

(i.e., a grade 3 skin event, any skin event resulting in permanent discontinuation of any or all study drugs, or any skin event defined as a serious adverse event) occurred in 5% of patients in the two telaprevir groups, as compared with no patients in the control group. In the two telaprevir groups, 4% of patients discontinued telaprevir and 1% of patients discontinued all drugs because of rash. No patients discontinued treatment because of rash in the control group.

## DISCUSSION

Telaprevir in combination with peginterferon alfa-2a plus ribavirin significantly improved the rates of sustained virologic response for patients who had received previous therapy for HCV infection. As in previous trials,[4,5,7] the rates of sustained virologic response differed among patients who had a previous relapse, those who had no response to previous therapy, and those who had a partial response. In another study,[8] investigators found improved rates of sustained virologic response for patients who had a previous relapse or partial response after the addition of boceprevir, another HCV serine protease inhibitor, to peginterferon alfa-2b plus ribavirin. Unlike the study of boceprevir, our study also included patients who had no response to previous therapy (i.e., a reduction of <2 $\log_{10}$ in HCV RNA at week 12). In these patients, telaprevir combined with peginterferon plus ribavirin increased the rate of sustained vi-

**Table 2. Key Virologic End Points, According to Previous Treatment Response and Histologic Characteristics.***

| Subgroup and End Point | T12PR48 | Lead-in T12PR48 | PR48 (Control) |
|---|---|---|---|
| | | *no./total no. (%)* | |
| **Previous relapse** | | | |
| Undetectable viral load | | | |
| At 4 wk | 101/145 (70) | 4/141 (3) | 2/68 (3) |
| At 8 wk | 135/145 (93) | 126/141 (89) | 7/68 (10) |
| Sustained virologic response | | | |
| All patients | 121/145 (83)† | 124/141 (88)† | 16/68 (24) |
| Patients with undetectable viral load | | | |
| At 4 wk | 91/101 (90) | 4/4 (100) | 2/2 (100) |
| At 8 wk | 121/135 (90) | 116/126 (92) | 7/7 (100) |
| Patients with bridging fibrosis or cirrhosis‡ | 54/64 (84) | 47/55 (85) | 4/30 (13) |
| Relapse at 72 wk§ | 10/135 (7) | 9/138 (7) | 30/46 (65) |
| Virologic failure¶ | 2/145 (1) | 1/141 (1) | 18/68 (26) |
| **No response or partial response to previous therapy** | | | |
| Sustained virologic response | 50/121 (41)† | 51/123 (41)† | 6/64 (9) |
| **Previous partial response** | | | |
| Undetectable viral load | | | |
| At 4 wk | 32/49 (65) | 0 | 0 |
| At 8 wk | 40/49 (82) | 31/48 (65) | 0 |
| Sustained virologic response | | | |
| All patients | 29/49 (59)† | 26/48 (54)† | 4/27 (15) |
| Patients with undetectable viral load | | | |
| At 4 wk | 23/32 (72) | NA | NA |
| At 8 wk | 27/40 (68) | 18/31 (58) | NA |
| Patients with bridging fibrosis or cirrhosis‡ | 11/25 (44) | 10/25 (40) | 1/10 (10) |
| Relapse at 72 wk§ | 8/39 (21) | 9/36 (25) | 0 |
| Virologic failure¶ | 9/49 (18) | 9/48 (19) | 19/27 (70) |

**Table 2. (Continued.)**

| Subgroup and End Point | T12PR48 | Lead-in T12PR48 | PR48 (Control) |
|---|---|---|---|
| | | *no./total no. (%)* | |
| **No previous response** | | | |
| Undetectable viral load | | | |
| At 4 wk | 19/72 (26) | 0 | 1/37 (3) |
| At 8 wk | 34/72 (47) | 31/75 (41) | 1/37 (3) |
| Sustained virologic response | | | |
| All patients | 21/72 (29)† | 25/75 (33)† | 2/37 (5) |
| Patients with undetectable viral load | | | |
| At 4 wk | 10/19 (53) | NA | 1/1 (100) |
| At 8 wk | 20/34 (59) | 21/31 (68) | 1/1 (100) |
| Patients with bridging fibrosis or cirrhosis‡ | 12/43 (28) | 10/45 (22) | 1/19 (5) |
| Relapse at 72 wk§ | 8/30 (27) | 9/36 (25) | 3/5 (60) |
| Virologic failure¶ | 41/72 (57) | 35/75 (47) | 31/37 (84) |

* Data are for all patients who received at least one dose of a study drug. NA denotes not applicable because there were no patients in this group with undetectable HCV RNA at the corresponding earlier time point (at 4 or 8 weeks).
† P<0.001 for the comparison with the control group by means of logistic-regression analysis.
‡ Statistical models showed that there was no significant association between the baseline viral load and sustained virologic response. The stage of liver fibrosis was shown to have a significant effect on outcome, particularly among patients who had no response or a partial response to previous therapy.
§ Values are for patients who had undetectable HCV RNA at the end of the assigned treatment.
¶ A determination of virologic failure was based on either viral breakthrough or discontinuation of a study drug because of meeting a virologic stopping rule.

rologic response from 5% to a range of 29 to 33%. Even though this therapy increased the rate of sustained virologic response by nearly six times, further improvements are warranted.

Among patients who have had no response or a partial response to previous therapy, those with a high baseline viral load and advanced liver fibrosis have disease that is particularly difficult to cure.[9,10] In our study, more than 85% of patients had a high baseline viral load (i.e., above 800,000 IU per milliliter), 26% had liver cirrhosis, and 22% had bridging fibrosis. No specific safety and tolerability issues were associated with the use of telaprevir in patients with an advanced stage of liver fibrosis, and in such patients the rates of sustained virologic response were higher in the telaprevir groups than in the control group. Although the baseline viral load was not a significant prognostic factor for rates of sustained virologic response among patients receiving telaprevir, the presence of advanced fibrosis appeared to have a negative effect on the rates of sustained virologic response among patients who had no response or a partial response to previous therapy, although there was no such effect on those who had a previous relapse.

We investigated the role of a 4-week lead-in phase with peginterferon alfa-2a plus ribavirin before the addition of telaprevir. In a smaller study of boceprevir, it seemed that lowering of the viral load with pretreatment with peginterferon alfa-2b plus ribavirin may have reduced the emergence of protease-resistant variants, lowered the rate of virologic breakthrough during treatment, and improved the rate of sustained virologic response.[11] However, we did not observe any significant differences between the concurrent and delayed initiation of telaprevir with peginterferon plus ribavirin in the rates of sustained virologic response.

Overall, virologic failure rates during therapy were lower in patients who had a previous relapse or a partial response than in patients who had no response to previous therapy. Selection and persistence of drug-resistant variants is a common concern in the use of direct-acting antiviral agents.[12] As described previously[4,13,14] and implemented in the present study, strict application of stopping rules may help to avoid the selection and long-term

persistence of HCV variants with telaprevir resistance. Furthermore, in 58% of patients who had variants with reduced sensitivity to telaprevir, such variants were no longer detectable by population sequencing at the end of the study.

The safety profile of telaprevir with peginterferon plus ribavirin was consistent across all phase 2 and phase 3 trials, which included more than 2800 patients.[4,5,13-17] The addition of telaprevir to peginterferon plus ribavirin was particularly associated with increased rates of fatigue, gastrointestinal side effects, pruritus, and rash[4,13,14] and was associated with an increase of 8 to 12 percentage points in discontinuation rates, as compared with placebo. Among patients receiving telaprevir, 4% discontinued telaprevir and 1% discontinued all study drugs because of rash. Although combining telaprevir with peginterferon plus ribavirin also increased the anemia rate, the rate of discontinuation of all study drugs because of anemia was low (1%), despite the prohibition of the use of erythropoietin-stimulating agents. A post hoc analysis showed that reductions in the dose of ribavirin in order to manage anemia were not associated with a decrease in rates of sustained virologic response (data not reported).

The presence of interleukin-28B genetic polymorphisms have been shown to be a key predictor of the response to peginterferon plus ribavirin in patients with HCV infection.[18,19] A potential limi-

**Table 3. Reasons for Discontinuation of Telaprevir or Placebo and the Incidence of the Most Common Serious Adverse Events.***

| Variable | T12PR48 (N=266) | Lead-in T12PR48 (N=264) | PR48 (Control) (N=132) |
|---|---|---|---|
| | | *no. (%)* | |
| **Reason for discontinuation†** | | | |
| Any adverse event | 39 (15) | 29 (11) | 4 (3) |
| Rash‡ | 12 (5) | 10 (4) | 0 |
| Anemia‡ | 6 (2) | 9 (3) | 0 |
| Pruritus‡ | 1 (<1) | 3 (1) | 0 |
| **Serious adverse event** | | | |
| Any | 33 (12) | 32 (12) | 7 (5) |
| Blood or lymphatic system disorder | | | |
| Any | 8 (3) | 7 (3) | 1 (1) |
| Anemia | 6 (2) | 7 (3) | 1 (1) |
| Infection | 6 (2) | 9 (3) | 2 (2) |
| Bronchitis | 2 (1) | 0 | 0 |
| Sepsis | 0 | 2 (1) | 0 |
| Skin or subcutaneous-tissue disorder | | | |
| Any | 3 (1) | 5 (2) | 0 |
| Toxic skin eruption | 0 | 2 (1) | 0 |
| Cardiac disorder | | | |
| Any | 5 (2) | 2 (1) | 1 (1) |
| Acute myocardial infarction | 3 (1) | 0 | 0 |
| Atrial fibrillation | 0 | 2 (1) | 1 (1) |
| Gastrointestinal disorder | 4 (2) | 3 (1) | 2 (2) |
| Neoplasm (benign, malignant, or unspecified, including cysts and polyps) | | | |
| Any | 3 (1) | 4 (2) | 0 |
| Gastric cancer | 0 | 2 (1) | 0 |
| Hepatic malignant neoplasm | 2 (1) | 0 | 0 |

**Table 3. (Continued.)**

| Variable | T12PR48 (N=266) | Lead-in T12PR48 (N=264) | PR48 (Control) (N=132) |
|---|---|---|---|
| | | *no. (%)* | |
| Injury, poisoning, or procedural complication | 1 (<1) | 3 (1) | 0 |
| Nervous system disorder | 1 (<1) | 3 (1) | 2 (2) |
| General disorder or injection-site condition | 1 (<1) | 2 (1) | 0 |
| Psychiatric disorder | 0 | 3 (1) | 0 |
| Renal or urinary disorder | 3 (1) | 0 | 0 |
| Corticotropin insufficiency | 1 (<1) | 0 | 0 |
| Metabolic or nutritional disorder | 3 (1) | 0 | 0 |
| **Decrease in laboratory value** | | | |
| Hemoglobin | | | |
| To 8.5 to ≤10 g/dl | 71 (27) | 73 (28) | 20 (15) |
| To <8.5 g/dl | 28 (11) | 36 (14) | 7 (5) |
| Neutrophil count | | | |
| Grade 3 | 54 (20) | 49 (19) | 18 (14) |
| Grade 4 | 8 (3) | 11 (4) | 6 (5) |

* Listed are serious adverse events that occurred in at least two patients in a study group.
† These discontinuations all occurred during the phase of the study in which telaprevir or placebo was being administered. Of the patients who discontinued telaprevir, 22 in the T12PR48 group and 18 in the lead-in T12PR48 group continued treatment with peginterferon plus ribavirin. (Details regarding discontinuations of peginterferon, ribavirin, and all study drugs together are available in Table 3 in the Supplementary Appendix.)
‡ Included in this category are all related events that were described with a variety of descriptive terms.

tation of our study was that patients were not randomly assigned according to this marker, since it had not been discovered at the time of enrollment. However, consent for genetic testing was collected from a sizable proportion of patients. Since consent for genetic testing requires the deidentification of samples and analysis by an independent group, results for interleukin-28B testing are not part of our study.

In conclusion, the addition of telaprevir to peginterferon alfa-2a plus ribavirin significantly increased the rates of sustained virologic response for patients who are chronically infected with HCV genotype 1 and in whom peginterferon plus ribavirin had failed to achieve viral eradication, including those with a high viral load, severe liver fibrosis, and cirrhosis. The safety profile of telaprevir was consistent with the findings in previous trials.

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## APPENDIX

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