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ORIGINAL ARTICLE

Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection

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ABSTRACT

BACKGROUND

In patients with chronic infection with hepatitis C virus (HCV) genotype 1, treatment with peginterferon alfa and ribavirin for 48 weeks results in rates of sustained virologic response of 40 to 50%. Telaprevir is a specific inhibitor of the HCV serine protease and could be of value in HCV treatment.

METHODS

A total of 334 patients who had chronic infection with HCV genotype 1 and had not been treated previously were randomly assigned to receive one of four treatments involving various combinations of telaprevir (1250 mg on day 1, then 750 mg every 8 hours), peginterferon alfa-2a (180 μg weekly), and ribavirin (dose according to body weight). The T12PR24 group (81 patients) received telaprevir, peginterferon alfa-2a, and ribavirin for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 more weeks. The T12PR12 group (82 patients) received telaprevir, peginterferon alfa-2a, and ribavirin for 12 weeks. The T12P12 group (78 patients) received telaprevir and peginterferon alfa-2a without ribavirin for 12 weeks. The PR48 (control) group (82 patients) received peginterferon alfa-2a and ribavirin for 48 weeks. The primary end point, a sustained virologic response (an undetectable HCV RNA level 24 weeks after the end of therapy), was compared between the control group and the combined T12P12 and T12PR12 groups.

RESULTS

The rate of sustained virologic response for the T12PR12 and T12P12 groups combined was 48% (77 of 160 patients), as compared with 46% (38 of 82) in the PR48 (control) group (P=0.89). The rate was 60% (49 of 82 patients) in the T12PR12 group (P=0.12 for the comparison with the PR48 group), as compared with 36% (28 of 78 patients) in the T12P12 group (P=0.003; P=0.20 for the comparison with the PR48 group). The rate was significantly higher in the T12PR24 group (69% [56 of 81 patients]) than in the PR48 group (P=0.004). The adverse events with increased frequency in the telaprevir-based groups were pruritus, rash, and anemia.

CONCLUSIONS

In this phase 2 study of patients infected with HCV genotype 1 who had not been treated previously, one of the three telaprevir groups had a significantly higher rate of sustained virologic response than that with standard therapy. Response rates were lowest with the regimen that did not include ribavirin. (ClinicalTrials.gov number, NCT00372385.)

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*Members of the Protease Inhibition for Viral Evaluation 2 (PROVE2) study team are listed in the Appendix.

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Hepatitis C virus (HCV) is the most common infectious cause of chronic liver disease in Europe and the United States. Chronic hepatitis C may result in life-threatening complications, including cirrhosis and hepatocellular carcinoma. Antiviral therapy may result in a sustained virologic response, characterized by an undetectable HCV RNA level 24 weeks after the end of therapy, which correlates with a long-term clinical benefit. In patients infected with HCV genotype 1, the most common genotype worldwide, the standard combination of peginterferon alfa and ribavirin for 48 weeks results in rates of sustained virologic response of only 40 to 50%.[1-3]

A number of new therapeutic approaches are being assessed.[4] The nonstructural 3/4A (NS3/4A) serine protease processes the HCV polyprotein to generate mature viral proteins. Direct protease inhibition emerged as a promising target for therapy when a reduction in viral replication of several $\log_{10}$ units was shown after 2 days of administration of an NS3/4A protease inhibitor.[5]

Telaprevir is a reversible, selective, orally bioavailable inhibitor of the HCV NS3/4A serine protease.[6] Telaprevir monotherapy for 14 days induced a median decline of more than 4.4 $\log_{10}$ units in the plasma HCV RNA level in patients with chronic HCV genotype 1 infection.[7] In an early study, all 12 patients with HCV genotype 1 who were receiving telaprevir with peginterferon and ribavirin for 28 days had undetectable HCV RNA levels at the end of the therapy with these three study drugs.[8]

The Protease Inhibition for Viral Evaluation 2 (PROVE2) trial was a multicenter, randomized, partially double-blind, placebo-controlled phase 2b trial conducted in Europe to assess the efficacy and adverse event profile of various regimens combining telaprevir with peginterferon alfa-2a, with or without ribavirin, as compared with peginterferon alfa-2a and ribavirin alone, in patients infected with HCV genotype 1 who had not been treated previously.

METHODS

PATIENTS

Patients were enrolled at 28 centers in France, Germany, the United Kingdom, and Austria between August 2, 2006, and January 17, 2007. Eligibility criteria included no previous treatment for HCV infection, an age of 18 to 65 years, chronic HCV genotype 1 infection with detectable plasma HCV RNA levels, and no histologic evidence of cirrhosis within 2 years before study day 1.

The protocol and informed-consent form were approved by appropriate ethics committees at all study centers, in accordance with national procedures. All patients provided written informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

STUDY DESIGN

This was a phase 2b, randomized, partially double-blind, placebo-controlled trial. Eligible patients were stratified on the basis of self-reported race or ethnic group (black or other) and baseline weight (>75 kg vs. ≤75 kg). Patients were randomly assigned to one of four treatment groups: the T12PR24 group, which received telaprevir (VX-950, Vertex Pharmaceuticals), peginterferon alfa-2a (Pegasys, Roche), and ribavirin (Copegus, Roche) for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 more weeks; the T12PR12 group, which received telaprevir, peginterferon alfa-2a, and ribavirin for 12 weeks; the T12P12 group, which received telaprevir and peginterferon alfa-2a, without ribavirin, for 12 weeks; and the PR48 (control) group, which received placebo, peginterferon alfa-2a, and ribavirin for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 36 more weeks. Randomization was performed through a central telephone-based system, in a 1:1:1:1 ratio (with randomization blocks of 4). In the PR48 group, as in clinical practice,[9] if there was a decline of 2 $\log_{10}$ units in the plasma HCV RNA level at week 12 and the HCV RNA level was undetectable at week 24, treatment was continued; if not, treatment was stopped, since the chance of clearing the infection was extremely low.[10,11]

Telaprevir was given as a single dose of 1250 mg on study day 1, followed by a dose of 750 mg every 8 hours; peginterferon alfa-2a was given subcutaneously at a dose of 180 μg per week; ribavirin was given orally at a dose of 1000 mg per day (for body weight <75 kg) or 1200 mg per day (for body weight ≥75 kg). Treatment of the PR48, T12PR12, and T12PR24 groups was double-blinded through week 10. Treatment of the T12P12 group was not blinded, because the absence of ribavirin would result in discernable hematologic effects. Patients in the T12PR24, T12PR12, and T12P12 groups were required to have undetectable HCV RNA lev-

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els at the last study visit before the planned end of treatment (i.e., at week 10 for the T12PR12 and T12P12 groups and at week 20 for the T12PR24 group). If patients had detectable HCV RNA levels at this visit, they were to continue to receive peginterferon alfa-2a and ribavirin through treatment week 48. Since the intention was to assess the efficacy of shorter treatment durations, these patients were considered to have treatment failure in the analysis of a sustained virologic response.

The study sponsor and the academic principal investigators were responsible for study design and protocol development. The manuscript was drafted by the principal academic authors with input from the publication committee (consisting of four academic authors). All authors had access to the data and assume responsibility for the accuracy and completeness of the data reported.

EFFICACY ASSESSMENTS

Plasma HCV RNA levels were measured with the use of the COBAS TaqMan HCV assay, version 1.0 (Roche Molecular Systems), with a lower limit of quantification of 30 IU per milliliter and a lower limit of detection of 10 IU per milliliter. HCV RNA assessments were performed at the screening visit, at days 1, 4, and 8, and at weeks 2, 3, 4, 6, 8, 10, and 12; additional assessments occurred at weeks 16, 20, and 24 in the T12PR24 and PR48 groups and at weeks 28, 36, and 48 in the PR48 group. All patients had a follow-up visit 2 weeks after completion of the study treatment. In patients in the three telaprevir-based groups who had completed all treatment (ending at week 12 or week 24), HCV RNA levels were also measured 1, 2, 4, 8, 12, 24, 36, and 48 weeks after completion of the study treatment.

Viral breakthrough during therapy was defined as an increase of more than 1 $\log_{10}$ IU per milliliter from the lowest HCV RNA level or as an HCV RNA level above 100 IU per milliliter in patients with previously undetectable HCV RNA. Relapse was defined as a detectable HCV RNA level during the 24-week post-treatment period in patients who had undetectable HCV RNA at the end of treatment.

SAFETY ASSESSMENTS

Safety assessments included physical examinations, recording of adverse events, and serum chemical and hematologic evaluations at all study visits, and electrocardiography at the start and end of the treatment period. The original protocol was amended in January 2007 to add specific evaluations for grade 3 or 4 rashes, including pharmacokinetic analysis and HLA typing of blood samples.

Stepwise temporary reductions or short interruptions of ribavirin or peginterferon alfa-2a therapy were permitted, to manage adverse events or laboratory abnormalities. Dose reduction or interruption of telaprevir was not allowed. The use of granulocyte colony-stimulating factor and erythropoietin was not allowed during the initial 12 weeks of study treatment.

STATISTICAL ANALYSIS

The main efficacy measure was the proportion of patients who had a sustained virologic response: an HCV RNA level that was undetectable (<10 IU per milliliter) 24 weeks after the completion of study treatment. The analysis included all patients who had undergone randomization and had received at least one dose of any study drug. The planned primary analysis was the comparison of the PR48 group with the T12PR12 group and the T12P12 group (which did not receive ribavirin) combined, and the planned secondary analysis was a comparison of each of the three telaprevir-based groups with the PR48 group. Assuming rates of sustained virologic response of 50% in the PR48 group and 70% in the combined T12PR12 and T12P12 groups, we calculated that with 80 patients who could be evaluated in the PR48 group and 160 who could be evaluated in the combined groups, the study would have a statistical power of at least 80% to show a significant difference.

Five planned interim analyses were conducted by the sponsor, Vertex Pharmaceuticals, to monitor safety and assess antiviral efficacy during the treatment period. Each interim analysis included descriptive analyses of safety data (adverse events and laboratory data) and HCV RNA results. There were no stopping rules or a priori plans for changes to the study conduct on the basis of interim analyses.

After the third interim analysis, it became apparent that the T12P12 group did not have a response during the treatment period that was similar to the response of the T12PR12 group, and the statistical-analysis plan was revised by the sponsor to remove the originally planned primary analysis. The original secondary analysis, a comparison of the sustained virologic response in each of the three telaprevir-based groups with the response in the PR48 group, became the primary analysis.

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Results of the fourth interim analysis (performed after all patients had reached the end of the treatment period and data on sustained virologic response were available for the T12PR24 group) and fifth interim analysis (conducted when the PR48 group was still undergoing follow-up but data on the post-treatment responses for the three telaprevir groups were available) were made available to the investigators and presented at scientific meetings. Because it is not clear how to adjust the interpretation of the analyses for these unplanned changes and multiple examinations of the data, the results are reported as originally planned.

Treatment assignments were unblinded at week 10 for all patients; therefore, there was no data and safety monitoring board. Safety of the patients was monitored by investigators and three study medical monitors, who reviewed all safety events, and by means of a review of adverse-event data during the interim analyses.

The comparisons between groups were performed with the use of Fisher's exact test. All reported P values are two-sided and have not been adjusted for multiple testing. A prespecified multivariate analysis to evaluate the possible relationship between a sustained virologic response and baseline variables (age, weight and body-mass index, and baseline HCV RNA level) was performed by means of a logistic-regression model with a sustained virologic response as the dependent variable. The following factors were added post hoc and were also explored in the model: sex, HCV genotype 1 subtype (1a vs. 1b), and alanine aminotransferase and fasting glucose levels at baseline. Variables that had a weak association (P>0.20) with a sustained virologic response in the initial logistic-regression model were excluded from the final model.

Figure 1 (facing page). Enrollment and Follow-up among the Study Patients.

The reasons for the exclusion of the 54 patients were as follows: 29 did not meet the eligibility criteria (2 were not between 18 and 65 years of age, 2 had concurrent medical conditions, 6 had cirrhosis or another hepatic finding on biopsy, 8 had an HCV genotype other than 1, and 11 did not meet other criteria), 10 patients withdrew consent after starting the screening process, and 15 were excluded or the screening failed because of unknown reasons. Two patients underwent randomization twice (and were thus assigned two randomization numbers) in error. Of the 334 patients (332, in actuality) who underwent randomization, 11 (9, in actuality) did not receive any study drug: 5 patients withdrew consent between the time of randomization (5 to 7 days before the start of dosing) and day 1, 2 were withdrawn by the investigators (1 at the discretion of the investigator and 1 for noncompliance with study requirements), 1 was lost to follow-up, and 1 had cirrhosis but was randomized and then withdrawn. The protocol-defined stopping rule (stating that patients must have had a drop of 2 $\log_{10}$ units in the HCV RNA level, as compared with the baseline level, at week 12 of treatment and an undetectable HCV RNA level at week 24 of treatment to continue to receive the study drugs) was applicable only to the PR48 group.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of 388 patients screened, 334 were randomly assigned to a treatment group and 323 received study medication (Fig. 1). The characteristics of the treatment groups were similar at baseline (Table 1).

VIROLOGIC RESPONSES DURING THE TREATMENT PERIOD

Table 2 shows the proportion of patients with undetectable HCV RNA (<10 IU per milliliter) at weeks 4, 12, and 24 during the treatment period as well as 24 weeks after completion of planned treatment (the time of assessment for a sustained virologic response) in the four groups. The median time to an undetectable HCV RNA level was 113 days (range, 15 to 337) in the PR48 group, 28 days (range, 8 to 172) in the T12PR24 group, 22 days (range, 4 to 85) in the T12PR12 group, and 29 days (range, 4 to 86) in the T12P12 group. Figure 2 shows the mean change in HCV RNA levels during the first 12 weeks of treatment.

The proportions of patients who had undetectable HCV RNA levels at weeks 4 and 12 were significantly higher in all telaprevir-based groups than in the PR48 group. At week 4, levels were undetectable in 69% of patients in the T12PR24 group, 80% in the T12PR12 group, and 50% in the T12P12 group (vs. 13% in the PR48 group, P<0.001 for each comparison). At week 12, levels were undetectable in 73% of patients in the T12PR24 group (vs. 43% in the PR48 group, P<0.001), 80% in the T12PR12 group (P<0.001), and 62% in the T12P12 group (P=0.02). At the end of treatment — i.e., at week 24 in the T12PR24 group, week 12 in the T12PR12 and T12P12 groups, and week 48 in the PR48 group — the proportions of patients with undetectable HCV RNA levels were higher in both groups receiving

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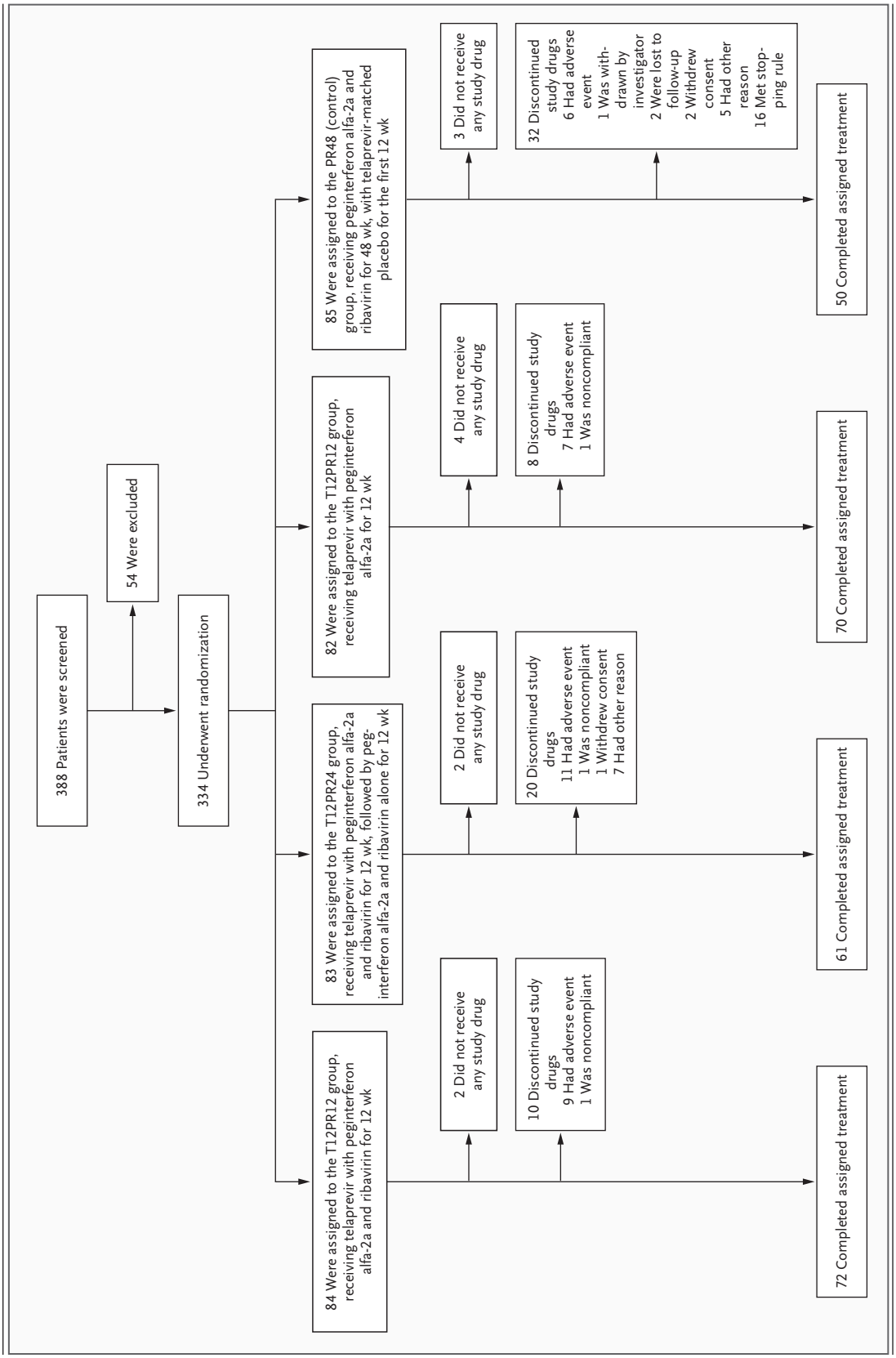

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Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (N=78)	PR48 (N=82)
Years of age — median (range)	46 (19–65)	44 (22–65)	45 (20–64)	45 (18–64)
BMI — median (range)†	24 (17–35)	23 (17–32)	24 (18–41)	24 (17–35)
Male sex — no. (%)	54 (67)	49 (60)	43 (55)	46 (56)
Race or ethnic group — no. (%)‡				
White	75 (93)	76 (93)	77 (99)	76 (93)
Black	1 (1)	2 (2)	1 (1)	2 (2)
Asian	3 (4)	2 (2)	0	4 (5)
Hispanic	1 (1)	1 (1)	0	0
Other	1 (1)	1 (1)	0	0
HCV RNA — $\log_{10}$ IU/ml	6.5±0.6	6.4±0.6	6.3±0.6	6.4±0.6
HCV RNA ≥800,000 IU/ml — no. (%)	73 (90)	67 (82)	63 (81)	68 (83)
Fibrosis on previous liver biopsy — no. (%)				
None or minimal	35 (43)	30 (37)	31 (40)	28 (34)
Portal	37 (46)	46 (56)	43 (55)	46 (56)
Bridging	9 (11)	6 (7)	3 (4)	8 (10)
Cirrhosis§	—	—	1 (1)	—
ALT, IU/ml — median (range)	56 (18–277)	50 (15–259)	58 (18–303)	55 (20–315)
HCV genotype 1 subtype — no. (%)¶				
1a	31 (38)	37 (45)	40 (51)	35 (43)
1b	50 (62)	45 (55)	38 (49)	45 (55)
Indeterminate	0	0	0	2 (2)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive one of four treatments involving various combinations of telaprevir (1250 mg on day 1, then 750 mg every 8 hours), peginterferon alfa-2a (180 μg weekly), and ribavirin (dose according to body weight). The T12PR24 group received telaprevir, peginterferon alfa-2a, and ribavirin for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 more weeks. The T12PR12 group received telaprevir, peginterferon alfa-2a, and ribavirin for 12 weeks. The T12P12 group received telaprevir and peginterferon alfa-2a without ribavirin for 12 weeks. The PR48 (control) group received peginterferon alfa-2a and ribavirin for 48 weeks. There were no significant differences between the control group and any of the three telaprevir-based groups. ALT denotes alanine aminotransferase, and HCV hepatitis C virus.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Race or ethnic group was self-reported. Percentages do not total 100 because of rounding.

§ Patients with cirrhosis on previous biopsy were excluded from the study; however, one such patient was enrolled in error by a site investigator.

¶ HCV genotype and subtype were determined through sequence analysis of the coding region of the nonstructural 3 protease, performed as part of resistance studies.

all three study drugs (70% in the T12PR24 group and 80% in the T12PR12 group) and in the T12P12 group (62%) than in the PR48 group (55%).

SUSTAINED VIROLOGIC RESPONSE

A sustained virologic response, defined as an undetectable HCV RNA 24 weeks after completion of therapy, was the primary end point. In the three telaprevir-based groups, 19 patients (14 in the T12P12 group) had detectable HCV RNA at the last study visit before the planned end of treatment and were therefore assigned to complete a total of 48 weeks of peginterferon alfa-2a and ribavirin, according to the protocol. Seven patients (all in the T12P12 group) completed this treatment; three of the seven had a sustained virologic response but were counted as having treatment failure in the analysis of the rate of sustained virologic response.

The rate of sustained virologic response for the PR48 group was 46% (38 of 82 patients). According to the originally planned primary analysis, the rate of sustained virologic response for the combined T12P12 and T12PR12 groups was 48% (77 of 160, P=0.89 for the comparison with the PR48 group).

In the T12PR24 group, a sustained virologic

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Table 2. Undetectable HCV RNA Levels during and after Treatment, According to Treatment Group.*

Week	Undetectable Viral RNA								
	T12PR24 (N=81)	P Value, vs. PR48	T12PR12 (N=82)	P Value, vs. PR48	T12P12 (N=78)	P Value, vs. PR48	T12PR12 and T12P12 (N=160)	P Value, vs. PR48	PR48 (N=82)
Treatment week — no. (%)									
4	56 (69)	<0.001	66 (80)	<0.001	39 (50)	<0.001	105 (66)	<0.001	11 (13)
12	59 (73)	<0.001	66 (80)	<0.001	48 (62)	0.02	114 (71)	<0.001	35 (43)
24	57 (70)		NA		NA		NA		48 (59)
48	NA		NA		NA		NA		45 (55)
Follow-up week 24, when SVR was assessed†									
No. (%)	56 (69)	0.004	49 (60)	0.12	28 (36)	0.20	77 (48)	0.89	38 (46)
95% CI‡	58–79		48–70		25–47		40–56		36–58

* An undetectable level was defined as less than 10 IU per milliliter, according to the COBAS TaqMan assay (Roche Molecular Systems). NA denotes not applicable. The PR48 group was the control group.

† The rates of sustained virologic response (SVR) differed significantly between the T12PR12 group and the T12P12 group (P = 0.003).

‡ The 95% confidence intervals for the difference between the PR48 group and the telaprevir-based groups are as follows: T12PR24, 0.08 to 0.38; T12PR12, –0.02 to 0.29; T12P12, –0.26 to 0.049; and T12PR12 and T12P12 combined, –0.12 to 0.15.

response was achieved in 47 of the 61 patients who completed the assigned treatment and in 9 of the 20 patients who discontinued the study treatment before week 24, for an overall rate of 69% (56 of 81 patients), which was significantly higher than that in the PR48 group (P=0.004). The rate of sustained virologic response was not significantly higher in the T12PR12 group or the T12P12 group than in the PR48 group. In the T12PR12 group, there was a sustained virologic response in 46 of the 72 patients who completed treatment and in 3 of the 10 who discontinued treatment, for an overall rate of 60% (49 of 82 patients, P=0.12 for the comparison with the PR48 group). In the group not receiving ribavirin (the T12P12 group), a sustained virologic response was achieved in 24 of the 70 patients who completed treatment and in 4 of the 8 who discontinued treatment, for an overall rate of 36% (28 of 78 patients, P=0.20 for the comparison with the PR48 group). The difference between the rates in the T12PR12 group and the T12P12 group was significant (P=0.003).

VIRAL BREAKTHROUGH AND RELAPSE

By week 12, a viral breakthrough had been observed in 1 of 82 patients (1%) in the PR48 group, 19 of 78 (24%) in the T12P12 group, 1 of 82 (1%) in the T12PR12 group, and 4 of 81 (5%) in the T12PR24 group. Additional viral breakthroughs occurred in 1 of the 81 patients in the T12PR24 group, after the completion of telaprevir, and in 3 of the 82 patients in the PR48 group between weeks 12 and 48.

Relapse (defined as a detectable HCV RNA level during the 24-week post-treatment period in patients who had undetectable HCV RNA at the end of the treatment period) occurred in 8 of 57 patients (14%) in the T12PR24 group, 19 of 63 (30%) in the T12PR12 group, 22 of 46 (48%) in the T12P12 group, and 10 of 45 (22%) in the PR48 group. In the T12PR24 group, the relapse rate among those who had undetectable HCV RNA at weeks 4 and 12 was 7% (3 of 45 patients).

In the T12PR24, T12PR12, and T12P12 groups, of the 133 patients with a sustained virologic response, 118 returned for follow-up visits through 48 weeks after the completion of treatment. Two of the 133 patients had a late relapse: 1 in the T12PR24 group had discontinued treatment on day 65 and had an HCV RNA level that became detectable 48 weeks after the end of treatment; the other, in the T12P12 group, had discontinued treatment on day 60 and had a detectable HCV RNA level 36 weeks after the end of treatment. In both patients, viral sequence analysis confirmed the recurrence of the original infection.

Analysis of the full-length NS3 protease sequence was carried out in patients with a breakthrough and in those who had a relapse after completion of telaprevir therapy. HCV virus that had low-level resistance to telaprevir was found at baseline in 1% of patients. Among the 22 patients

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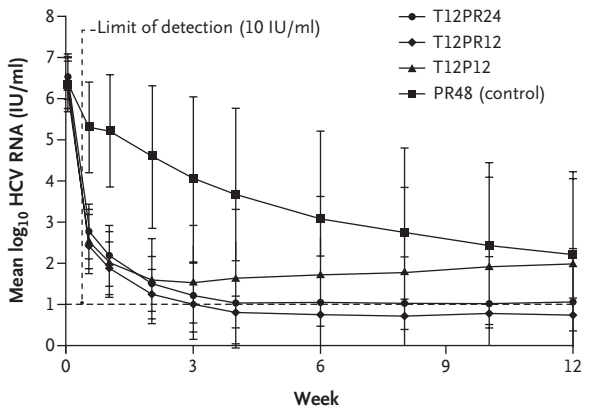

No. of Patients										
T12PR24	81	74	80	77	76	74	73	70	68	67
T12PR12	82	79	81	80	80	80	79	78	75	72
T12P12	78	72	78	74	74	73	73	72	70	70
PR48 (control)	82	78	80	80	79	79	78	77	77	77

Figure 2. Mean Log_{10} HCV RNA Levels during the First 12 Weeks of Treatment, According to Treatment Group.

If HCV RNA values were detectable but not quantifiable (<30 IU per milliliter), for purposes of calculation, the value was considered as 20 IU per milliliter; if the value was undetectable (<10 IU per milliliter), the value was considered as 5 IU per milliliter. Data are shown for 81 patients in the T12PR24 group, 82 in the T12PR12 group, 78 in the T12P12 group, and 82 in the PR48 (control) group.

who had a viral breakthrough during the 12 weeks of telaprevir administration and had a viral RNA level above the limit of detection of the sequencing assay, wild-type virus was found in 1 (5%), variants with low-level resistance in 9 (41%), and variants with high-level resistance in 12 (55%) (Table 3). Among the 42 patients who had a relapse after completion of treatment with telaprevir and had a viral RNA level above the limit of detection of the sequencing assay, wild-type virus was found in 2 (5%), low-level resistant variants in 33 (79%) and high-level resistant variants in 7 (17%). In some patients who did not receive ribavirin, complex changes in sequence were seen during the study.

INDEPENDENT PREDICTORS OF SUSTAINED VIROLOGIC RESPONSE

The association between a sustained virologic response and independent variables was explored with the use of a logistic-regression model. Treatment group and baseline HCV RNA level were the only two variables significantly associated with a sustained virologic response ($P<0.001$) (Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

SAFETY

Table 4 lists the principal adverse events reported in each group. Pruritus and rash were more frequent in the telaprevir groups than in the control group. Pruritus occurred in 51% of patients (41 of 81) in the T12PR24 group, 63% (52 of 82) in the T12PR12 group, and 59% (46 of 78) in the T12P12 group, as compared with 35% (29 of 82) in the PR48 group. The incidence of rash was 49% (40 of 81 patients) in the T12PR24 group, 44% (36 of 82) in the T12PR12 group, and 47% (37 of 78) in the T12P12 group, as compared with 35% (29 of 82) in the PR48 group. The rashes in patients in the telaprevir-based groups were generally maculopapular and were clinically similar to those observed in drug reactions. The median time to the appearance of a rash of any severity in the telaprevir-based groups was 9 to 12 days. Severe (grade 3) rash was found in 7% of patients (6 of 81) in the T12PR24 group, 6% (5 of 82) in the T12PR12 group, and 3% (2 of 78) in the T12P12 group, but was not seen in the PR48 group (Table 4). There were no grade 4 rashes reported. Twelve of the 163 patients (7%) in the combined T12PR24 and T12PR12 groups discontinued treatment because of rash.

Telaprevir administration also affected hemoglobin levels during the treatment period. During the first 12 weeks of treatment, the median decrease in the baseline hemoglobin level was 3.0 g per deciliter in the PR48 group, 3.1 g per deciliter in the T12P12 group, and 3.6 and 3.9 g per deciliter in the T12PR24 and T12PR12 groups, respectively.

Other adverse events were similar in type and frequency in the telaprevir-based groups and the control group. Twenty-eight of the 241 patients (12%) in the telaprevir-based groups discontinued the study treatment because of adverse events, including 18 patients who did so before week 12 (i.e., during the period of telaprevir administration), as compared with 6 of 82 patients (7%) in the control group.

DISCUSSION

In this phase 2 study of patients infected with HCV genotype 1 who had not been treated previously, one of the three telaprevir-containing regimens tested — treatment with telaprevir for 12 weeks and peginterferon alfa-2a and ribavirin for 24 weeks (T12PR24) — resulted in a significantly higher rate, by approximately 20 percentage points, of sustained virologic response than was found

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Table 3. Incidence of Amino Acid Substitutions in Patients Who Had Viral Breakthrough or Relapse.*

Viral Activity	Total No.	No. with Viral Level below LOD	No. with Wild-Type Variant	Low-Level Resistance					High-Level Resistance	
				V36A/M	T54A	R155K/T	A156S	Various†	V36M and R155K	A156T
				number of patients						
T12PR24										
Breakthrough	4								3	1
Relapse	8		1	2	1		1		3	
T12PR12										
Breakthrough	1		1							
Relapse	19	3	1	2	4	3	3	1	2	
T12P12										
Breakthrough	19	2			1	4	1	3	6	2
Relapse	22	4		2	4	6	2	2	2	

* Breakthrough was defined as viral breakthrough during the 12 weeks of telaprevir administration. Relapse was defined as a detectable HCV RNA level during the 24-week post-treatment period in patients who had undetectable HCV RNA at the time of completion of the assigned treatment. The limit of detection (LOD) was an HCV RNA level of 1000 IU per milliliter, as measured with the use of the nonstructural 3 serine protease sequencing assay.

† The specific combinations of substitutions were V36V/M and R155R/K for the one patient in the T12PR12 group who had a relapse; V36V/A and A156S/T in one patient, T54T/A and A156A/S in the second, and T54T/A, R155R/K, and A156A/S/T in the third who had a breakthrough in the T12P12 group; and V36V/M, R155R/K, and V36V/A in one patient and V36V/A and T54T/A in the other who had a relapse in the T12P12 group.

with the standard therapy of 48 weeks of peginterferon alfa-2a and ribavirin (PR48). These data, together with those from a similar phase 2 study performed in the United States (PROVE1, described elsewhere in this issue of the *Journal*),[12] support the performance of a larger, phase 3 trial of telaprevir in combination with peginterferon alfa-2a and ribavirin.

However, several questions remain unanswered. Patients with cirrhosis were not evaluated. Durations of triple-combination therapies with peginterferon alfa, ribavirin, and telaprevir that differ from the durations tested in PROVE2 will require further investigation, as will the criteria for extension of peginterferon alfa and ribavirin therapy. Further investigation will shed light on the usefulness of tailoring therapy on the basis of the kinetics of the early viral response.

Our results show the necessity of administering ribavirin in combination with peginterferon alfa and telaprevir. Ribavirin will most likely be required in combination with the use of other specific HCV inhibitors and peginterferon alfa to achieve the high rates of sustained virologic response seen in our study. Among patients receiving telaprevir-based regimens, the addition of ribavirin increased the sustained virologic response rates by preventing relapse and the emergence of both low-level and high-level telaprevir resistance. In spite of its moderate, transient antiviral effect on HCV replication when administered as monotherapy,[13] ribavirin has been shown to prevent viral breakthrough during, and relapse after, the treatment period by significantly accelerating the second slope of viral-RNA decrease in patients who have a response to the antiviral effect of peginterferon alfa.[14] The modes of action of ribavirin remain under debate.[15-19] Our study results are consistent with the notion that ribavirin does not act by directly inhibiting HCV replication, since it cannot be replaced by a potent HCV inhibitor in combination with peginterferon alfa-2a.

Both rash and pruritus were frequently reported in this study, but they did not always occur in combination. Severe rash occurred in approximately 5% of patients treated with telaprevir. Both rash and pruritus regressed after withdrawal of telaprevir and administration of appropriate therapy, including topical treatments for symptoms and corticosteroids (in some cases, systemic corticosteroids). Patients receiving telaprevir should be clinically monitored for dermatologic reactions and treated appropriately. The optimal management of rash and its effect on treatment adherence

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Table 4. Incidence of Adverse Events and Severe (Grade 3) Adverse Events between Baseline and Week 48, According to Treatment Group.*

System Organ Class or Preferred Term	Adverse Events				Severe Adverse Events			
	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (N=78)	PR48 (N=82)	T12PR24 (N=81)	T12PR12 (N=82)	T12P12 (N=78)	PR48 (N=82)
	number of patients (percent)							
Any	80 (99)	82 (100)	78 (100)	81 (99)	13 (16)	17 (21)	10 (13)	13 (16)
General disorder or administration-site condition	72 (89)	75 (91)	65 (83)	73 (89)	1 (1)	4 (5)	2 (3)	2 (2)
Asthenia	**37 (46)**	**43 (52)**	**30 (38)**	**26 (32)**	**1 (1)**	**3 (4)**	**1 (1)**	**1 (1)**
Influenza-like illness	32 (40)	32 (39)	28 (36)	43 (52)	0	0	0	0
Fatigue	21 (26)	23 (28)	26 (33)	30 (37)	0	1 (1)	0	0
Pyrexia	14 (17)	15 (18)	15 (19)	19 (23)	0	1 (1)	0	0
Skin or subcutaneous-tissue disorder	74 (91)	78 (95)	68 (87)	60 (73)	7 (9)	7 (9)	2 (3)	0
Pruritus	**41 (51)**	**52 (63)**	**46 (59)**	**29 (35)**	**2 (2)**	**1 (1)**	**1 (1)**	**0**
Dry skin	21 (26)	21 (26)	22 (28)	29 (35)	0	0	0	0
Any rash	**40 (49)**	**36 (44)**	**37 (47)**	**29 (35)**	**6 (7)**	**5 (6)**	**2 (3)**	**0**
Alopecia	15 (19)	3 (4)	11 (14)	17 (21)	0	0	0	0
Gastrointestinal disorder	62 (77)	68 (83)	56 (72)	69 (84)	2 (2)	1 (1)	1 (1)	0
Nausea	39 (48)	39 (48)	24 (31)	33 (40)	1 (1)	0	0	0
Diarrhea	20 (25)	26 (32)	20 (26)	23 (28)	0	0	0	0
Nervous system disorder	48 (59)	49 (60)	43 (55)	45 (55)	1 (1)	2 (2)	1 (1)	1 (1)
Headache	36 (44)	32 (39)	37 (47)	37 (45)	0	0	0	0
Psychiatric disorder	44 (54)	45 (55)	35 (45)	49 (60)	0	2 (2)	3 (4)	1 (1)
Insomnia	23 (28)	28 (34)	11 (14)	32 (39)	0	0	1 (1)	0
Depression	16 (20)	18 (22)	17 (22)	19 (23)	0	2 (2)	2 (3)	0
Respiratory, thoracic and mediastinal disorder	39 (48)	44 (54)	27 (35)	39 (48)	3 (4)	0	0	0
Dyspnea	18 (22)	21 (26)	11 (14)	13 (16)	1 (1)	0	0	0
Cough	15 (19)	14 (17)	8 (10)	21 (26)	0	0	0	0
Musculoskeletal or connective-tissue disorder	27 (33)	28 (34)	38 (49)	44 (54)	0	0	1 (1)	1 (1)
Myalgia	11 (14)	12 (15)	12 (15)	17 (21)	0	0	0	0
Arthralgia	8 (10)	8 (10)	20 (26)	14 (17)	0	0	0	1 (1)
Blood or lymphatic system disorder	25 (31)	23 (28)	15 (19)	26 (32)	3 (4)	5 (6)	3 (4)	7 (9)
Anemia†	22 (27)	15 (18)	7 (9)	14 (17)	3 (4)	3 (4)	1 (1)	2 (2)
Metabolic or nutritional disorder	10 (12)	16 (20)	20 (26)	20 (24)	0	0	0	0
Decreased appetite	5 (6)	9 (11)	16 (21)	16 (20)	0	0	0	0

* The adverse events listed occurred in 20% or more of patients in any group, such that the number for the total system organ class may exceed the sum of the numbers for the preferred terms. The severe adverse events listed were all grade 3. The system organ classes and preferred terms are from the *Medical Dictionary for Regulatory Activities*, version 10. Bold text indicates an adverse event or serious adverse event for which the incidence in any telaprevir-based group was at least 10 percentage points higher than the incidence in the control group. Four adverse events (in three patients) were reported as grade 4 by site investigators: a life-threatening car accident and subsequent splenectomy in one patient, paranoia in another, and anemia in the third. The PR48 group was the control group.

† Anemia, with regard to adverse events as listed here, was reported by the site investigators, with no requirement for a specific value or change in the hemoglobin level.

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and efficacy requires further investigation. Decreased hemoglobin levels were also more frequent among the patients receiving telaprevir than among those in the control group, though the condition was not often a cause of treatment discontinuation.

In conclusion, although a significant improvement in sustained virologic response was not shown in association with two of the telaprevir regimens tested, 12 weeks of telaprevir combined with 24 weeks of peginterferon alfa-2a and ribavirin resulted in significantly higher rates of sustained virologic response than 48 weeks of peginterferon and ribavirin alone. This study therefore suggests that the use of telaprevir may improve the rate of sustained virologic response in patients with a chronic HCV genotype 1 infection. A drug-induced rash necessitated that telaprevir be discontinued in some patients. Larger and longer studies are required to assess the efficacy and safety of telaprevir for HCV infection.

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APPENDIX

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