ORIGINAL ARTICLE

Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection

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ABSTRACT

BACKGROUND

Patients with chronic infection with hepatitis C virus (HCV) genotype 1 often need 48 weeks of peginterferon–ribavirin treatment for a sustained virologic response. We designed a noninferiority trial (noninferiority margin, –10.5%) to compare rates of sustained virologic response among patients receiving two treatment durations.

METHODS

We enrolled patients with chronic infection with HCV genotype 1 who had not previously received treatment. All patients received telaprevir at a dose of 750 mg every 8 hours, peginterferon alfa-2a at a dose of 180 μg per week, and ribavirin at a dose of 1000 to 1200 mg per day, for 12 weeks (T12PR12), followed by peginterferon–ribavirin. Patients who had an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) were randomly assigned after week 20 to receive the dual therapy for 4 more weeks (T12PR24) or 28 more weeks (T12PR48). Patients without an extended rapid virologic response were assigned to T12PR48.

RESULTS

Of the 540 patients, a total of 352 (65%) had an extended rapid virologic response. The overall rate of sustained virologic response was 72%. Among the 322 patients with an extended rapid virologic response who were randomly assigned to a study group, 149 (92%) in the T12PR24 group and 140 (88%) in the T12PR48 group had a sustained virologic response (absolute difference, 4 percentage points; 95% confidence interval, –2 to 11), establishing noninferiority. Adverse events included rash (in 37% of patients, severe in 5%) and anemia (in 39%, severe in 6%). Discontinuation of all the study drugs was based on adverse events in 18% of patients overall, as well as in 1% of patients (all of whom were randomly assigned) in the T12PR24 group and 12% of the patients randomly assigned to the T12PR48 group (P<0.001).

CONCLUSIONS

In this study, among patients with chronic HCV infection who had not received treatment previously, a regimen of peginterferon–ribavirin for 24 weeks, with telaprevir for the first 12 weeks, was noninferior to the same regimen for 48 weeks in patients with undetectable HCV RNA at weeks 4 and 12, with an extended rapid virologic response achieved in nearly two thirds of patients. (Funded by Vertex Pharmaceuticals and Tibotec; ILLUMINATE ClinicalTrials.gov number, NCT00758043.)

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Chronic infection with hepatitis C virus (HCV) represents a serious health issue for nearly 200 million infected persons worldwide.[1] Achievement of a sustained virologic response may be associated with improved long-term clinical outcomes, including increased survival.[2,3] In patients infected with HCV genotype 1, 48 weeks of treatment with peginterferon alfa and ribavirin results in a rate of sustained virologic response of 40 to 50%.[4,5]

Telaprevir administered in combination with peginterferon and ribavirin has led to high rates of sustained virologic response in phase 2 and phase 3 trials involving patients with HCV genotype 1 infection, who have not previously received treatment, in the United States and Europe.[6-8] Telaprevir is an orally bioavailable inhibitor of the nonstructural 3/4A (NS3/4A) HCV protease. Phase 2 data have suggested that a high proportion of patients have a rapid decline in viral levels during early treatment stages and that a response-guided treatment regimen based on viral response may permit a shorter treatment duration while preserving high rates of sustained virologic response. Such a strategy may decrease the risk of exposure of patients to not only potential side effects from telaprevir but also to the well-characterized adverse events associated with the 48-week use of peginterferon and ribavirin.

In this multinational, randomized study, we assessed the efficacy and safety of response-guided therapy consisting of a three-drug regimen of telaprevir, peginterferon alfa-2a, and ribavirin in patients with chronic HCV genotype 1 infection who had not previously received treatment. The primary goal was to assess the noninferiority of a 24-week versus a 48-week telaprevir-based regimen among patients who had an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12).

METHODS

STUDY PATIENTS

Eligible patients were enrolled at 74 sites in Belgium, the Netherlands, and the United States (including Puerto Rico). Inclusion criteria for enrollment were the presence of chronic infection with HCV genotype 1, indicated by a diagnosis at more than 6 months before the screening visit, with a detectable HCV RNA level at the visit, as well as no previous treatment for HCV infection; age between 18 and 70 years; seronegative test for hepatitis B virus and human immunodeficiency virus; an absolute neutrophil count of 1500 or more per cubic millimeter; a platelet count of 90,000 or more per cubic millimeter; and a hemoglobin level of 12 g or more per deciliter for female patients and 13 g or more per deciliter for male patients. All patients had undergone a liver biopsy within 1 year before the screening visit or underwent the procedure during the screening period unless a biopsy more than 1 year previously showed evidence of cirrhosis. Patients with hepatic decompensation, clinically significant liver disease from another cause, or active cancer within the previous 5 years (except treated basal-cell carcinoma) were excluded.

STUDY DESIGN AND CONDUCT

All patients provided written informed consent. The study was approved by the institutional review boards of all study centers and was performed in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonization and the Declaration of Helsinki. The study protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

Vertex Pharmaceuticals and Tibotec funded the study. The academic principal investigator participated in study design and protocol development with the study sponsors, had unrestricted access to the data, prepared the first draft of the manuscript, and made the decision to submit the manuscript for publication. All authors reviewed and approved the final manuscript and assume responsibility for the accuracy and completeness of the data reported. An employee of Vertex Pharmaceuticals provided medical writing, editorial, and coordination services.

The ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir) trial was an open-label, randomized, phase 3 noninferiority trial in which the results of HCV RNA testing were double-blinded through week 24. All patients received triple therapy for 12 weeks, consisting of telaprevir (Vertex Pharmaceuticals) at a dose of 750 mg orally every 8 hours, peginterferon alfa-2a (40 kD) (Pegasys, Roche) at a dose of 180 μg injected subcutaneously once weekly, and ribavirin (Copegus, Roche) at a dose of 1000 mg per day for patients weighing less

than 75 kg or 1200 mg per day for patients weighing 75 kg or more. After 12 weeks, all patients continued to receive peginterferon–ribavirin only.

ASSESSMENT OF EFFICACY

At study visits, the HCV RNA level was measured with the use of the COBAS TaqMan assay (Roche Molecular Systems, version 2.0), which has a lower limit of quantification of 25 IU per milliliter and a lower limit of detection of approximately 10 to 15 IU per milliliter.

After the week 20 visit, patients who had had an undetectable HCV RNA level at week 4 and week 12 (i.e., an extended rapid virologic response) were randomly assigned, in a 1:1 ratio, to stop treatment at week 24 (the T12PR24 group) or to continue peginterferon–ribavirin therapy through 48 weeks (the T12PR48 group). Randomization was centrally managed, blocked, and stratified to optimize balance with regard to HCV genotype subtype (1a, 1b, or unknown) and self-reported race (black or nonblack). Patients who had not had an extended rapid virologic response were nonrandomly assigned to the T12PR48 group.

Upon the completion of treatment, all patients entered the follow-up phase, consisting of 48 weeks for the T12PR24 group and 24 weeks for the T12PR48 group. Patients who discontinued treatment before randomization were also followed for 24 weeks. All patients were assessed for a sustained virologic response at 24 weeks of follow-up and, in patients in the T12PR24 group, at 48 weeks of follow-up. All patients who completed the follow-up period were assessed for a response to treatment.

Virologic failure was defined as an HCV RNA level greater than 1000 IU per milliliter at week 4, a decline from baseline by less than 2 $\log_{10}$ units in the level of detectable HCV RNA at week 12, or a detectable HCV RNA level at any time between weeks 24 and 36. According to the study protocol, telaprevir was stopped in patients with an HCV RNA level greater than 1000 IU per milliliter at week 4, and all study drugs were stopped in patients who had virologic failure at week 12 or between weeks 24 and 36.

Samples for sequence-based virologic assessment of changes in the NS3/4A coding domain were collected at baseline. These were compared with samples obtained during the study for patients in whom HCV RNA did not become undetectable.

SAFETY

Planned safety evaluations included physical examinations, laboratory evaluation of key safety variables, and adverse-event reporting according to the Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria for the assessment of severity. For adverse events not listed in the DAIDS criteria, severity assessment was based on protocol-defined criteria. Electrocardiography was performed at baseline. During the first 12 weeks of the study, investigators could discontinue the use of telaprevir (while continuing to administer peginterferon–ribavirin) if serious adverse events potentially attributable to telaprevir were observed. These included, but were not restricted to, rash and anemia. The use of erythropoietin or other hematopoietic growth factors was prohibited per the final amended protocol, as were reductions of telaprevir dose.

Planned reviews of safety data were conducted by an independent data and safety monitoring committee to evaluate the safety and tolerability of the study-drug regimens. A statistical group independent of the sponsors performed the analyses and safety-data preparation for each review.

STATISTICAL ANALYSIS

The primary efficacy variable was a sustained virologic response, defined as an undetectable HCV RNA level at the end of the treatment phase and 24 weeks after the last planned dose of study medication. The primary analysis was the estimation of the difference in sustained virologic response between patients who had extended rapid virologic response and were randomly assigned to receive T12PR24 versus T12PR48. The sample size was chosen to permit a noninferiority comparison between these two randomized subgroups with a predefined noninferiority margin of –10.5%. A sample size of 157 randomly assigned patients per study group was estimated to have 80% power to rule out the noninferiority of T12PR24 as compared with T12PR48 if the observed rate of sustained virologic response was 90%.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY PATIENTS

A total of 540 patients received at least one dose of a study drug (Fig. 1) and represent the overall study population (Table 1). Black race was self-

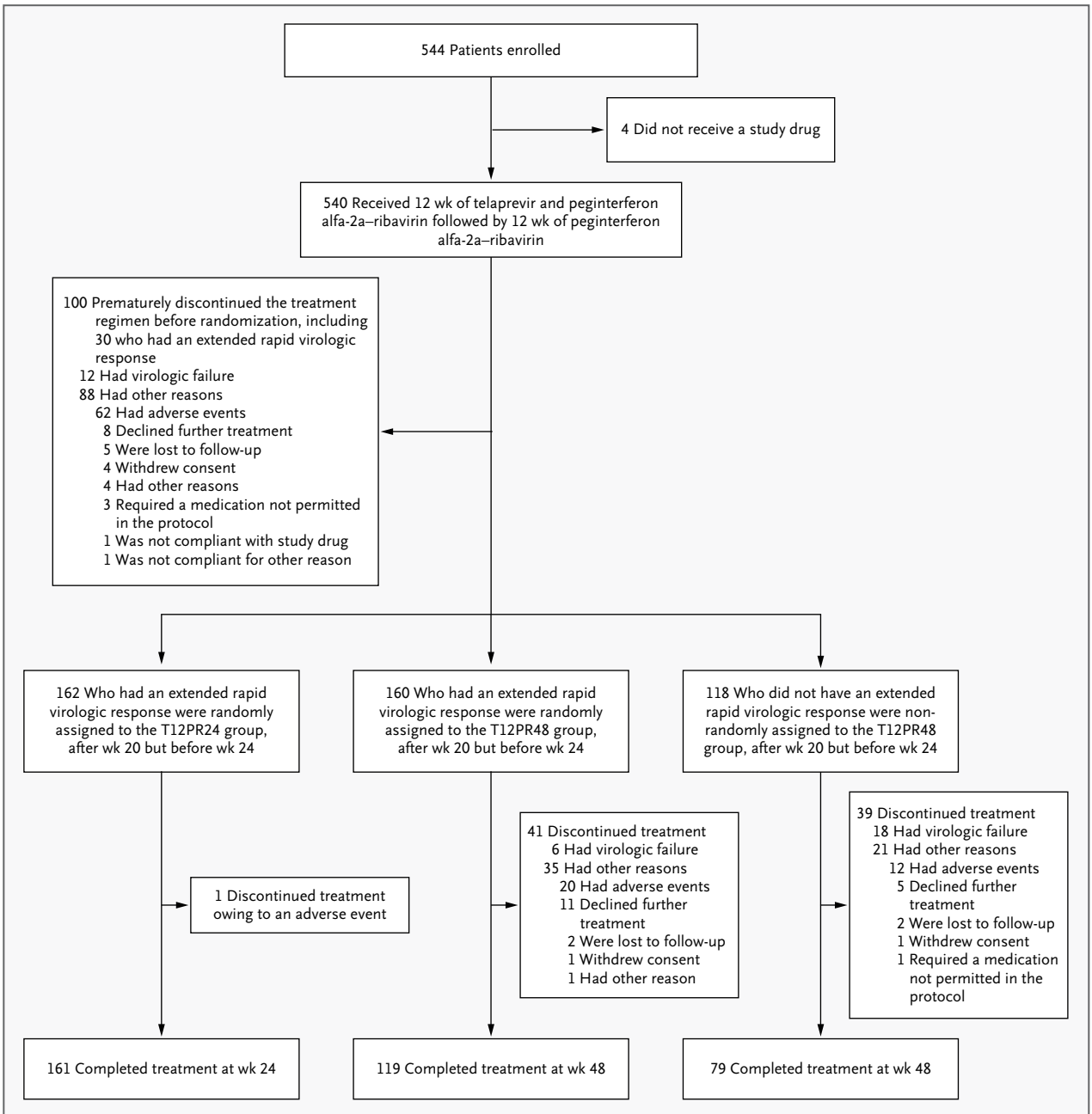

Figure 1. Enrollment, Randomization or Assignment, and Follow-up of the Study Patients.

Virologic failure was defined as an HCV RNA level greater than 1000 IU per milliliter at week 4, a decline from baseline by less than 2 $\log_{10}$ units in the level of detectable HCV RNA at week 12, or a detectable HCV RNA level at any time between weeks 24 and 36.

reported in 73 patients (14%); 54 patients (10%) identified themselves as Hispanic or Latino; and 3 (1%) identified themselves as black and Hispanic or Latino. A total of 149 patients (28%) had bridging fibrosis or cirrhosis. Genotype subtype 1a was predominant (388 patients [72%]).

EFFICACY AND NONINFERIORITY

Overall, 72% (389 of 540) of the study patients had a rapid virologic response, defined as undetectable HCV RNA at week 4; 65% (352 of 540) had an extended rapid virologic response. One hundred patients, including 30 who had an extended rapid

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

Characteristic	Randomly Assigned to T12PR24 (N=162)	Randomly Assigned to T12PR48 (N=160)	Nonrandomly Assigned to T12PR48 (N=118)	Discontinued Treatment before Wk 20 (N=100)
Age — yr				
Median	51	50	51	52
Range	22–70	19–67	20–63	21–66
Body-mass index†				
Median	28	27	27	27
Range	18–53	19–49	19–54	19–44
Distribution				
<25	44 (27)	60 (38)	35 (30)	38 (38)
≥25 to <30	56 (35)	51 (32)	49 (42)	32 (32)
≥30	61 (38)	49 (31)	34 (29)	30 (30)
Missing data	1 (1)	0	0	0
Male sex — no. (%)	104 (64)	97 (61)	70 (59)	54 (54)
Race — no. (%)‡				
White	135 (83)	131 (82)	86 (73)	75 (75)
Black	17 (10)	17 (11)	20 (17)	19 (19)
Other	10 (6)	12 (8)	12 (10)	6 (6)
Hispanic or Latino ethnic group — no. (%)‡				
Yes	18 (11)	11 (7)	8 (7)	17 (17)
No	140 (86)	146 (91)	105 (89)	82 (82)
Missing data	4 (2)	3 (2)	5 (4)	1 (1)
HCV genotype 1 subtype — no. (%)§				
1a	115 (71)	117 (73)	84 (71)	72 (72)
1b	46 (28)	43 (27)	33 (28)	27 (27)
Unknown	1 (1)	0	1 (1)	1 (1)
HCV RNA $\log_{10}$ — IU/ml¶	6.3±0.9	6.4±0.7	6.7±0.6	6.4±0.7
HCV RNA level ≥800,000 IU/ml — no. (%)¶	124 (77)	126 (79)	108 (92)	87 (87)
Stage of fibrosis and cirrhosis — no. (%)				
None or minimal fibrosis	46 (28)	48 (30)	27 (23)	26 (26)
Portal fibrosis	78 (48)	79 (49)	49 (42)	38 (38)
Bridging fibrosis	20 (12)	21 (13)	30 (25)	17 (17)
Cirrhosis	18 (11)	12 (8)	12 (10)	19 (19)

* Plus–minus values are means ±SD. None of the characteristics differed significantly between the randomized groups (P>0.05 for all comparisons). Patients received telaprevir (750 mg every 8 hours) for 12 weeks, as well as peginterferon alfa-2a (180 μg per week) and ribavirin (1000 or 1200 mg per day, according to body weight) for a total of either 24 weeks (T12PR24) or 48 weeks (T12PR48). Patients who had an extended rapid virologic response were randomly assigned to either the T12PR24 group or the T12PR48 group. Patients who did not have an extended rapid virologic response were nonrandomly assigned to the T12PR48 group. The remaining patients discontinued the treatment regimen before week 20 or nonrandom assignment. HCV denotes hepatitis C virus.

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

‡ Race and ethnic group were self-reported and were not mutually exclusive. The "other" race category included patients self-identifying as Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other self-reported races, as well as 13 patients for whom local regulations did not permit asking about race or ethnic group.

§ HCV genotype and subtype were ascertained by means of line-probe assay (Inno-LiPA, Innogenetics).

¶ HCV RNA levels were measured with the use of the COBAS TaqMan HCV assay (Roche Molecular Systems), which has a lower limit of quantification of 25 IU per milliliter and a lower limit of detection of approximately 10 to 15 IU per milliliter.

virologic response, discontinued the study drugs owing to adverse events, withdrawal of consent, or other reasons. The overall rate of sustained virologic response was 72% (Table 2). Of the 322 patients who had an extended rapid virologic response and a week 20 visit, 162 were randomly assigned to the T12PR24 group, of whom 149 (92%) had a sustained virologic response; and 160 were randomly assigned to the T12PR48 group, of whom 140 (88%) had a sustained virologic response. A total of 118 patients who had not had an extended rapid virologic response were assigned to the T12PR48 group, and 76 (64%) had a sustained virologic response. Of the remaining 100 patients, who prematurely discontinued treatment before week 20, 23 (23%) had a sustained virologic response.

The primary study objective was the noninferiority of the T12PR24 regimen to the T12PR48 regimen; specifically, the rate of sustained virologic response among patients with an undetectable HCV RNA level at weeks 4 and 12 who were randomly assigned to 24-week versus 48-week treatment. The majority of patients (99%) in the 24-week group completed the treatment, as compared with 74% in the 48-week group (P<0.001). The absolute difference in the rate of sustained virologic response between the T12PR24 group and the T12PR48 group was 4 percentage points (95% confidence interval [CI], –2 to 11). The lower limit of this 95% CI (–2%) excluded the noninferiority margin of –10.5%.

Low rates of relapse were observed after the completion of treatment (6% with T12PR24 and 3% with T12PR48), with an overall relapse rate of 8% (Table 2). The HCV RNA level was undetectable at 72 weeks after the start of treatment in 70% (377 of 540) of patients overall, with an absolute difference of –0.5 percentage points between the T12PR24 group (87.0%) and the patients in the T12PR48 group who had had an extended rapid virologic response (87.5%) (95% CI, –7.7 to 6.8).

Rates of response in subgroups with host or baseline characteristics that have been historically associated with poor treatment outcome were also examined. Overall, 69% of patients with a high viral load (≥800,000 IU per milliliter) had a sustained virologic response. Among those with an extended rapid virologic response, HCV RNA levels at baseline were not a predictor of a sustained virologic response, which was achieved in nearly 90% of patients with high viral load. Similarly, genotype subtype (1a vs. 1b) did not affect the treatment outcome, either in the overall population or among randomly assigned patients (Table 2). In all, 63% of patients with bridging fibrosis or cirrhosis had a sustained virologic response. Among patients with an extended rapid virologic response and bridging fibrosis or cirrhosis, rates of sustained virologic response were 82% in the T12PR24 group and 88% in the T12PR48 group (Table 2). This difference was not significant. Overall, 74% of white patients versus 60% of black patients had a sustained virologic response (P=0.02) (Table 2). Neither race nor ethnic group was associated with any decrease in the rate of sustained virologic response among the patients who had had an extended rapid virologic response; no significant differences were observed between the two randomized subgroups.

VIROLOGIC FAILURE AND TELAPREVIR-RESISTANT VARIANTS

Virologic failure during the treatment phase, including in patients who met the stopping rules and had detectable HCV RNA levels at the end of treatment, was uncommon, found in 8% of the overall population and in 2% of patients in the T12PR24 group and 3% of the patients in the T12PR48 group who had had an extended rapid virologic response (P=0.22). HCV variants with decreased sensitivity to telaprevir were observed in the majority of patients in whom HCV RNA did not become undetectable, including the previously described variants with NS3/4A positions 36, 54, 155, and 156.[9] Follow-up of patients without a sustained virologic response showed that 55% of those with resistant variants at baseline no longer had them (as detected by means of population sequencing) at their last visit (median follow-up, 43 weeks).

SAFETY AND SIDE-EFFECT PROFILE

In the overall treatment phase, 9% of patients had serious adverse events, anemia being the most common, reported in 2% of patients (Table 3). A total of 2% of patients in the T12PR24 group, as compared with 10% of the patients in the T12PR48 group who had had an extended rapid virologic response, had serious adverse events (P=0.005). Fatigue was the most common adverse event (68%), followed by pruritus (51%), nausea (47%), anemia (39%), headache (38%), rash (37%),

Table 2. Undetectable HCV RNA Levels during and after the Treatment Period, According to Study Group and Baseline Characteristic.*

Time Point	Total (N=540)	Randomly Assigned to T12PR24 (N=162)	Randomly Assigned to T12PR48 (N=160)	Nonrandomly Assigned to T12PR48 (N=118)	Discontinued Treatment before Wk 20 (N=100)
	number/total number (percent)				
Wk 4 (rapid virologic response)	389 (72)	162 (100)	159 (99)	15 (13)	53 (53)
Wk 4 and wk 12 (extended rapid virologic response)	352 (65)	162 (100)	159 (99)	0	31 (31)
End of treatment	469 (87)	159 (98)	154 (96)	97 (82)	59 (59)
24 Wk after end of treatment (sustained virologic response): primary end point	388 (72)	149 (92)	140 (88)	76 (64)	23 (23)
Wk 4 (rapid virologic response)					
Yes	317/389 (81)	149/162 (92)	139/159 (87)	11/15 (73)	18/53 (34)
No	71/151 (47)	0/0	1/1 (100)	65/103 (63)	5/47 (11)
Body-mass index					
<25	125/177 (71)	42/44 (95)	51/60 (85)	22/35 (63)	10/38 (26)
≥25 to <30	135/188 (72)	51/56 (91)	46/51 (90)	32/49 (65)	6/32 (19)
≥30	127/174 (73)	55/61 (90)	43/49 (88)	22/34 (65)	7/30 (23)
Missing data	1/1 (100)	1/1 (100)	0	0	0
HCV 1 genotype subtype					
1a	273/388 (70)	103/115 (90)	103/117 (88)	49/84 (58)	18/72 (25)
1b	112/149 (75)	45/46 (98)	37/43 (86)	26/33 (79)	4/27 (15)
Unknown	3 (1)	1 (1)	0	1 (1)	1 (1)
Liver disease					
None or minimal or portal fibrosis	294/391 (75)	118/124 (95)	111/127 (87)	53/76 (70)	12/64 (19)
Bridging fibrosis or cirrhosis	94/149 (63)	31/38 (82)	29/33 (88)	23/42 (55)	11/36 (31)
Race†					
White	315/427 (74)	126/135 (93)	114/131 (87)	56/86 (65)	19/75 (25)
Black	44/73 (60)	15/17 (88)	15/17 (88)	13/20 (65)	1/19 (5)
Asian or other	29/40 (72)	8/10 (80)	11/12 (92)	7/12 (58)	3/6 (50)
Hispanic or Latino ethnic group†					
Yes	36/54 (67)	17/18 (94)	9/11 (82)	6/8 (75)	4/17 (24)
No	343/473 (73)	129/140 (92)	128/146 (88)	67/105 (64)	19/82 (23)
Missing data	9/13 (69)	3/4 (75)	3/3 (100)	3/5 (60)	0/1 (0)
Diabetes					
Yes	16/35 (46)	6/8 (75)	4/5 (80)	4/8 (50)	2/14 (14)
No	372/505 (74)	143/154 (93)	136/155 (88)	72/110 (65)	21/86 (24)
Relapse after having undetectable HCV RNA at end of treatment period	37/469 (8)	9/159 (6)	4/154 (3)	11/97 (11)	13/59 (22)

* All patients who received at least one dose of a study drug were included in the analysis. HCV RNA levels were measured on day 1 and at weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 (the last treatment visit for the T12PR24 group), 28, 36, 40, 48 (the last treatment visit for the T12PR48 group), 60, and 72 and at all post-treatment follow-up visits.
† Race and ethnic group were self-reported.

insomnia (32%), diarrhea (28%), and influenza-like illness (26%).

During the telaprevir treatment phase (i.e., the first 12 weeks), 7% of all patients discontinued all study drugs, with 1% attributable to rash events and 1% to anemia events. Twelve percent of patients discontinued telaprevir only, owing to adverse events, with 7% due to rash events and 2% to anemia events (Table 3).

Roughly two thirds of the observed rashes occurred in the first 8 weeks. Rashes were primarily eczematous in nature and were typically treated with topical medications (e.g., topical glucocorticoids or antihistamines), oral antihistamines, or both. Severe rash occurred in 5% of patients and was managed by means of discontinuation of telaprevir first, with continuation of peginterferon–ribavirin; if the rash did not improve within 7 days after telaprevir discontinuation, ribavirin (with or without peginterferon) was to be either interrupted or discontinued.

Severe anemia was reported in 6% of patients. During the treatment phase, 14 patients had low hemoglobin levels (<7 g per deciliter), classified as a grade 4 adverse event, with 11 of the 14 going on to have a sustained virologic response. A total of 32 patients received blood transfusions for treatment of anemia during the study; 7 patients (1%) received an erythropoiesis-stimulating agent, and a sustained virologic response was achieved in 6 of these 7. The ribavirin dose was modified in 46% of patients because of decreased hemoglobin levels. A total of 73% of the patients whose ribavirin dose was not modified had a sustained virologic response, as did 68% and 75% of patients who had at least one dose reduction and at least one dose reduction and interruption, respectively. Among all study patients, 18% discontinued all study drugs because of adverse events, including 1% of the patients in the T12PR24 group and 12% of the patients in the T12PR48 group who had had an extended rapid virologic response ($P<0.001$) (Table 3).

DISCUSSION

We found that a 24-week treatment regimen of peginterferon–ribavirin, with telaprevir added for the first 12 weeks, was noninferior to a 48-week regimen of peginterferon–ribavirin, with telaprevir added for the first 12 weeks in patients with chronic infection with HCV genotype 1 who have not received treatment previously and who had an extended rapid virologic response. Nearly two thirds of the enrolled patients met this definition and were eligible for an abbreviated course of therapy. Thus, this study supports the concept of response-guided therapy. Relapse rates were low and were not significantly different between the 24-week group and the 48-week group. The sustained virologic response among all study patients was 72%.

Telaprevir-based therapy guided by the presence or absence of an extended rapid virologic response selected for a population that demonstrated uniformly high rates of sustained virologic response regardless of race, ethnic group, or presence or absence of advanced fibrosis. There were high rates of response among blacks (60%) and Hispanics or Latinos (67%), in contrast with the historically poor responses in these subgroups reported in large published trials. The Viral Resistance to Antiviral Therapy of Chronic Hepatitis C study (VIRAHEP-C; ClinicalTrials.gov number, NCT00038974) reported a sustained virologic response of 28% among blacks receiving peginterferon–ribavirin.[10] Response rates among patients with bridging fibrosis or cirrhosis were high; however, few patients had cirrhosis in our study, and further investigation is warranted.

Virologic failure was frequently associated with the appearance of mutations related to resistance to telaprevir and other class-specific serine protease inhibitors. Follow-up of patients without a sustained virologic response in our study showed that 55% of patients who originally had resistant variants no longer had resistant variants at their last visit (median follow-up, 43 weeks). In addition, long-term follow-up of patients who had virologic failure in phase 2 telaprevir studies showed that in 89% of patients, telaprevir-resistant variants were no longer detectable after a median follow-up time of 22 months, on the basis of population sequencing.[11]

Rates of drug discontinuation were similar to those in other clinical trials of telaprevir-based therapy[6-8] and were slightly higher than those observed in pivotal trials of peginterferon–ribavirin only.[4,5] The overall incidences of rash (37%) and severe rash (5%) were similar to those in the 12-week telaprevir-based treatment groups in the ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir) trial (NCT00627926) (37% and 6%, respectively).[8] Although rash was common in our

study, it was usually mild and was a relatively infrequent cause of discontinuation of all study medications. Our protocol differed from earlier phase 2 trials of telaprevir in that investigators were permitted to discontinue administration of telaprevir, in cases of severe or worsening rash, while maintaining the administration of peginterferon–ribavirin. Since most of these discontinuations occurred after HCV was undetectable (i.e., after 8 weeks of treatment), the discontinuation of telaprevir did not negatively affect the rate of sustained virologic response.

The incidence of anemia in our study (39%) was similar to that in the 12-week telaprevir-based groups in ADVANCE (37%).[8] Rates of discontinuation of telaprevir and all study drugs owing to anemia-associated events were low. High rates of sustained virologic response were observed despite ribavirin-dose modifications, as well as in the small number of patients who received an erythropoiesis-stimulating agent.

In our phase 3 study, 24 weeks of peginterferon and ribavirin treatment was noninferior to 48 weeks of treatment for patients infected with HCV genotype 1 who had not previously received treatment and who had undetectable HCV RNA levels at weeks 4 and 12. This response-guided regimen resulted in a shorter treatment duration with high rates of sustained virologic response for approximately two thirds of treated patients. The treatment regimen was highly effective in patients with a historically poor treatment response, including

Table 3. Adverse Events and Reasons for Discontinuation of Telaprevir Only and of All Study Drugs.*

Event	Total (N=540)	Randomly Assigned to T12PR24 (N=162)	Randomly Assigned to T12PR48 (N=160)	Nonrandomly Assigned to T12PR48 (N=118)	Discontinued Treatment before Wk 20 (N=100)
			number (percent)		
Any serious adverse event	49 (9)	4 (2)	16 (10)	7 (6)	22 (22)
Blood and lymphatic system disorders	15 (3)	2 (1)	5 (3)	0	8 (8)
Anemia	12 (2)	1 (1)	0	7 (6)	4 (4)
Infections and infestations	10 (2)	1 (1)	5 (3)	3 (3)	1 (1)
Pneumonia	3 (1)	0	2 (1)	1 (1)	0
Gastrointestinal disorders	2 (<1)	0	0	0	2 (2)
Injury, poisoning, and procedural complications	3 (1)	0	0	0	3 (3)
Metabolism and nutrition disorders	3 (1)	0	3 (2)	0	0
Dehydration	2 (<1)	0	2 (1)	0	0
Respiratory, thoracic, and mediastinal disorders	3 (1)	0	0	0	3 (3)
Any adverse event	537 (99)	161 (99)	160 (100)	117 (99)	99 (99)
General disorders	472 (87)	138 (85)	139 (87)	106 (90)	89 (89)
Fatigue	369 (68)	110 (68)	111 (69)	81 (69)	67 (67)
Gastrointestinal disorders	440 (81)	132 (81)	135 (84)	99 (84)	74 (74)
Nausea	253 (47)	71 (44)	76 (48)	61 (52)	45 (45)
Diarrhea	164 (30)	48 (30)	54 (34)	38 (32)	24 (24)
Skin and subcutaneous-tissue disorders	461 (85)	142 (88)	145 (91)	102 (86)	72 (72)
Pruritus	273 (51)	95 (59)	83 (52)	55 (47)	40 (40)
Rash†	202 (37)	60 (37)	62 (39)	47 (40)	33 (33)
Nervous system disorders	311 (58)	94 (58)	90 (56)	79 (67)	48 (48)
Headache	204 (38)	61 (38)	57 (36)	51 (43)	35 (35)
Psychiatric disorders	288 (53)	73 (45)	95 (59)	72 (61)	48 (48)
Insomnia	182 (34)	50 (31)	62 (39)	44 (37)	26 (26)
Blood and lymphatic system disorders	287 (53)	86 (53)	89 (56)	62 (53)	50 (50)
Anemia‡	212 (39)	68 (42)	66 (41)	38 (32)	40 (40)

Table 3. (Continued.)

Event	Total (N=540)	Randomly Assigned to T12PR24 (N=162)	Randomly Assigned to T12PR48 (N=160)	Nonrandomly Assigned to T12PR48 (N=118)	Discontinued Treatment before Wk 20 (N=100)
			number (percent)		
Discontinuation of telaprevir only owing to adverse events§					
Total	65 (12)	21 (13)	20 (12)	13 (11)	11 (11)
Rash events of any severity†	40 (7)	14 (9)	10 (6)	9 (8)	7 (7)
Anemia events of any severity‡	13 (2)	6 (4)	3 (2)	2 (2)	2 (2)
Discontinuation of all study drugs					
Total¶	181 (34)	1 (1)	41 (26)	39 (33)	100 (100)
Owing to adverse events	95 (18)	1 (1)	20 (12)	12 (10)¶	62 (62)
Rash events of any severity†	8 (1)	0	1 (1)	0	7 (7)
Anemia events of any severity‡	13 (2)	0	2 (1)	0	11 (11)
Other‖	50 (9)	0	15 (9)	9 (8)	26 (26)

* Serious adverse events listed are those that occurred in at least three patients. Adverse events listed are those that occurred in at least 30% of patients. Both are listed according to preferred term of the *Medical Dictionary for Regulatory Activities* (version 11.0).

† Rash was primarily eczematous and resolved after cessation of therapy. Severe rash was observed in 5% of the study patients. Rash events, as assessed with the use of a group of related terms to identify all dermatologic events, were observed in 63% of patients during the telaprevir treatment phase.

‡ Per the study protocol, anemia was to be managed with modification of the ribavirin dose; the use of therapy involving erythropoietin or other hematopoietic growth factors was prohibited according to the final amended protocol. Severe anemia was observed in 6% of the study patients.

§ The adverse events listed as the cause of telaprevir discontinuation are those of any grade reported during treatment in at least 1% of patients in at least one of the four study groups.

¶ One patient randomly assigned to the T12PR24 group died after having completed treatment during the extended follow-up phase, 277 days after the last dose of study drug; the death was the result of a fall that led to head trauma and was considered unrelated to telaprevir. One patient nonrandomly assigned to the T12PR48 group had completed telaprevir therapy but discontinued peginterferon–ribavirin therapy owing to an adverse event during the post-telaprevir treatment phase. This patient was considered to have discontinued treatment except in safety analyses, since all three study drugs were not discontinued owing to an adverse event.

‖ Other reasons for discontinuation of all the study drugs included withdrawal of consent, loss to follow-up, noncompliance with the drug regimen or other types of noncompliance, refusal of further treatment, and requirement for medication not permitted in the protocol.

blacks, patients with bridging fibrosis or cirrhosis, and patients with high HCV RNA levels. Response-guided therapy also resulted in decreased rates of adverse events and treatment discontinuation among patients who received treatment over the shorter period.

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