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Extended Therapy With Pegylated Interferon and Weight-Based Ribavirin for HCV-HIV Coinfected Patients

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Abstract

Background—It is unknown whether extended treatment with pegylated interferon (PEG) and weight-based ribavirin (WBR) results in higher rates of sustained virologic response (SVR) among HCV-HIV coinfected patients compared with standard duration therapy.

Objective—The study aimed to measure rates of SVR among coinfected patients who received extended therapy with PEG plus WBR.

Methods—HCV-HIV coinfected subjects were treated with PEG and WBR, and those who achieved early virologic response (EVR; ≥2 log decrease in HCV RNA from baseline or HCV RNA<600 IU/mL) at week 12 were eligible to continue treatment for 72 weeks. SVR (HCV RNA<60 IU/mL) was measured 24 weeks after treatment discontinuation. Predictors of SVR were assessed in simple and multivariate logistic regression.

Results—A total of 329 subjects enrolled at 36 sites. Of 184 subjects who achieved EVR, 169 entered Step 3: 89% male, 52% White, 29% Black, and 71% HCV treatment naïve. The overall SVR rate was 27% (95% CI, 22%–32%) among all subjects, and 33% (95% CI, 27%–40%) among the 223 who were HCV treatment naïve. In exploratory analyses, among 120 treatment-naïve subjects who entered Step 3, the SVR rate was 62% (95% CI, 52%–70%). In this subgroup, predictors of SVR were HCV genotype 2 or 3 ($P = .03$), HCV RNA <800,000 IU/mL at study entry ($P = .05$), and achievement of complete EVR (HCV RNA<600 IU/mL at week 12; $P < .0001$).

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Conclusion—Among all subjects, we observed a comparable overall SVR rate to prior studies of subjects treated for 48 weeks. Extended treatment with PEG and WBR may be beneficial to subsets of coinfected patients, specifically those who are treatment naïve and achieve complete EVR.

Keywords

extended therapy; HCV; HIV; weight-based ribavirin

Since the introduction of potent antiretroviral therapy, chronic infection with hepatitis C virus (HCV) among persons with HIV has emerged as a major cause of morbidity and mortality. HCV-HIV coinfection is associated with more rapid liver disease progression compared with HCV monoinfection.[1–4] Suboptimal responses to treatment with pegylated interferon (PEG) and ribavirin, specifically lower rates of sustained virologic response (SVR), have been observed among HCV-HIV coinfected patients compared to those with HCV monoinfection.[5–10] The basis for the lower response rates is unclear, but may relate to higher viral load, altered cytokine environment, or higher rates of intolerability of PEG and ribavirin.

The assessment of viral kinetics during treatment has permitted the identification of patients who may benefit from modification of therapy. For persons with HCV monoinfection who experience at least a 2 log reduction in HCV RNA with detectable HCV RNA at week 12 but undetectable HCV RNA at week 24 (classified as slow responders), studies have suggested a benefit for extended periods of therapy compared to the standard duration of 48 weeks.[11–16] Furthermore, a viral kinetic modeling study suggested that high viral load in coinfected patients was an important predictor of time to clearance and might necessitate a treatment cycle longer than 48 weeks in most HCV-HIV patients.[17] In addition, among HCV monoinfected subjects, the use of weight-based ribavirin (WBR) has been associated with higher rates of SVR compared to flat dose ribavirin.[6]

It remains unclear whether extended treatment with PEG and WBR among HCV-HIV coinfected patients results in higher rates of SVR, or whether they are able to tolerate a prolonged treatment period. The optimal duration of treatment among patients coinfected with HCV-HIV thus remains unknown. We therefore evaluated the safety, efficacy, and tolerability of extended treatment with PEG and WBR among HCV-HIV coinfected patients.

METHODS

Study Design

Step 3 was an important component of A5178, a clinical trial designed to determine whether pegylated interferon alfa-2a (PEG) maintenance therapy slows fibrosis progression in HCV-HIV coinfected subjects.[18] The overall study design is shown in Figure 1. Subjects were enrolled at 36 AIDS Clinical Trials Group (ACTG) sites and were initially treated with PEG 180 μg subcutaneously (SC) weekly plus WBR administered orally in divided doses according to body weight (1000 mg/day for ≤75 kg; 1200 mg/day for >75 kg) (Step 1). At week 12, subjects were classified as early virologic responder (EVR) if they had at least a 2 log decrease in HCV RNA from study entry with HCV RNA ≥600 (partial EVR) or had HCV RNA<600 IU/mL (complete EVR); all others were classified as nonresponders. Subjects who failed to achieve EVR after 12 weeks of treatment were randomized to receive PEG alone for 72 additional weeks or to be observed for 72 weeks with no treatment (Step 2); the results of Step 2 have been reported elsewhere.[18] By definition, subjects who entered Step 2 were classified as not achieving SVR in analyses of overall study results. Subjects

who were classified as EVR and tolerated the first 12 weeks of treatment on Step 1 were eligible to enter a nonrandomized treatment arm (Step 3), during which they were to continue their regimen of PEG plus WBR for a total of 72 weeks from Step 1 entry. After 72 weeks (or after premature treatment discontinuation), they were monitored off treatment for an additional 24 weeks, and SVR was determined.

Study Population

Subjects at least 18 years of age who were coinfected with HCV and HIV were enrolled in Step 1 of A5178. HIV-1 infection was documented by a positive ELISA assay confirmed by Western blot, HIV-1 culture, HIV-1 antigen, or HIV-1 RNA. All subjects were required to have HIV-1 RNA < 50,000 copies/mL, a CD4 cell count of >200 cells/mm^3, and HCV viremia, defined as detectable levels of HCV RNA by RT-PCR or bDNA. All study subjects underwent liver biopsy within 2 years prior to Step 1 and were required to have at least stage 1 fibrosis as determined by the local pathologist. Subjects could be either HCV treatment experienced, defined as receipt of prior interferon therapy for at least 12 weeks and HCV RNA positive following treatment, or HCV treatment naïve. Laboratory criteria required for entry included absolute neutrophil count (ANC) ≥1000/mm^3; hemoglobin ≥11 for men and ≥10 g/dL for women; platelets ≥70,000/mm^3; creatinine ≤1.5 mg/dL; international normalized ratio (INR) <1.5; alanine transaminase (ALT) and aspartate aminotransferase (AST) and alkaline phosphatase ≤10x upper limit of normal (ULN); direct bilirubin <1.5 mg/dL; lipase ≤1.5x ULN; and a normal thyroid-stimulating hormone (TSH) or normal thyroid function on full thyroid panel. Subjects with reproductive potential agreed to use 2 forms of approved contraception.

Subjects were eligible for Step 3 if they achieved EVR and tolerated PEG on Step 1, which was defined as not missing 3 or more consecutive PEG doses during the first 12 weeks of treatment and 5 or more total doses of PEG prior to Step 3 entry.

Subjects were excluded from Step 1 and from Step 3 if they had AIDS-defining opportunistic infections within 12 weeks prior to entry. Additional exclusion criteria included evidence of decompensated liver disease or other significant liver disease (including hepatitis B, acute hepatitis A, hemochromatosis, or homozygotic alpha-1 antitrypsin deficiency), recent steroid use, active drug/alcohol abuse that would interfere with study adherence, uncontrolled seizure disorders, uncontrolled active depression, history of autoimmune processes that could be exacerbated by the treatment regimen, or history of major organ transplantation.

HCV RNA was tested at a central laboratory using Roche Cobas Amplicor assay (Roche Molecular Systems) with a lower detection limit of 600 IU/mL for the quantitative assay (used in Step 1) and 60 IU/mL for the qualitative assay (used in Step 3). HIV RNA was tested at a central laboratory using Roche Ultrasensitive HIV RT PCR (Roche Molecular Systems) with a lower limit of quantification of 50 copies/mL.

Statistical Analysis

The primary endpoint of Step 3 was SVR, defined as an undetectable HCV RNA (<60 IU/mL for the qualitative assay) 24 weeks after treatment discontinuation. SVR was evaluated using intention-to-treat (ITT) criteria wherein subjects without HCV RNA data 24 weeks after treatment discontinuation were considered failures. SVR rates were summarized with exact 2-sided 95% binomial confidence intervals to allow comparisons with SVR rates observed in previous studies.

Age, race, sex, prior interferon use, HCV genotype, presence of cirrhosis on pre-entry liver biopsy, injection drug use history, baseline body mass index (BMI), CD4 cell count, HIV

RNA, HCV RNA, ALT, AST, alkaline phosphatase, ANC, platelet count, hemoglobin, and Karnofsky score at study entry were chosen a priori to be studied as predictors of SVR in overall (Step 1) analyses. Race, sex, prior interferon use, HCV genotype, presence of cirrhosis on pre-entry liver biopsy, injection drug use history, Karnofsky score, and HCV RNA at study entry; achievement of complete early virologic response (cEVR) on Step 1; and age, BMI, CD4 cell count, HIV RNA, HCV RNA, ANC, platelet count, and hemoglobin at Step 3 entry were included in Step 3 analyses. Fibrosis stage was not included in the analyses, because the data on fibrosis collected at the study sites were not converted by a single pathologist into a standardized score. Exact tests were used for associations between 2 categorical measures. Predictors of SVR were also assessed in simple and multi-covariate logistic regression. The multi-covariate model was reduced using stepwise selection procedure. Interactions between HCV genotype and prior interferon use with other predictor variables were assessed in logistic regression models with main effects of HCV genotype (or prior interferon use) and of the other predictor variables, respectively, and their interaction.

Exploratory analyses focused on the predictors of SVR among a priori specified subsets such as subjects with HCV genotype 1 or 4 and ad hoc subsets based on prior HCV treatment and achievement of cEVR at week 12.

Statistical analysis was performed using Statistical Analysis System, Version 9.2 (SAS Institute Inc, Cary, North Carolina, USA). Statistical significance level of 0.05 (2-sided) was used, and no adjustment for multiple testing was made.

Study Approval

The study protocol was reviewed and approved by National Institute of Allergy and Infectious Diseases and the US Food and Drug Administration. All subjects provided informed consent, which was approved by the institutional review board at all clinical sites. An independent study monitoring committee provided oversight during the conduct of the trial.

RESULTS

Baseline Characteristics

From August 2004 to April 2007, 330 subjects were enrolled at 36 sites in Step 1. One subject never started the study and was excluded from the analysis. Of the 329 subjects included in the analysis, 297 had week 12 HCV RNA data available for EVR evaluation. Of the 184 subjects who achieved EVR, 169 (92%) were enrolled in Step 3, and 15 subjects did not enroll (1 subject was inadvertently registered to Step 2; 2 subjects had protocol defined toxicity; 4 subjects were severely debilitated; and the remaining 8 subjects were ineligible for Step 3 due to missing doses of PEG) (Figure 2).

Baseline demographic characteristics at Step 1 entry and at Step 3 entry are displayed in Table 1. Among 329 subjects who entered the study, 83% were male, 43% were White, 37% Black, and 15% Hispanic. The median age was 48 years, and 59% of the subjects reported current or previous use of injection drugs. Among 169 Step 3 subjects, 89% were male, 52% were White, 29% Black, and 14% Hispanic. The median age was 48 years, and 57% of the subjects reported current or previous use of injection drugs. Eighty-six percent had undetectable HIV RNA at Step 3 entry, and the median CD4 cell count was 316 cells/mm^3. Seventy-eight percent had HCV genotype 1 or 4, and 21% had HCV genotype 2 or 3. Sixty-six percent had undetectable (<60 IU/mL) HCV RNA at Step 3 entry, and 9% had cirrhosis detected by prestudy biopsy. Among the 169 subjects, 29% had previously received HCV treatment.

Sustained Virologic Response

Step 1—Among the 329 subjects who enrolled in Step 1, the observed overall SVR rate was 27% (95% CI, 22%–32%). Achievement of SVR was jointly associated with non-Black race (32% vs 19%; odds ratio [OR], 2.1; $P = .02$), no prior interferon use (33% vs 13%; OR, 3.9; $P = .0001$), genotype 2 or 3 (63% vs 21%; OR, 5.0; $P < .0001$), and entry HCV RNA <800,000 IU/mL (49% vs 22%; OR, 3.5; $P = .0002$). There was one marginally statistically significant interaction between HCV genotype and entry ANC. There were no other statistically significant interactions between HCV genotype or prior interferon use and the variables listed in the Statistical Analysis section.

Because of the strength of prior HCV treatment and HCV genotype in predicting SVR from Step 1 entry, we focused on the 188 subjects who were HCV treatment naïve and had HCV genotype 1 or 4. Predictors of SVR among this subset in univariate logistic regression models are shown in Table 2 and included age <40 years old, non-Black race, Karnofsky score equal to 100, and HCV RNA<800,000 IU/mL at Step 1 entry. In the multi-covariate logistic regression model, the effects of age, Karnofsky score, and Step 1 entry HCV RNA remained statistically significant, and the association between race and SVR approached statistical significance ($P = .07$). Achievement of cEVR was a very strong predictor for SVR: Among the 74 subjects who achieved cEVR, 65% achieved SVR ($P < .0001$).

Step 3—Among the 169 subjects who continued therapy on Step 3, the observed SVR rate was 52% (95% CI, 44%–60%). Treatment-naïve subjects (n=120) achieved an SVR rate of 62% (95% CI, 52%–70%) (Figure 2). The SVR rate among subjects with HCV genotype 1 or 4 was 46% compared with 75% of those with genotype 2 or 3 ($P = .0024$). Among all 169, SVR was associated with undetectable HCV RNA at Step 3 entry ($P < .0001$), HCV RNA<800,000 IU/mL at Step 1 entry ($P = .005$), and achievement of cEVR on Step 1 ($P < .0001$). There were no statistically significant interactions between HCV genotype or prior interferon use and the variables listed in the Statistical Analysis section.

As shown in Table 3, among 120 treatment-naïve subjects who achieved EVR and entered Step 3, SVR was associated with HCV RNA< 800,000 IU/mL at Step 1 entry and HCV genotype 2 or 3. In addition, achievement of cEVR was highly associated with SVR: Of 100 subjects who achieved cEVR, 71 (71%; 95% CI, 61%–80%) subsequently achieved SVR. In contrast, among the 20 subjects who achieved partial early virologic response (pEVR) at week 12, 11 had undetectable serum HCV RNA by week 28 (classified as slow responders), of whom 3 (27%) achieved SVR ($P = .01$). Of note, the effect of race was not significant, as SVR was attained in 51% of Blacks with EVR compared to 67% of non-Blacks with EVR ($P = .11$) (Table 4).

Not surprisingly, we observed significantly higher rates of SVR among subjects who were treatment naïve compared to those who received prior interferon-based therapy among all Step 1 subjects (33% vs 13%; $P < .0001$) and among Step 3 subjects (62% vs 29%; $P = .0002$) (Table 4).

Tolerability—Among the 169 subjects who entered Step 3, 54 (32%) experienced grade 3 or higher signs and symptoms. Prominent symptoms reported among the 169 subjects included pain, fatigue, and weight loss (19%) and neuropsychiatric (11%), respiratory (8%), and gastrointestinal (7%) complaints. There were 102 (60%) subjects who experienced grade 3 or higher laboratory toxicity. Fifty-eight (34%) subjects had grade 3 or higher neutropenia.

Fifty-five (33%) subjects discontinued treatment prematurely. There were 4 deaths (3 occurred between 48–72 weeks of treatment); 2 of these deaths were associated with

coronary artery disease, 1 with a heroin overdose, and 1 with epiglottitis (occurred during the follow-up period). Among the 52 subjects who discontinued therapy prematurely on Step 3, 2 reported severe debilitation, 4 had experienced a protocol-defined toxicity (2 neutropenia, and 1 depression and 1 anemia which both occurred during 48–72 weeks of treatment), 27 had a nonprotocol-defined toxicity (11 of those during 48–72 weeks of treatment), 3 required disallowed medications (1 occurred between 48–72 weeks), 3 were not able to get to clinic (1 each due to immigration issues, out of state move, and incarceration, all between 48–72 weeks), 2 completed the standard duration of 48 weeks and refused further treatment; 6 voluntarily withdrew because of the perceived high medication burden (4 between 48–72 weeks), and 5 were nonadherent with visit schedule (4 between 48–72 weeks).

The median time on study treatment among Step 3 subjects was 71 weeks (min = 17, max = 85 weeks). Of the 55 subjects who prematurely discontinued treatment, most (55%) discontinued between weeks 48 and 72 (Figure 3).

Figures 4 and 5 summarize dose modifications of PEG and WBR for Step 3 subjects starting from study entry and reveal an increased rate of permanent discontinuation of both PEG and WBR, particularly after week 48.

DISCUSSION

In this study, we evaluated the efficacy and tolerability of extended treatment with PEG and WBR among HCV-HIV coinfected patients. We observed overall SVR rates of 27% (95% CI, 22%–32%) among all 329 subjects who enrolled in Step 1, and 33% (95% CI, 27%–40%) among those who were treatment naïve (27% among genotype 1 and 4).

In exploratory analyses, we observed an SVR rate of 62% (95% CI, 52%–70%) among 120 treatment-naïve subjects who achieved early virologic response and entered Step 3. While similar to overall historical rates among coinfected subjects treated for 48 weeks with PEG plus ribavirin, which range from 27% to 40%,[7,9,10,19] the genotype 1 response rates appeared to compare favorably to those observed in prior trials (14%, 17%, 29%),[7,9,10,19] particularly among those in an analogous US ACTG-based study[7] with a similar patient population. In contrast to prior studies of coinfected subjects,[7,9,10] we used weight-based dosing of ribavirin throughout our study. Achievement of cEVR was a strong positive predictor for SVR among Step 1 subjects, which has been reported previously among coinfected patients by Van den Eynde et al.[20]

Currently, there are limited data regarding SVR rates among coinfected subjects who achieve EVR and undergo extended duration of therapy. Nunez et al reported results from the PRESCO trial, describing a higher rate of SVR among 237 subjects with HCV genotype 1 or 4 with undetectable serum HCV RNA at week 24 who received treatment with PEG plus WBR for 72 weeks compared to those who received therapy for 48 weeks (53% vs 31%; $P = .0005$).[21] In addition, they noted that slow responders (those with positive HCV RNA at weeks 4 and 12 and undetectable HCV RNA at week 24) experienced comparable rates of SVR irrespective of treatment duration and HCV genotype, but had fewer relapses with longer courses of therapy. Uriel, in a study of 206 coinfected subjects of all genotypes with undetectable HCV RNA at week 24 who were randomized to receive either 48 or 72 weeks of PEG plus WBR, reported no significant difference between rates of SVR (50% vs 55%, respectively; $P = .7$).[22]

In our study, among treatment-naïve subjects who achieved EVR and entered Step 3, we observed an SVR rate of 62%. We observed a significantly higher SVR rate among those who achieved cEVR compared to those classified as slow responders (the 11 subjects who

achieved pEVR with detectable HCV RNA at week 12 but undetectable HCV RNA at week 28) (71% vs 27%). Perhaps just as important, these findings suggest that extended therapy for those who achieve pEVR is unlikely to produce SVR, with a negative predictive value of 87% for all pEVRs and 73% for slow responders. Although prior studies among HCV-monoinfected[23,24] and HCV-HIV coinfected[25,26] patients have utilized the achievement of rapid virological response (RVR; defined as undetectable plasma HCV RNA at week 4) as an important predictor of treatment response, we did not have access to RVR data and thus could not study the efficacy of extended therapy according to achievement of this benchmark.

We observed a 33% rate of premature treatment discontinuation, in comparison to the historical rates of 12% to 39% observed among coinfected subjects who received PEG plus ribavirin for only 48 weeks.[7,9,10] The majority of subjects in our study who discontinued treatment did so between weeks 48 and 72, suggesting that the burden of continuing therapy for 72 weeks was particularly manifest during the last 24 weeks of treatment.

Among Step 1 subjects, race was associated with achievement of EVR[18] and SVR; however, race was not associated with SVR among those who achieved EVR and continued therapy on Step 3. Although the numbers are small, the observation is consistent with the premise that on-treatment virologic response supersedes race as a predictive factor. The identification of the association between possession of single nucleotide polymorphisms (SNP) near the IL28B gene locus on chromosome 19 and HCV clearance in mono- and coinfected patients has had widespread implications on the understanding of the pathogenesis of HCV and the contribution of innate immunity as well as on potential treatment options, including antiviral drug development and the use of genetic testing to guide patient-tailored therapy.[27–33] In addition, the population distribution of the polymorphism may partially explain the significantly poor outcomes observed among African Americans compared to other ethnic groups, because the favorable *IL28B* allele is present at lower frequency in Africans, intermediate frequency in Europeans and Caucasians, and high frequency in East Asians.[19, 20] We did not have *IL28B* polymorphism genotype data in this population, therefore additional studies will be helpful to determine the significance of the possession of favorable genotypes on rate of SVR, particularly among coinfected patients who achieve EVR and undergo extended therapy compared to those who receive standard therapy.

Our study had several limitations. First, given its design as a single, unrandomized arm of a clinical trial, we were unable to directly compare rates of SVR as well as rates of relapse between those who achieved EVR and continued treatment for 72 weeks with those who received treatment for 48 weeks. Moreover, we were unable to quantify the tolerability of treatment for 72 weeks compared to that of placebo. Multi-covariate analysis of response in some subsets of subjects (eg, HCV treatment-naive subjects who entered Step 3) was limited by sample size availability.

Our study findings suggest that longer treatment duration and use of WBR may be of benefit to a subset of patients, specifically those without prior HCV treatment and those who achieve cEVR. Moreover, those who achieve pEVR may wish to strongly weigh the risks of discontinuing treatment because of the low likelihood of SVR and the higher rates of intolerance with extended therapy. Although the development of small molecule antiviral inhibitors promises to advance treatment of HCV, there are still some coinfected patients who could benefit from PEG plus WBR and who cannot defer treatment, particularly those patients with advanced liver fibrosis stage. It is also unclear whether direct-acting antiviral therapy agents will be routinely available for safe use in HCV-HIV coinfected persons in the

near future. If PEG plus WBR is used, it will be important to balance gains in SVR with the adverse effects of extended duration of treatment that contribute to impaired quality of life.

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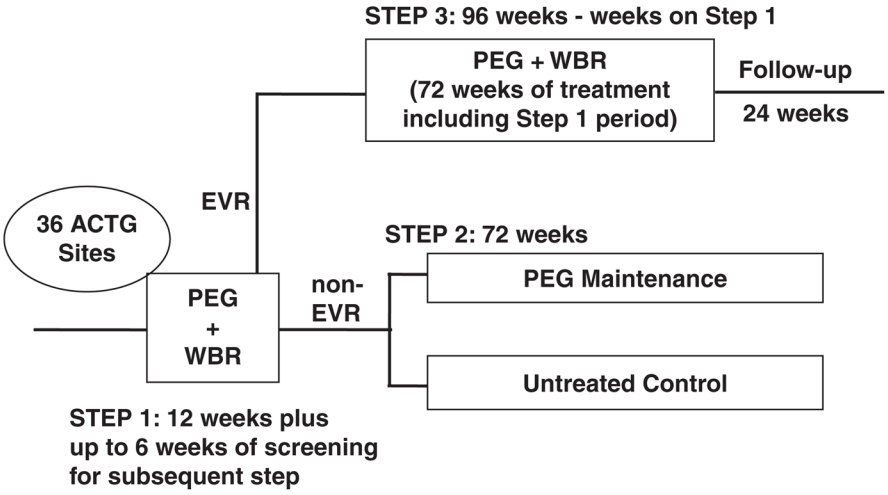

Figure 1.

Study design. PEG = pegylated interferon; WBR = weight-based ribavirin; EVR = early virologic response (defined as at least a 2 log drop in HCV RNA from Step 1 entry or HCV RNA < 600 IU/mL at week 12).

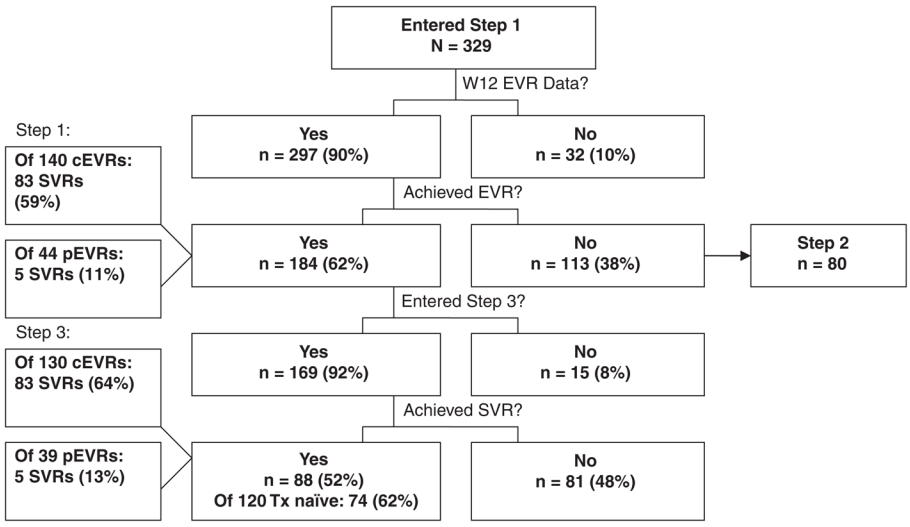

Figure 2.

Study flow diagram. *W12 EVR refers to Step 1 week 12 early virologic response. cEVR = complete early virologic response, defined as HCV RNA < 600 IU/mL at week 12 of therapy; pEVR = partial early virologic response, defined as at least 2 log decrease from Step 1 entry at week 12 but HCV RNA ≥600 IU/mL; Tx naïve = treatment naïve.

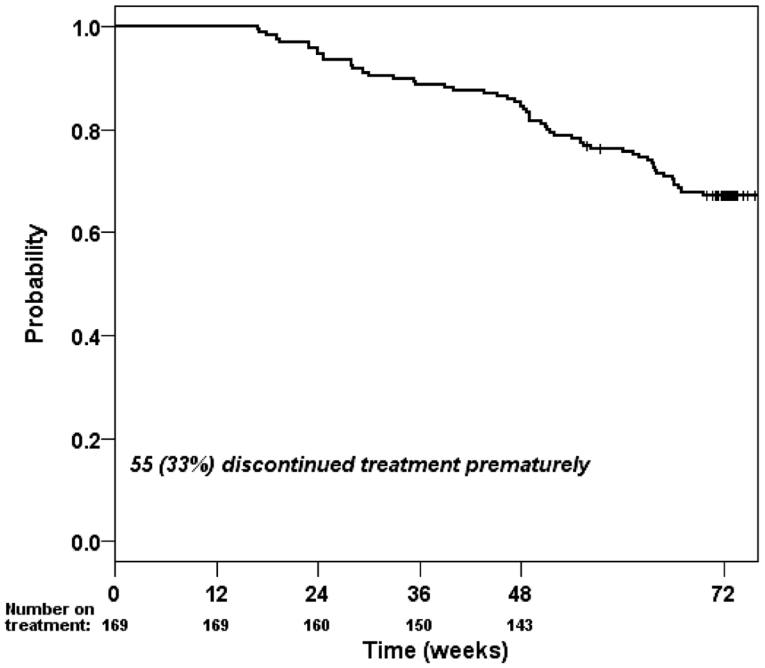

Figure 3.
Time to premature treatment discontinuation among subjects who achieved early virologic response (EVR) and entered Step 3.

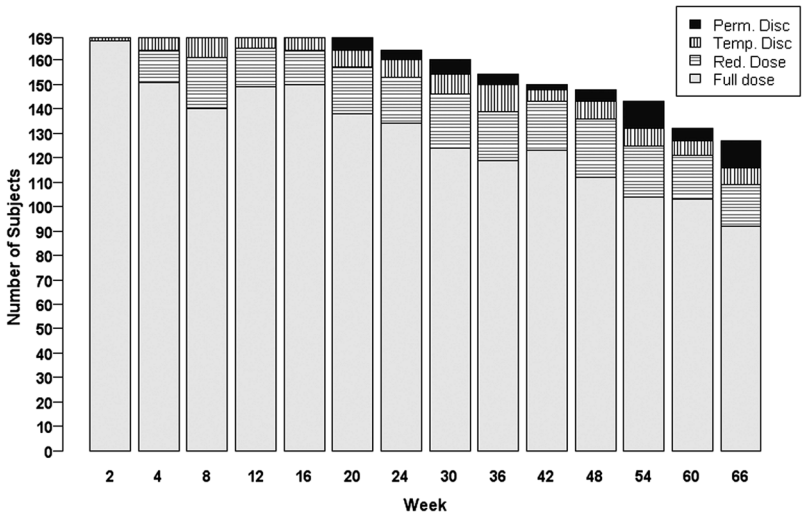

Figure 4.

Pegylated interferon (PEG) weekly dose status from Step 1 study entry among subjects who achieved early virologic response (EVR) and entered Step 3. Dose reduction of PEG was specified for grade 2 neutropenia experienced within 2 weeks of treatment initiation; delay or temporary stop for grade 3 and higher neutropenia and for grade 3 thrombocytopenia; and permanent discontinuation for grade 4 thrombocytopenia. Permanent discontinuation was also specified for grade 4 psychiatric or neuropsychiatric toxicities. Disc = discontinuation; Perm. = permanent; Red. = reduction; Temp. = temporary.

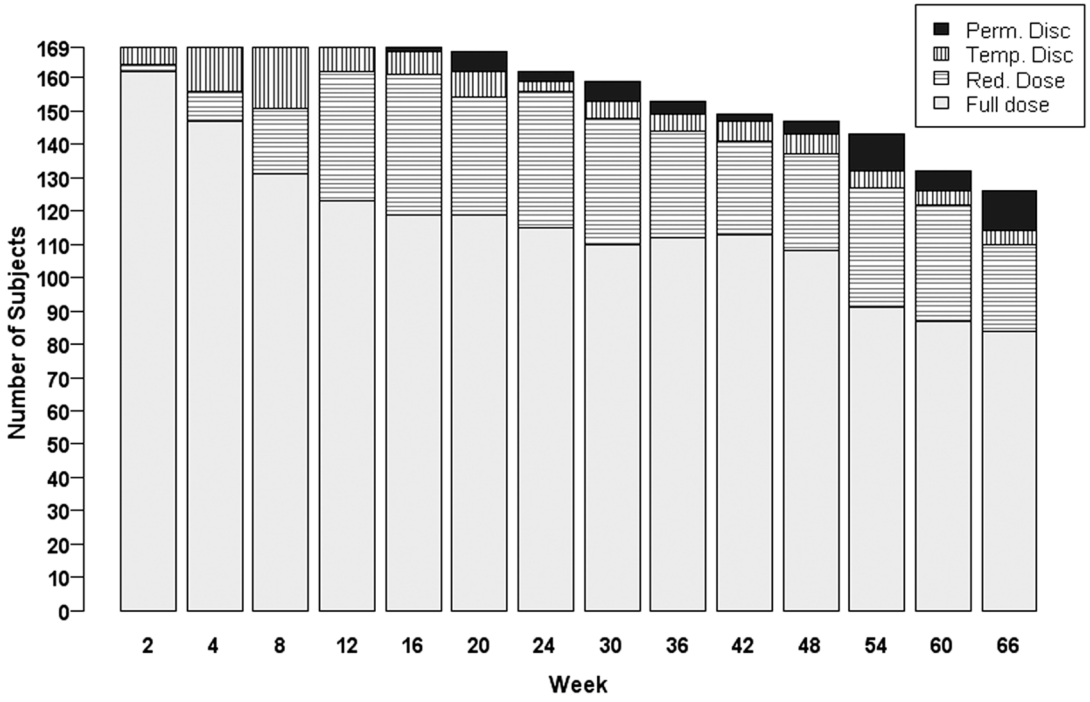

Figure 5.

Weight-based ribavirin weekly dose status from Step 1 study entry among subjects who achieved early virologic response (EVR) and entered Step 3. The dose of ribavirin was reduced for a decrease in hemoglobin to <11 g/dL in men and to <10 g/dL in women. The study drug was stopped temporarily for a hemoglobin of <8.5 g/dL in men and <8.0 g/dL in women, or <10 g/dL in men and <9.0 g/dL while on reduced ribavirin dose of 600 mg/day, or for a ≥4 g/dL decrease in hemoglobin during any 4-week period. Permanent discontinuation was specified for grade 4 psychiatric or neuropsychiatric toxicities. Disc = discontinuation; Perm. = permanent; Red. = reduction; Temp. = temporary.

Table 1

Baseline demographics at Step 1 and Step 3 entry

	Demographics	Step 1 entry (n = 329)	Step 3 entry (n = 169)
Sex	Male	274 (83%)	150 (89%)
	Female	55 (17%)	19 (11%)
Race/Ethnicity[a]	White	142 (43%)	88 (52%)
	Black	123 (37%)	49 (29%)
	Hispanic	50 (15%)	23 (14%)
	Other	13 (4%)	9 (5%)
IV drug history	Never	135 (41%)	72 (43%)
	Currently or previously	194 (59%)	97 (57%)
Age, years	Median	48	48
	18–39	52 (16%)	29 (17%)
	40–59	269 (82%)	137 (81%)
	Over 60	8 (2%)	3 (2%)
BMI, kg/m^2	Underweight (<18.5)	5 (2%)	5 (3%)
	Normal (18.5–24.9)	138 (42%)	91 (54%)
	Overweight or obese (≥25)	186 (56%)	73 (43%)
HIV RNA, copies/mL	Undetectable (<50)	245 (74%)	146 (86%)
	Detectable (≥50)	84 (26%)	23 (14%)
CD4 count, cells/mm^3	Median	498	316
	< 500	165 (50%)	137 (81%)
	≥500	164 (50%)	32 (19%)
HCV genotype[b]	Genotype 1	273 (83%)	128 (76%)
	Genotype 2	30 (9%)	26 (15%)
	Genotype 3	13 (4%)	10 (6%)
	Genotype 4	10 (3%)	3 (2%)
HCV RNA, IU/mL[c]	Median	3,980,000	
	<600	2 (1%)	**[d]
	600–500,000	30 (9%)	
	500,000–5,000,000	171 (52%)	
	>5,000,000	126 (38%)	
Prior HCV treatment	Yes	106 (32%)	49 (29%)
	No	223 (68%)	120 (71%)
Karnofsky score[e]	100	146 (44%)	76 (45%)
	< 100	163 (50%)	82 (49%)
Cirrhosis	Yes	43 (13%)	15 (9%)
	No	286 (87%)	154 (91%)

Note: IV = intravenous; BMI = body mass index; HCV = hepatitis C virus.

[a] One subject did not disclose race/ethnicity at Step 1 entry.

[b] Three subjects were missing data on HCV genotype at Step 1 entry, and 2 subjects were missing data at Step 3 entry.

[c] At Step 1 entry, HCV RNA was performed using a quantitative assay.

[d] At Step 3 entry, HCV RNA was performed using a qualitative assay, with HCV RNA <60 IU/mL defined as undetectable serum HCV RNA and HCV RNA ≥60 IU/mL defined as detectable serum HCV RNA. Among subjects who entered Step 3, 111 (66%) had undetectable HCV RNA, 53 (31%) had detectable HCV RNA, and 5 (3%) had missing HCV RNA at Step 3 entry.

[e] There were 20 subjects with missing data on Karnofsky score at Step 1 entry and 11 subjects with missing data at Step 3 entry.

Table 2

Predictors of sustained virologic response among Step 1 treatment-naïve subjects with HCV genotype 1 or 4 (n=188)

	Simple logistic regression models[a]		Multi-covariate logistic regression model[b]	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age <40 vs ≥40	2.9 (1.3–6.2)	.0085	3.5 (1.3–9.1)	.0101
Non-Black vs Black	2.3 (1.2–4.5)	.0132	2.2 (0.9–5.0)	.0697
Karnofsky score 100 vs <100	2.6 (1.3–5.3)	.0074	3.5 (1.5–8.2)	.0032
HCV RNA <800,000 vs ≥800,000	4.6 (2.1–10.1)	.0001	9.5 (3.6–25.1)	<.0001

Note: HCV = hepatitis C virus; OR = odds ratio.

[a] Estimates and *P* values are from simple logistic regression models with sustained virologic response (SVR) as the dependent variable and age, race, Karnofsky score, and HCV RNA, respectively, as the single predictor variable.

[b] Estimates and *P* values are from a multi-covariate logistic regression model with SVR as the dependent variable and age, race, Karnofsky score, and HCV RNA as predictor variables.

Table 3

Predictors of sustained virologic response (SVR) among treatment-naïve subjects who achieved early virologic response (EVR) and entered Step 3

			SVR (ITT)		
		Total (N=120)	**Yes (n=74)**	**No (n=46)**	***P*[c]**
Age	<40 years	25	15 (60%)	10 (40%)	1.0000
	≥40 years	95	59 (62%)	36 (38%)	
Race	Black	39	20 (51%)	19 (49%)	.1137
	Non-Black	81	54 (67%)	27 (33%)	
Injection drug use	Previous/Current	68	38 (56%)	30 (44%)	.1847
	Never	52	36 (69%)	16 (31%)	
Sex	Male	104	66 (63%)	38 (37%)	.4081
	Female	16	8 (50%)	8 (50%)	
Step 3 entry HIV RNA	Undetectable (<50)	102	65 (64%)	37 (36%)	.3005
	Detectable (≥50)	18	9 (50%)	9 (50%)	
Step 1 entry HCV RNA	<800,000	28	22 (79%)	6 (21%)	.0457
	≥800,000	92	52 (57%)	40 (43%)	
HCV genotype[a]	Genotypes 1 or 4	89	50 (56%)	39 (44%)	.0290
	Genotypes 2 or 3	29	23 (79%)	6 (21%)	
Complete EVR[b]	Yes	100	71 (71%)	29 (29%)	<.0001
	No	20	3 (15%)	17 (85%)	

Note: HCV = hepatitis C virus.

[a] Among Step 3 subjects, 2 had missing data regarding HCV genotype.

[b] Defined as HCV RNA <600 IU/mL at week 12 of therapy.

[c] *P* values are from Fisher exact tests.

Table 4

Rates of sustained virologic response (SVR) by prior hepatitis C virus (HCV) treatment exposure

	Overall		Treatment naïve		Treatment experienced	
Race/Ethnicity	**Total (n)**	**SVR rate**	**Total (n)**	**SVR rate**	**Total (n)**	**SVR rate**
All subjects (N=329)						
Any HCV genotype						
Overall[a]	329	27% (22%–32%)	223	33% (27%–40%)	106	13% (7%–21%)
White	142	33% (26%–41%)	83	46% (35%–57%)	59	15% (7%–27%)
Black	123	19% (12%–27%)	96	21% (13%–30%)	27	11% (2%–29%)
Hispanic	50	26% (15%–40%)	33	36% (20%–55%)	17	6% (0%–29%)
HCV genotype 1 or 4						
Overall	283	21% (17%–26%)	188	27% (20%–34%)	95	11% (5–19%)
White	116	26% (18%–35%)	63	40% (28%–53%)	53	9% (3%–21%)
Black	117	17% (11%–25%)	92	18% (11%–28%)	25	12% (3%–31%)
Hispanic	40	17% (7%–33%)	25	24% (9%–45%)	15	7% (0%–32%)
HCV genotype 2 or 3						
Overall	43	63% (47%–77%)	32	72% (53%–86%)	11	36% (11%–69%)
White	24	71% (49%–87%)	18	72% (47%–90%)	6	67% (22%–96%)
Black	5	40% (5%–85%)	3	67% (9%–99%)	2	0% (0%–84%)
Hispanic	10	60% (26%–88%)	8	75% (35%–97%)	2	0% (0%–84%)
Subjects who achieved EVR and entered Step 3 (n = 169)						
Any HCV genotype						
Overall	169	52% (44%–60%)	120	62% (52%–70%)	49	29% (17%–43%)
White	88	53% (42%–64%)	57	67% (53%–79%)	31	29% (14%–48%)
Black	49	47% (33%–62%)	39	51% (35%–68%)	10	30% (7%–65%)
Hispanic	23	57% (34%–77%)	17	71% (44%–90%)	6	17% (0%–64%)
HCV genotype 1 or 4						
Overall	131	46% (37%–55%)	89	56% (45%–67%)	42	24% (12%–39%)
White	65	46% (34%–59%)	39	64% (47%–79%)	26	19% (7%–39%)
Black	46	44% (29%–59%)	36	47% (30%–65%)	10	30% (7%–65%)
Hispanic	15	47% (21%–73%)	10	60% (26%–88%)	5	20% (1%–72%)

	Overall		Treatment naïve		Treatment experienced	
Race/Ethnicity	**Total (n)**	**SVR rate**	**Total (n)**	**SVR rate**	**Total (n)**	**SVR rate**
HCV genotype 2 or 3						
Overall	36	75% (58%–88%)	29	79% (60%–92%)	7	57% (18%–90%)
White	22	77% (55%–92%)	17	76% (50%–93%)	5	80% (28%–99%)
Black	2	100% (16%–100%)	2	100% (16%–100%)	0	N/A
Hispanic	8	75% (35%–97%)	7	86% (42%–100%)	1	0% (0%–98%)

Note: EVR = early virologic response.

[a]The overall race/ethnicity category included White Non–Hispanic; Black Non–Hispanic; Hispanic, regardless of race; Asian; and American Indian.