

ORIGINAL ARTICLE

Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites

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ABSTRACT

BACKGROUND

Several small studies have reported a lower response rate to interferon alfa among black patients with chronic hepatitis C infection than among white patients. The increased prevalence of infection with hepatitis C virus (HCV) genotype 1, which has a lower response rate than other genotypes, has been suggested as the cause.

METHODS

We treated 100 black patients and 100 non-Hispanic white patients with chronic hepatitis C with peginterferon alfa-2b and ribavirin for 48 weeks. Enrollment was controlled so that the two groups had similar proportions of patients with genotype 1 infection. The primary end point was a sustained virologic response, which was defined as a negative test for serum HCV RNA six months after the completion of therapy.

RESULTS

In both cohorts, 98 percent of patients had genotype 1 infection. The rate of sustained virologic response was higher among non-Hispanic white patients than among black patients (52 percent vs. 19 percent, $P < 0.001$). The black patients also had significantly lower rates of virologic response at 12 weeks and at the end of treatment. Multivariable analyses examining sociodemographic and clinical characteristics found that black race was the only variable significantly associated with the difference in response rate.

CONCLUSIONS

Black patients with chronic hepatitis C have a lower rate of response to treatment with peginterferon alfa-2b and ribavirin than non-Hispanic white patients, a difference that is not explained by differences in the viral genotype.

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HEPATITIS C VIRUS (HCV) INFECTION is a major cause of liver disease and the most frequent indication for liver transplantation in the United States.¹ The Third National Health and Nutrition Examination Survey estimated that 1.8 percent of the American population had detectable HCV antibodies.² This study also found a racial or ethnic variation in rates, with detectable HCV antibodies among 3.2 percent of non-Hispanic blacks and 9.8 percent of non-Hispanic black men 40 to 49 years of age.

Recent advances in the treatment of HCV infection have led to improved rates of response.^{3,4} However, several series reported lower response rates among blacks than among other racial or ethnic groups.⁵⁻⁷ Blacks are more likely to be infected with HCV genotype 1, which has a lower response rate than do other genotypes, although one study reported no difference in response rates between black patients and white patients with HCV genotype 1 infections.⁸ Previous studies were limited by low enrollment of blacks and retrospective designs. Therefore, we prospectively compared the rates of response to treatment with peginterferon alfa-2b and ribavirin among blacks and non-Hispanic whites with chronic hepatitis C.

METHODS

PATIENT SELECTION

Adult black and non-Hispanic white patients who had detectable levels of serum HCV RNA and liver-biopsy findings consistent with the presence of chronic HCV infection were eligible for the study. Exclusion criteria included decompensated cirrhosis, organ transplantation, human immunodeficiency virus infection, hepatitis B virus infection, anemia, neutropenia, severe psychiatric conditions, hemoglobinopathy, autoimmune disease, and an inability or unwillingness to practice contraception.

STUDY DESIGN

This trial was conducted at 16 centers in North Carolina, South Carolina, Virginia, and Tennessee. The study was approved by the institutional review boards at each center and at Duke University. All patients provided written informed consent. To guarantee that there were equal proportions of patients with genotype 1 infection in each cohort, we placed non-Hispanic whites with non-genotype 1 infection on a waiting list until a black patient with a non-genotype 1 infection was enrolled. Race and

ethnic group were self-reported by the patients. Enrollment began in August 2000. The trial was completed in March 2003.

All patients received 1.5 μg of peginterferon alfa-2b (PEG-Intron, Schering-Plough) per kilogram of body weight subcutaneously once weekly for 48 weeks and 1000 mg of ribavirin (Rebetol, Schering-Plough) orally daily for the first 12 weeks and then 800 mg per day for weeks 13 to 48. Growth factors were not used.

Safety was assessed at weeks 1, 2, and 4 and then every four weeks during treatment and again at weeks 52, 56, 60, and 72. Compliance was assessed by monitoring the empty peginterferon alfa-2b vials and used syringes returned for disposal. Peginterferon alfa-2b and ribavirin dosing were reviewed with patients at each visit to ensure that the regimens were being followed. Serum HCV RNA was measured by a reverse-transcription-polymerase-chain-reaction assay with a sensitivity of 100 copies per milliliter (39 IU per milliliter) (National Genetics Institute); measurements were made at weeks 12, 24, and 48 during therapy and then 24 weeks after therapy was discontinued. Liver biopsy was performed within 2 years before treatment and again 24 weeks after the scheduled termination of treatment. Specimens were analyzed by a single pathologist who was unaware of the patients' identity, treatment assignment, response to treatment, or timing of biopsy. The Metavir scale was used to assess liver-biopsy specimens for disease activity (with a score of A0 indicating no activity, A1 mild activity, A2 moderate activity, and A3 severe activity) and fibrosis (with a score of 0 indicating no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis).⁹ Steatosis was assessed as absent, involving less than 33 percent of cells, involving 33 percent to 66 percent of cells, or involving more than 66 percent of cells.

Adverse events were evaluated with the use of World Health Organization grades.¹⁰ For grade 3 adverse events, the dose of peginterferon alfa-2b was reduced to 1.0 μg per kilogram and that of ribavirin to 800 or 600 mg per day. For grade 4 adverse events, both medications were discontinued permanently. Patients were evaluated for depression with the 20-item Centers for Epidemiological Studies Depression Scale.¹¹ Scores range from 0 to 60; a score of 16 to 20 suggests the presence of moderate depression, and scores greater than 20 suggest the presence of major clinical depression. If the investigator confirmed that the patient had moder-

ate depression, the peginterferon alfa-2b dose was reduced by half and the patient was monitored weekly until his or her condition stabilized. In the event of severe depression or suicidal ideation, all study medications were discontinued and a psychiatric consultation was obtained.

ASSESSMENT OF EFFICACY

The primary end point was a sustained virologic response, defined as the absence of detectable HCV RNA in serum 24 weeks after treatment was completed. Secondary end points included the histologic response and the virologic response at the end of treatment.

STATISTICAL ANALYSIS

Descriptive statistics for patients were reported. Continuous variables were summarized as means \pm SD, and comparisons were performed with use of the two-sample t-test.¹¹ The chi-square test was used to compare categorical variables between the two groups.

The study was designed to have a statistical power of 80 percent to detect an absolute difference of 17 percent in the rates of sustained virologic response (42 percent in non-Hispanic whites vs. 25 percent in blacks) at a 5 percent level of significance (with the use of a one-sided test) and given the enrollment of 100 patients in each group. Treatment responses were compared with use of Fisher's exact test.¹² Predictors of the treatment response were examined by stepwise logistic-regression analysis.¹³ For histologic responses, scores were calculated before and after treatment, and the changes in scores were compared with use of the Wilcoxon rank-sum test. In the analyses, missing HCV RNA samples were regarded as having detectable viral loads. All reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 116 black patients and 128 non-Hispanic white patients were screened. The most common reasons for exclusion were neutropenia (in 10 black patients) and a non-genotype 1 infection (in 19 non-Hispanic white patients). The enrollment of the cohorts occurred concurrently. The baseline characteristics of the two groups were similar except that the black patients were heavier and had a higher incidence of diabetes mellitus and hypertension than the non-Hispanic white patients (Table 1).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Blacks (N=100)	Non-Hispanic Whites (N=100)	P Value
Male sex (%)	67	53	0.04
Age (yr)	47.5 \pm 7.2	44.2 \pm 7.4	0.06
Education (yr)	13.7 \pm 2.0	13.9 \pm 2.2	0.43
Weight (kg)	89.0 \pm 18.5	81.6 \pm 20.9	0.01
Duration of infection (yr)	19.3 \pm 8.6	18.8 \pm 8.3	0.74
HCV genotype 1a or 1b (%)	98	98	1.0
HCV RNA ($\times 10^{-6}$ IU/ml)	1.45 \pm 1.64	1.26 \pm 1.48	0.40
Alanine aminotransferase (IU/ml)	97.1 \pm 81.6	102.9 \pm 85.8	0.62
Total bilirubin (mg/dl)	0.6 \pm 0.3	0.7 \pm 0.3	0.40
Prothrombin time (INR)	1.05 \pm 0.14	1.06 \pm 0.18	0.84
Albumin (mg/dl)	4.0 \pm 0.6	4.1 \pm 0.6	0.77
Fibrosis [†]			0.74
Median	2	2	
Interquartile range	2–3	2–3	
Steatosis >33% of cells (%)	3	5	0.82
Cirrhosis (%)	6	5	0.75
History of transfusion (%)	18	26	0.11
History of injection-drug use (%)	52	43	0.35
History of alcohol abuse (%)	35	30	0.45
Hypertension (%)	46	12	<0.001
Diabetes mellitus (%)	23	6	0.001

* Plus-minus values are means \pm SD. To convert values for bilirubin to micro-moles per liter, multiply by 17.1. INR denotes international normalized ratio.

[†] Scores can range from 0 to 4, with higher scores indicating more severe fibrosis.

Eighty-one percent of the black patients and 79 percent of the non-Hispanic white patients completed therapy. Five black patients and seven non-Hispanic white patients discontinued therapy before week 12, and 14 additional patients in each group withdrew before week 24. The reasons for discontinuation were similar in the two groups (Table 2). The most common reason for the discontinuation of therapy was depression, which occurred in 4 percent of black patients and 6 percent of non-Hispanic white patients. Two black patients and four non-Hispanic white patients were withdrawn because of noncompliance.

VIROLOGIC AND HISTOLOGIC RESPONSES

The rates of virologic response are presented in Table 3. The rate of sustained virologic response was higher among non-Hispanic white patients than black patients (52 percent vs. 19 percent, $P < 0.001$).

Table 2. Rates of Adverse Events, Dose Reduction, and Discontinuation of Treatment.

Variable	Blacks (N=100)	Non-Hispanic Whites (N=100)
	percent	
Discontinuation	19	21
Depression	4	6
Constitutional symptoms	4	5
Noncompliance	2	4
Neutropenia	4	3
Anemia	0	1
Thrombocytopenia	1	0
Other	4	2
Dose reduction	22	24
Adverse event*	7	10
Laboratory event		
Neutropenia	13	14
Anemia	4	4
Thrombocytopenia	2	0
Adverse events		
Headache	39	43
Fatigue	68	60
Myalgia	40	37
Nausea	21	26
Fever	52	58
Alopecia	37	31
Insomnia	45	42
Irritability	29	24

* This category comprised constitutional and psychiatric symptoms.

When the response rates were examined in patients who completed therapy, 19 of 81 black patients had a sustained virologic response, as compared with 52 of 79 non-Hispanic white patients (23 percent vs. 66 percent, $P<0.001$).

An early virologic response, defined as a reduction in the HCV RNA level by at least 2 log IU (on a base-10 scale) per milliliter at 12 weeks, has been reported to predict sustained virologic response.¹⁴ In our study, 19 of 40 black patients with an early virologic response had a sustained virologic response, as compared with 52 of 69 non-Hispanic white patients (48 percent vs. 75 percent, $P<0.001$). The finding of undetectable levels of HCV RNA at 12 weeks was also examined as a predictor of sus-

tained virologic response. Of the 28 black patients with no detectable HCV RNA at 12 weeks, 18 (64 percent) had a sustained virologic response, as compared with 48 of the 58 non-Hispanic white patients (83 percent). In both groups, no patient without an early virologic response ultimately had a sustained virologic response.

Biopsies were performed after treatment in very few patients with a sustained virologic response, and therefore, no related analyses were performed. Post-treatment biopsies were performed in 44 of 81 black patients without a sustained virologic response (54 percent) and 28 of 48 non-Hispanic white patients without a sustained virologic response (58 percent). The mean change in disease activity scores was -0.29 in black patients and -0.52 in non-Hispanic white patients ($P=0.37$). The mean change in fibrosis scores was 0.02 in the black patients and 0.10 in the non-Hispanic white patients ($P=0.79$).

VARIABLES ASSOCIATED WITH RESPONSE

To identify predictors of a sustained virologic response, the following factors were evaluated: racial or ethnic group (black vs. non-Hispanic white), sex, age (younger than 40 years vs. 40 years or older), weight (less than 75 kg vs. 75 kg or more), level of education (high school or less vs. more than high school), ribavirin dose (less than 10.6 mg per kilogram vs. 10.6 mg per kilogram or more), HCV RNA level (500,000 IU per milliliter or more vs. less than 500,000 IU per milliliter), duration of infection (less than 20 years vs. 20 years or more), the presence or absence of cirrhosis on histologic analysis, the presence or absence of steatosis on histologic analysis, and the presence or absence of diabetes mellitus. Univariate logistic models showed that the rates of sustained virologic response were lower among black patients than among non-Hispanic white patients ($P<0.001$) and among patients who were at least 40 years of age than among those who were younger ($P=0.04$). To evaluate the potential effect of each of the prognostic factors on the relationship between racial or ethnic group and a sustained virologic response, each variable was added into a model that included racial or ethnic group. The addition of each variable singly did not significantly change the effect of black race on sustained virologic response. The results of the univariate and multivariable models are summarized in Table 4. In addition, there were no significant differences between university and community sites in response

rates (16 percent vs. 20 percent) or dropout rates (22 percent vs. 19 percent) among black patients.

SAFETY

The rates and types of adverse events were similar in the two groups (Table 2). Dose reductions occurred in 22 percent of blacks and 24 percent of non-Hispanic whites. Bone marrow suppression was observed in both groups, and mean hemoglobin levels and neutrophil counts are presented in Figure 1. The rates of reduction in the dose of peginterferon alfa-2b because of neutropenia and of ribavirin because of anemia were similar in the two groups (Table 2). Moderate depression (as defined by a Centers for Epidemiological Studies Depression Scale score of 16 to 20) was reported in 18 percent of black patients and 20 percent of non-Hispanic white patients. In addition, 21 percent of black patients and 22 percent of non-Hispanic white patients required the initiation of antidepressant medication during treatment.

DISCUSSION

In patients with HCV infection, improvements in therapy have resulted in higher response rates.^{3,4} However, several studies have suggested that black patients have lower response rates than other racial or ethnic groups.⁵⁻⁷ McHutchison et al. found similar response rates among white patients and black patients with HCV genotype 1 infection and suggested that the disparity in treatment responses was due to the increased incidence of genotype 1 infections among blacks.⁸ All previous studies, however, were limited by their retrospective designs and low enrollment of blacks.

We treated 100 black patients and 100 non-Hispanic white patients with chronic hepatitis C. Ninety-eight percent of the patients in each group had HCV genotype 1 infection. We found a clear difference in the rates of sustained virologic response between black patients (19 percent) and non-Hispanic white patients (52 percent). Black race was the only predictor of response in regression analyses. Compliance was similar in the groups, and the similar education levels of our groups suggested that there was no difference in socioeconomic status.

The two groups had similar types and severities of adverse events, with similar numbers of episodes of anemia and neutropenia, rates of dose reduction, and discontinuation rates. Ten black patients were excluded because of neutropenia. Recent data indi-

Table 3. Virologic Response Rates.*

Virologic Response	Blacks (N=100)	Non-Hispanic Whites (N=100)	P Value
	% (95% CI)		
Early†	40 (30–50)	69 (60–78)	<0.001
End of treatment	20 (12–28)	58 (48–68)	<0.001
Sustained	19 (12–28)	52 (42–62)	<0.001

* Missing values that were due to a patient's withdrawal were considered non-responses. CI denotes confidence interval.

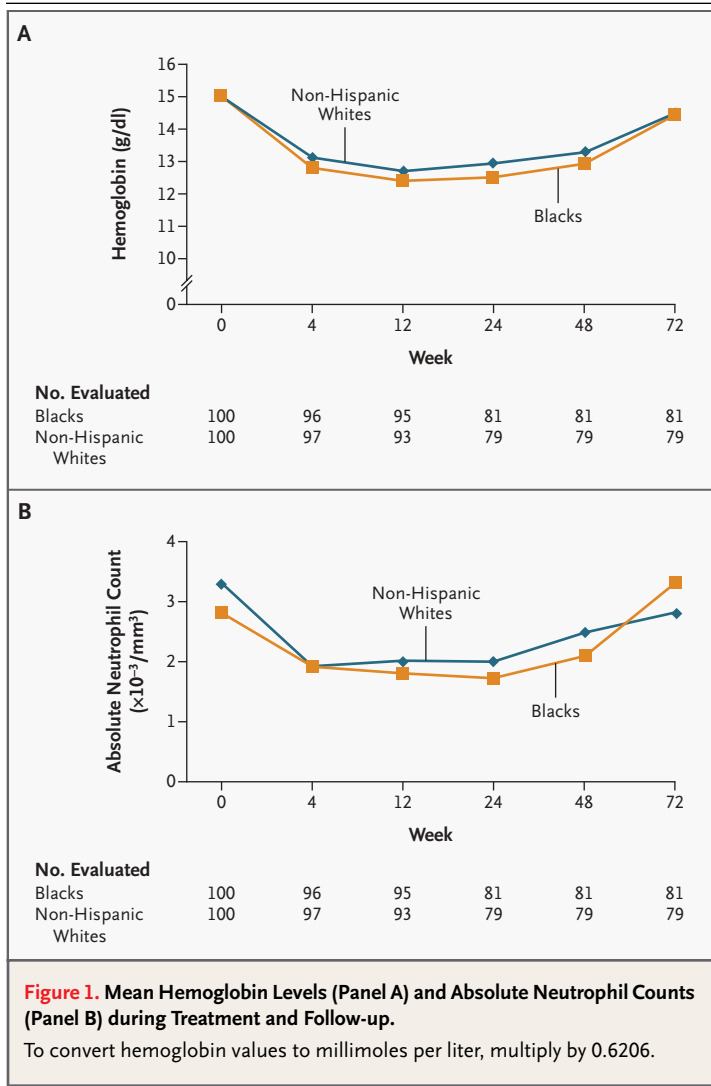
† An early response was defined as a reduction in the HCV RNA level by at least 2 log IU per milliliter at 12 weeks of treatment.

Table 4. Results of Regression Analyses Examining Effects of Prognostic Factors on Sustained Virologic Response.

Variable	Univariate Logistic Regression		Stepwise Logistic Regression	
	Regression Estimate	P Value	Regression Estimate	P Value
Black race	-1.53	<0.001	-1.53	<0.001
Male sex	-0.33	0.28	-0.13	0.67
Age ≥40 yr	-0.79	0.04	-0.69	0.10
>High-school education	0.14	0.63	0.21	0.48
Weight ≥75 kg	-0.58	0.09	-0.22	0.54
Ribavirin dose ≥10.6 mg/kg	0.11	0.71	0.32	0.32
HCV RNA level ≥500,000 IU/ml	-0.16	0.22	-0.12	0.39
Duration of infection ≥20 yr	-0.03	0.11	-0.03	0.12
Cirrhosis	-0.11	0.72	-0.12	0.70
Steatosis	-0.38	0.23	-0.28	0.42
Diabetes	-0.63	0.17	-0.12	0.81

cate that neutropenia related to interferon alfa therapy is not associated with an increased risk of infection, and black patients have minimal decreases in neutrophil counts during therapy.¹⁵ Neutropenia in blacks should thus not be an absolute contraindication to interferon alfa therapy.

We examined the ability of the early virologic response to predict the likelihood of a sustained virologic response.¹⁴ The negative predictive value of the lack of an early virologic response was 100 percent among black patients, since none of these patients ultimately had a sustained virologic response. However, only 19 of 40 black patients with an early virologic response (48 percent) had a sustained vi-



rologic response. Thus, the positive predictive value of an early virologic response may not be adequate among black patients. Our data suggest that the finding of undetectable levels of HCV RNA after 12 weeks of treatment may be a better predictor of sustained virologic response among blacks.

The reason for the differences in response between black patients and non-Hispanic white patients with chronic hepatitis C remains unclear. In addition to the discrepancy in treatment responses, blacks also appear less likely to clear acute HCV infection.¹⁶ Recent analyses have noted differences in viral kinetics¹⁷ and increased iron stores¹⁸ among black patients with HCV infection. Differences in the immune response among racial and ethnic groups, however, have repeatedly been implicated as a potential explanation for the disparity in response rates. The presence of the HLA-DQB1*0301 allele has been associated with viral clearance, and work in an ethnically diverse cohort found that this association was strongest in black patients.¹⁹ Another study reported that black patients with HCV infection had higher levels of tumor necrosis factor α and interleukin-2 than white patients.²⁰ One study examined the response to HCV antigens and found that black patients had a greater CD4 proliferative T-cell response but surprisingly, did not have increased interferon- γ production. These findings suggest that the dysregulation of a CD4 T-cell effect or function may be related to HCV infection.²¹

Our findings demonstrate a limitation of current HCV therapy. Many novel therapies are under investigation, and our study highlights the importance of adequate enrollment of all racial and ethnic groups. Further research is also necessary to understand the poor response to therapy for chronic hepatitis C with interferon alfa among black patients, since such an understanding might lead to new therapies for all patients.

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Dr. Muir reports having received grant support from Schering-Plough and having served as a paid speaker for Schering-Plough. Dr. Bornstein reports having served as a paid speaker for Ortho Biotech and holding equity interests in Schering-Plough and GlaxoSmith-Kline. Dr. Killenberg reports having received grant support from Schering-Plough.

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APPENDIX

Members of the Atlantic Coast Hepatitis Treatment Group were as follows: F. Fowler, Charlotte, N.C.; J. Gilliam, Winston-Salem, N.C.; W. Harlan, Asheville, N.C.; J. Hayes, Greensboro, N.C.; S. Marcuard, Greenville, N.C.; J. McCone, Alexandria, Va.; J. Medoff, Greensboro, N.C.; J. Mertesdorf, Wilmington, N.C.; D. Newton, Greenville, N.C.; F. Pancotto, Concord, N.C.; G. Poleynard, Winston-Salem, N.C.; C. Riely, Memphis, Tenn.; J. Strohecker, Columbia, S.C.; T. Werth, Charlotte, N.C.; and D. Williams, Pinehurst, N.C.

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CORRECTION

Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites

Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites . On page 2266, in the right-hand column, lines 7 and 8 should have read "1000 mg of ribavirin (Rebetol, Schering-Plough) orally daily," rather than "twice daily," as printed. The Web version of the article has been corrected. We regret the error.