

## Peginterferon Alfa-2a and Ribavirin in Patients With Chronic Hepatitis C Who Have Failed Prior Treatment

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**Background & Aims:** The most effective therapy currently available for treatment of chronic hepatitis C virus (HCV) is the combination of peginterferon and ribavirin. This study evaluated the effectiveness of this treatment in patients who were nonresponders to previous interferon-based therapy. **Methods:** The first 604 patients enrolled in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial were evaluated. All were HCV RNA positive, previous nonresponders to interferon, with or without ribavirin, and had bridging fibrosis or cirrhosis on liver biopsy (Ishak fibrosis stage 3–6). Patients were retreated with peginterferon alfa-2a 180 µg/wk plus ribavirin 1000–1200 mg/day. Those with no detectable HCV RNA in serum at week 20 continued treatment for a total of 48 weeks and were then followed for an additional 24 weeks. **Results:** Thirty-five percent of patients had no detectable HCV RNA in serum at treatment week 20, and 18% achieved sustained virologic response (SVR). Factors associated with an SVR included previous treatment with interferon monotherapy, infection with genotypes 2 or 3, a lower AST:ALT ratio, and absence of cirrhosis. Reducing the dose of ribavirin from ≥80% to ≤60% of the starting dose during the first 20 weeks of treatment was associated with a decline in SVR from 21% to 11% ( $P \leq 0.05$ ). In contrast, reducing the dose of peginterferon or reducing ribavirin after week 20, when HCV RNA was already undetectable, did not significantly affect SVR. **Conclusions:** Selected nonresponders to previous interferon-based therapy can achieve SVR following retreatment with peginterferon alfa-2a and ribavirin.

The current optimal therapy for patients with chronic hepatitis C virus (HCV) infection is the combination of peginterferon and ribavirin. Data from 2 large, randomized, controlled trials have shown that peginterferon alfa-2a or peginterferon alfa-2b when combined with ribavirin achieved sustained virologic response (SVR) rates that were significantly greater than that achieved with standard interferon and ribavirin.<sup>1,2</sup> Additional benefits of peginterferons are that these agents can be administered once weekly and that they have more prolonged and potent antiviral activity even in patients with advanced fibrosis and cirrhosis.<sup>2–5</sup>

As the treatment for chronic hepatitis C has improved, the question has arisen as to whether patients who failed previous HCV treatment regimens should be retreated. Several recent studies involving retreatment have established that a small but significant increase in SVR resulted when nonresponders to prior interferon monotherapy were retreated with interferon and ribavirin.<sup>6–9</sup> Given the superior results observed with peginterferon and ribavirin in the treatment naive population, it is now appropriate to consider whether retreating previous nonresponders, particularly nonresponders to interferon and

*Abbreviations used in this paper:* HAI, Histologic Activity Index; HCV, hepatitis C virus; SVR, sustained virologic response.

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ribavirin, will be effective. Such treatment would be most advantageous for patients with advanced fibrosis or cirrhosis, who are at the highest risk for developing complications of advanced liver disease, including hepatocellular carcinoma.<sup>10–14</sup>

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial was designed to evaluate the clinical and histologic benefits of long-term peginterferon maintenance therapy in patients with advanced liver fibrosis or cirrhosis who failed previous efforts to achieve an SVR with optimal antiviral therapy. All patients entering this trial who were nonresponders to previous treatment with interferon, with or without ribavirin, were first retreated with peginterferon alfa-2a and ribavirin. Patients who had no detectable HCV RNA in serum at week 20 of this “lead-in phase” remained on combination therapy for 48 weeks and were monitored for SVR. This report describes the effects of retreatment with peginterferon alfa-2a and ribavirin and the factors associated with SVR in this population of nonresponders with advanced fibrosis and cirrhosis.

## Patients and Methods

The HALT-C trial is a prospective, randomized, controlled study of long-term peginterferon therapy vs. no treatment for patients with chronic hepatitis C and advanced fibrosis or cirrhosis who failed to achieve an SVR following treatment with peginterferon and ribavirin. The study is being conducted at 10 clinical centers in the United States. Randomization, data collection, and analyses are performed by a central data-coordinating center (New England Research Institutes, Watertown, MA), and all virologic testing is performed by a single laboratory (University of Washington, Seattle, WA).

### Patient Population

Qualification for admission to the study included a positive test for anti-HCV and HCV RNA in serum, a liver biopsy performed within 12 months of enrollment demonstrating either bridging fibrosis or cirrhosis (Ishak fibrosis score of 3–6), and evidence of nonresponse to the most recent treatment of standard interferon, with or without ribavirin. Nonresponse was defined as having detectable HCV RNA in serum after treatment for at least 12 weeks and within 4 weeks of completing therapy. Patients without documentation of virologic nonresponse were required to have had elevations in serum ALT levels prior to, during, and at the completion of therapy.

Patients were excluded if they had any other coexistent liver disorder identified by appropriate serologic, genetic, or histologic criteria. Those with coexistent steatohepatitis were excluded if this was judged to be severe on liver biopsy. Patients with >3+ iron on liver biopsy who did not have primary

hemochromatosis by genetic testing could enter the trial only after undergoing phlebotomy to reduce tissue iron to under 2+. Patients were also excluded if they had a Child-Turcotte Pugh score >6 or if they had a history of variceal hemorrhage, ascites, or hepatic encephalopathy. Additional exclusion criteria included reactivity to anti-HIV, active use of illicit injection drugs, ongoing regular excessive alcohol consumption, a history of an uncontrolled psychiatric condition, pregnancy, or a history of organ transplantation. Laboratory values that excluded patients from enrollment included a serum creatinine greater than 1.5 mg/dL, an absolute neutrophil count less than 1000/ $\mu$ L, a platelet count less than 50,000/ $\mu$ L, or a hemoglobin less than 11.0 gm/dL.

### Study Design

All patients were treated with peginterferon alfa-2a (Pegasys, Roche Laboratories, Nutley, NJ) at a dose of 180  $\mu$ g/week and ribavirin (Copegus, Roche Laboratories, Nutley, NJ), either 1000 mg/day (body weight  $\leq$ 75 kg) or 1200 mg/day (body weight >75 kg). Sixteen patients who were intolerant to ribavirin during previous therapy were started on lower doses of this drug. While on therapy, patients were evaluated at monthly intervals to monitor for side effects and changes in serum liver chemistries, complete blood count, and serum HCV RNA level. Patients with no detectable HCV RNA in serum at week 20 remained on peginterferon alfa-2a and ribavirin for 48 weeks regardless of HCV genotype and then were followed for an additional 24 weeks after discontinuation of therapy to assess for an SVR. Patients who remained HCV RNA positive entered the maintenance phase of the HALT-C Trial and were randomly assigned either to continue peginterferon alfa-2a alone at a reduced dose of 90  $\mu$ g/week for an additional 3.5 years or to discontinue both peginterferon and ribavirin and be followed on no specific therapy. The present study describes the clinical, biochemical, histologic, and virologic characteristics of the first 604 consecutive patients enrolled in the lead-in phase of the HALT-C Trial between August and December 2001.

### Definitions of Response

Virologic response was defined as the absence of detectable HCV RNA (<100 IU/mL) in serum at 20 weeks rather than the traditional 24 weeks after starting treatment. This interval was chosen to provide sufficient time for completion of virologic testing and randomization into the maintenance phase of the HALT-C Trial at week 24. Early virologic response (EVR) was defined as a 2 log or greater decline in serum HCV RNA level from the pretreatment baseline or the absence of detectable HCV RNA in serum at treatment week 12. End-of-treatment (EOT) virologic response was defined as absence of detectable HCV RNA in serum at treatment week 48. SVR was defined as absence of detectable serum HCV RNA at week 72, at least 24 weeks after treatment was discontinued.

## Dose Reduction

The dose of peginterferon alfa-2a was reduced stepwise from 180 to 135 to 90  $\mu\text{g}/\text{wk}$  and then to 45  $\mu\text{g}/\text{wk}$  if the neutrophil count declined to less than  $750/\text{mm}^3$  or the platelet count declined to less than  $40,000/\text{mm}^3$ . Ribavirin was reduced to 600 mg/day if the hemoglobin declined to 10 g/dL or by greater than 4 g/dL from the pretreatment baseline. Further dose reductions or discontinuation of one or both drugs could be performed at the discretion of the various investigators at each of the clinical centers for ongoing hematologic adverse events, severe flu-like symptoms, neuropsychiatric, cutaneous, and other adverse effects thought to be related to these medications. The doses of peginterferon and ribavirin could be increased back to the starting doses if these adverse events resolved. The use of hematologic growth factors, such as erythropoietin alfa or granulocyte-macrophage stimulating factor, were not permitted during the first 20 weeks of treatment. Eight patients who had undetectable HCV RNA in serum at week 20 received growth factor support between weeks 21 and 48.

The doses of both peginterferon and ribavirin actually taken by each patient during the course of the study were evaluated by reviewing nursing records and patient diaries. This process captured physician-directed dose reductions for adverse events and doses missed by patients for both medical and nonmedical reasons. The amount of each medication taken by each patient during the first 20 weeks was expressed as a percentage of the total prescribed dose (target dose), calculated as  $180 \mu\text{g} \times 20$  weeks for peginterferon alfa-2a and either  $1000$  or  $1200 \text{ mg} \times 140$  days for ribavirin. The amount of drug received during weeks 21 to 48 was calculated in a similar fashion.

## Liver Histology

All patients underwent liver biopsy within 12 months of enrollment. Biopsy specimens were reviewed by a team of pathologists representing each of the clinical centers participating in this trial. All biopsy specimens were assigned an inflammatory and fibrosis score based on the criteria of Ishak et al.<sup>14</sup> and assessed for steatosis by criteria similar to that developed by Brunt et al.<sup>15</sup> All specimens were also stained with Prussian blue. Estimates of hepatocellular iron were made by a system similar to that described previously.<sup>16</sup>

## Assessment of HCV RNA

Serum was collected for detection of HCV RNA twice prior to therapy; at weeks 12, 20, 36, and 48, following the start of therapy; and at weeks 60 and 72 (12 and 24 weeks following discontinuation of therapy). All samples were frozen at  $-70^\circ\text{C}$  and shipped to the virology core laboratory at the University of Washington for analysis. The level of HCV RNA in serum was determined with the quantitative COBAS Amplicor HCV Monitor test v.2.0 (Roche Molecular Systems, Branchburg, NJ). Patient specimens were initially tested after 1:100 dilution with HCV RNA-negative plasma; if the HCV RNA level was below the limit of detection in the diluted

specimen, the sample was retested without dilution. All samples with undetectable HCV RNA were retested with the qualitative COBAS Amplicor HCV Test, v. 2.0 assay (Roche Molecular Systems), which has a sensitivity of 100 IU/mL. Serum specimens collected at treatment week 20 were tested in duplicate with the qualitative assay to identify patients who achieved a virologic response during treatment. HCV genotype was determined with the INNO-LiPA HCV II kit (Bayer Diagnostics, Emeryville, CA).

## Statistical Analysis

Predictors of virologic response were assessed with  $\chi^2$  tests and *t* tests. Predictors that were related to response in univariate analyses were entered into a multivariate logistic regression to assess their relative importance. Analyses were performed using the Statistical Analysis System version 8.2.

## Results

### Patient Population

The study population consisted of the first 604 patients enrolled in the lead-in phase of the HALT-C trial between August 2000 and December 2001. The demographic and clinical characteristics of these patients are summarized in Table 1. All patients were nonresponders to their most recent course of interferon-based therapy. Sixty-four percent had been previously treated with interferon and ribavirin. The mean age of the patients was 49.9 years; 73% were male and 77% white. The average estimated duration of HCV infection was 26.5 years. Serum ALT values averaged 2.37 times the upper limit of the normal range for each local laboratory, and 10% of the patients had a normal ALT level at screening. Eighty-nine percent were infected with HCV genotype 1. The mean serum level of HCV RNA was  $\log_{10}$  6.46 IU/mL, and 75% had an HCV RNA level greater than 1.5 million IU/mL. The mean Histologic Activity Index (HAI) score was 7.46 and cirrhosis (Ishak fibrosis score of 5 or 6) was present in 39%.

### Response to Therapy

Virologic response rates to retreatment with peginterferon alfa-2a and ribavirin are summarized in Table 2. Thirty-four of the 604 patients (5.6%) withdrew from the trial before week 20 (24 for adverse events, 2 hepatic decompensation, 5 decided not to continue participation, and 3 were lost to follow-up). At treatment week 20, 360 patients (60%) had detectable HCV RNA in serum and were eligible for randomization into the maintenance phase of the HALT-C Trial. The remaining 210 patients (35%) had no detectable HCV RNA in serum at week 20 and remained on therapy. During the

**Table 1.** Demographic and Clinical Characteristics of Study Population

	Mean $\pm$ SD (range) or N (%)
N	604
Age (yr)	49.9 $\pm$ 7.5 (19–80)
Race and ethnicity (%)	
White	466 (77)
Black	84 (14)
Hispanic	39 (6)
Other	15 (3)
Male	438 (73)
Body weight (kg)	89.2 $\pm$ 18.1 (48–191)
Body mass index (kg/m <sup>2</sup> )	29.7 $\pm$ 5.4 (18–58)
Serum aminotransferases	
ALT ( $\times$ ULN)	2.37 $\pm$ 1.71 (0.43–17.2)
AST/ALT ratio	0.84 $\pm$ 0.29 (0.33–2.72)
Estimated duration of infection (yr)	26.5 $\pm$ 7.8 (3–53)
Prior nonresponse to interferon and ribavirin	385 (64)
Serum HCV RNA (IU/mL)	
Mean serum level	4.76 $\times 10^6 \pm 4.57 \times 10^6$ (3.66 $\times 10^3$ –3.32 $\times 10^7$ )
Mean of log <sub>10</sub> serum level >1.5 $\times 10^6$ (%)	6.46 $\pm$ 0.51 (3.6–7.5) 452 (75)
Genotype	
1	539 (89)
2	31 (5)
3	26 (4)
Other	6 (1)
Not typeable	2 (0.3)
Histology	
Histologic activity index	7.46 $\pm$ 2.05 (1–14)
Cirrhosis	233 (39)
Hematology	
White blood cells ( $\times 1000/\mu\text{L}$ )	5.82 $\pm$ 1.76 (2.6–13.5)
Neutrophils ( $\times 1000/\mu\text{L}$ )	3.11 $\pm$ 1.23 (0.8–10.7)
Hemoglobin (g/dL)	15.1 $\pm$ 1.3 (10.7–19.5)
Platelets ( $\times 1000/\mu\text{L}$ )	166.0 $\pm$ 58.7 (57–421)

remaining 28 weeks of treatment, 18 (3%) of these patients developed virologic breakthrough and became HCV RNA positive. The remaining 192 patients (32%) achieved an EOT response and remained HCV RNA negative in serum through week 48. Following discontinuation of peginterferon and ribavirin, virologic relapse occurred in 78 patients (41%). Another 5 patients withdrew from the study before week 72. Thus, SVR was observed in 109 (18%) patients.

Factors that correlated with week 20, EOT and sustained virologic responses are listed in Table 2. Factors identified by univariate analysis to be associated with an EOT response included previous treatment with interferon monotherapy ( $P < 0.0001$ ), race other than black ( $P < 0.0001$ ), age less than 60 years ( $P = 0.0002$ ), HCV genotypes 2 or 3 ( $P < 0.0001$ ), absence of cirrhosis ( $P = 0.0002$ ), and an AST:ALT ratio of less than 1.0 ( $P < 0.0001$ ). When all of these variables were included in a multivariate regression analysis, only previous treatment

with interferon monotherapy, HCV genotype 2 or 3, an AST:ALT ratio less than 1.0, absence of cirrhosis on liver biopsy, and white race were associated with an increased probability for EOT virologic response.

Univariate analysis showed that factors associated with an SVR were previous treatment with interferon monotherapy ( $P < 0.0001$ ), race other than black ( $P = 0.0019$ ), HCV genotypes 2 or 3 ( $P < 0.0001$ ), baseline serum HCV RNA levels of less than 1.5 million IU/mL ( $P = 0.0012$ ), absence of cirrhosis ( $P = 0.0004$ ), and an AST:ALT ratio less than 1.0 ( $P < 0.0001$ ). Body weight, BMI, HAI score, or baseline values for total white blood cell count or neutrophil count did not correlate with SVR. Among patients with an EVR at week 12, 34% went on to achieve SVR. In contrast, only 3 patients who did not achieve a week 12 EVR had a subsequent SVR ( $P < 0.0001$ ). When these baseline variables were entered into a multivariate regression analysis, previous treatment with interferon monotherapy, genotype 2 or 3, a serum HCV RNA level less than 1.5 million IU/mL, an AST:ALT ratio less than 1.0, and the absence of cirrhosis on liver biopsy were associated with an increased probability of SVR.

Because the great majority of patients with previous nonresponse to interferon-based therapy were infected with HCV genotype 1 (89%), an analysis of factors associated with virologic response in these patients was performed. The same factors identified in the analysis of the entire cohort were found to be significant for patients with genotype 1 (data not shown). Patients with multiple poor prognostic factors had the lowest rate of SVR. For example, of the 82 genotype 1 white patients with cirrhosis, previously treated with interferon and ribavirin, and with baseline HCV RNA greater than  $1.5 \times 10^6$  IU/mL, the SVR was only 6%.

### Adverse Events

Adverse effects requiring reduction in either the dose of peginterferon alfa-2a or ribavirin to less than 96% of the originally prescribed dose are summarized in Table 3. Sixteen patients who were started on less than the full dose of ribavirin, 7 patients who were started on less than the full dose of peginterferon, and 8 patients who were lost to follow-up or who refused to continue in the study were excluded from these analyses. Of the remaining 573 patients, 84 (15%) required a reduction only in the dose of peginterferon, 103 (18%) required a reduction only in the dose of ribavirin, and 122 (21%) required a reduction in the dose of both medications. However, only 7% of patients required discontinuation of ribavirin alone, 0.3% peginterferon alone, and 3%

**Table 2.** Characteristics Associated With Virologic Response

	N	Week 20 response <sup>a</sup> (%)	Week 48 response <sup>a</sup> (%)	Week 72 response <sup>a</sup> (%)
Overall population	604	35	32	18
Prior treatment		<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
Interferon alone	219	47	44	28
Interferon and ribavirin	385	28	25	12
Race and Ethnicity <sup>b</sup>		<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> = 0.0019
White	466	38	35	20
Black	84	11	10	6
Hispanic	39	49	41	18
Other	15	40	40	33
Age		<i>P</i> = 0.0003	<i>P</i> = 0.0002	<i>P</i> = 0.0107
<60 years	541	37	34	19
≥60 years	63	14	11	6
HCV genotype <sup>c</sup>		<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
1	539	30	27	14
2	31	81	81	65
3	26	81	77	54
Others	6	33	33	17
Baseline HCV RNA (IU/mL)		<i>P</i> = 0.11	<i>P</i> = 0.12	<i>P</i> < 0.0009
≥1.5 × 10 <sup>6</sup>	452	33	30	15
<1.5 × 10 <sup>6</sup>	152	40	37	27
Cirrhosis		<i>P</i> = 0.0004	<i>P</i> = 0.0002	<i>P</i> = 0.0005
Yes	233	26	23	11
No	371	40	37	23
AST/ALT		<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
>1.0	122	19	17	6
≤1.0	482	39	35	21
Body mass index (kg/m <sup>2</sup> )		<i>P</i> = 0.17	<i>P</i> = 0.14	<i>P</i> = 0.46
<25	109	38	35	22
25–29	239	37	34	18
30+	254	32	28	17
Early virologic response <sup>d</sup>		<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
Yes	309	66	61	34
No	295	2	1	1

<sup>a</sup>Response is defined as HCV RNA undetectable at treatment weeks 20, 48, or 72.

<sup>b</sup>*P* value is for a comparison of black vs. others.

<sup>c</sup>*P* value is for a comparison of genotype 2 or 3 vs. others.

<sup>d</sup>Early virologic response was defined as a 2 log<sub>10</sub> decline in HCV RNA from baseline or HCV RNA undetectable at treatment week 12.

both medications. The most common adverse effects leading to dose reduction or discontinuation included hematologic abnormalities, neuropsychiatric events, fatigue, flu-like, and other nonspecific symptoms. Infections requiring dose reduction of peginterferon occurred in 1% of patients. No other single reason for dose reduction was present in greater than 1% of patients.

### Effect of Dose Reduction

The effect of reducing the dose of peginterferon or ribavirin on virologic response is summarized in Table 4. For these analyses, the amount of peginterferon alfa-2a and ribavirin taken by each patient was expressed as a percentage of the originally prescribed or target dose. Reducing the dose of peginterferon alfa-2a during the first 20 weeks of treatment from greater than 80% to less

than 60% of the target dose did not appear to impact significantly either virologic response at week 20 (response declined from 38% to 32%) or SVR (response declined from 20% to 13%). In contrast, reducing the dose of ribavirin from greater than 80% to less than 60% of the target dose during the first 20 weeks of treatment significantly reduced the week 20 virologic response (response declined from 38% to 26%; *P* = 0.041) and SVR (response declined from 21% to 11%; *P* = 0.031). A reduction in the doses of either peginterferon alfa-2a or ribavirin after week 20, when patients already had no detectable HCV RNA in serum, had no significant impact on SVR. The mean ± SD doses of peginterferon alfa-2a (166 ± 25 vs. 162 ± 31 μg/wk, respectively) or ribavirin (1048 ± 176 vs. 1007 ± 251 mg/day, respectively) taken during the first 20 weeks by patients with

**Table 3.** Indications for Dose Reduction

Reason	Peginterferon alfa-2a (n = 573) <sup>a</sup>	Ribavirin (n = 573) <sup>a</sup>
	N (%)	N (%)
Dose reduced for any reason <sup>b</sup>	206 (36)	225 (39)
Anemia, neutropenia, or thrombocytopenia	158 (28)	136 (24)
Depression, anxiety, confusion, or insomnia	22 (4)	15 (3)
Fatigue	30 (5)	34 (6)
Flu syndrome	16 (3)	13 (2)
Dizziness or syncope	10 (2)	16 (3)
Shortness of breath or cough	5 (1)	35 (6)
Nausea, vomiting, diarrhea, or abdominal pain	7 (1)	28 (5)
Rash	8 (1)	24 (4)
Infection	5 (1)	5 (1)
Other adverse events or symptoms <sup>c</sup>	23 (4)	32 (6)
Other reasons unrelated to adverse events	5 (2)	17 (3)

<sup>a</sup>Excludes 7 patients started on less than full-dose peginterferon alfa-2a, 16 patients started on less than full-dose ribavirin, and 8 patients who withdrew from the study or were lost to follow-up.

<sup>b</sup>Reasons are tabulated for only those patients who received less than 96% of the prescribed doses of peginterferon alfa-2a or ribavirin. Doses may have been reduced for multiple reasons.

<sup>c</sup>No single adverse event resulting in dose reduction occurred in greater than 1% of patients.

an SVR and those who failed to achieve SVR were not significantly different.

## Discussion

Impressive gains have been made in the treatment of chronic hepatitis C virus infection during the past decade. The currently accepted primary end point of therapy is an SVR. With the combination of peginterferon and ribavirin, this can be achieved in 40%–45% of patients with HCV genotype 1 and approximately 80% of patients with genotype 2 or 3 infection.<sup>1,2</sup> These are significantly improved outcomes when compared with those achieved with standard interferon monotherapy or interferon and ribavirin, particularly in patients with HCV genotype 1.<sup>1,2,17</sup> As a result, many patients who were nonresponders to these previous therapies are now considered candidates for retreatment with the more effective regimen. In the present study, a substantial proportion of previous nonresponders (35%) became HCV RNA undetectable during retreatment despite having a profile associated with poor response (a high percentage of patients were HCV genotype 1 with high baseline serum levels of HCV RNA and advanced fibrosis or cirrhosis). Unfortunately, a large proportion relapsed when therapy was stopped, and SVR was observed in only 18% of the total cohort. Factors associated with an

SVR included previous treatment with interferon monotherapy, infection with HCV genotypes 2 or 3, a baseline level of HCV RNA greater than  $1.5 \times 10^6$  IU/mL, and the absence of cirrhosis. As observed in previous studies, black patients had a low rate of response; only 6% achieved SVR. The lowest likelihood of response occurred in patients who had multiple poor prognostic factors. White patients with HCV genotype 1, cirrhosis, a serum HCV RNA greater than  $1.5 \times 10^6$  IU/mL, and who were previous nonresponders to interferon and ribavirin combination therapy had an SVR of only 6%.

The rate of relapse in this cohort of patients, nearly 50%, was approximately twice the 15%–20% rate reported in studies of treatment naive patients. A high rate of relapse has been found commonly in studies of retreatment.<sup>7,8</sup> However, the reasons for this observation remain obscure and require further study. A potential contributing factor was the high rate of ribavirin dose reduction in this study, nearly 40% compared with only about 20% in 2 large clinical trials in treatment naive patients with less advanced liver disease.<sup>1,2</sup> However, the major difference was that the present study was confined to previous nonresponders, who may simply be incapable of achieving long-term viral eradication and an SVR.

**Table 4.** Effect of Dose Reductions on Virologic Response

	N	Week 20 response <sup>a</sup> (%)	Week 72 response <sup>a</sup> (%)
Dose reductions during weeks 1–20			
Overall population <sup>b</sup>	565	36	19
Peginterferon dose		<i>P</i> = 0.25 <sup>c</sup>	<i>P</i> = 0.22 <sup>c</sup>
>80%	446	38	20
61%–80%	66	29	18
≤60%	53	32	13
Ribavirin dose		<i>P</i> = 0.041 <sup>c</sup>	<i>P</i> = 0.031 <sup>c</sup>
>80%	403	38	21
61%–80%	88	36	17
≤60%	74	26	11
Dose reductions during weeks 21–48			
Overall population <sup>d</sup>	205		53
Peginterferon dose			<i>P</i> = 0.81 <sup>c</sup>
>80%	125		50
61%–80%	40		68
≤60%	40		48
Ribavirin dose			<i>P</i> = 0.32 <sup>c</sup>
>80%	123		55
≤60%	47		47
61%–80%	35		54

<sup>a</sup>Response is defined as no detectable HCV RNA in serum.

<sup>b</sup>This analysis excludes patients for whom HCV RNA results are missing at week 20 or week 72.

<sup>c</sup> $\chi^2$  test for trend.

<sup>d</sup>This analysis includes only patients who had no detectable HCV RNA in serum at week 20 and were not withdrawn from the study before week 72.

Patients who achieve an EVR, defined by a  $2 \log_{10}$  (100-fold) or greater decline in the serum level of HCV RNA or no detectable HCV RNA within the first 12 weeks of treatment, have a higher likelihood of achieving an SVR.<sup>2,18</sup> In contrast, an SVR is only rarely seen in patients who do not have an EVR. Identical findings were observed during retreatment of nonresponders in the present study; 35% of patients with an EVR went on to achieve an SVR, whereas an SVR occurred in only 3 patients (1%) without an EVR.

The adverse effect profile of antiviral therapy in this cohort of patients with advanced liver disease was similar to that previously described in other studies including a trial of peginterferon alfa-2a monotherapy in patients with advanced fibrosis and cirrhosis.<sup>1,2,5</sup> Adverse effects leading to dose reduction or discontinuation of therapy were predominately hematologic, neuropsychiatric, systemic flu-like symptoms, and fatigue. Of note, no major episodes of spontaneous bleeding occurred despite the fact that patients could enroll in this study with a baseline platelet count as low as  $50,000/\text{mm}^3$  and that dose reduction was mandated only if the platelet count fell to  $40,000/\text{mm}^3$  or less during therapy. Furthermore, despite a mean baseline neutrophil count of only  $3.1 \times 10^3/\text{mm}^3$ , only 1% of patients enrolled into the study required dose reduction for bacterial infections, and no relationship between neutrophil count and infectious complications was observed.

Adherence to therapy has recently been identified as an important determinant of an SVR.<sup>1,18,19</sup> In these studies, noncompliance was defined as a dose reduction in either interferon or ribavirin to less than 80% of the original prescribed dose or discontinuation of treatment prior to receiving 80% of the planned duration of therapy. The primary reason for noncompliance in these studies was physician-directed dose reduction for management of treatment-related adverse events. In addition, once dose reduction was performed, the dose of interferon, peginterferon, or ribavirin was not increased. Genotype 1 patients who did not require dose reduction had a significantly higher SVR when compared with patients who were instructed to reduce their dose. Patients who were unable to adhere to full dose therapy within the first 12 weeks after initiating treatment had a lower rate of SVR compared with patients who required dose reduction after week 12.<sup>19</sup> Furthermore, the EVR was significantly lower in patients whose ribavirin dose had to be reduced within the first 12 weeks of therapy, whereas the EVR was not significantly affected by reducing the dose of peginterferon during this same time interval.<sup>18</sup> However, these studies did not evaluate the relative importance of

reducing these 2 medications independently, the effect of reducing these medications by variable amounts, or the timing of the dose reduction on SVR. In the present study, the total dose of peginterferon alfa-2a and ribavirin taken by each patient was assessed independently and expressed as a percentage of the starting or target dose. By calculating dose reduction in this manner, the effect of missed doses, dose reductions, and subsequent dose increases were taken into account. Reducing the dose of peginterferon alfa-2a from greater than 80% to less than 60% of the target dose within the first 20 weeks of treatment did not appear to affect either virologic response at week 20 or SVR. Reducing the dose of ribavirin from greater than 80% to less than 60% of the target dose within the first 20 weeks of therapy was associated with a significant reduction in both week 20 virologic response and SVR. In contrast, reducing the dose of either peginterferon alfa-2a or ribavirin after week 20, when patients already had undetectable serum HCV RNA, had no significant effect on SVR. These observations have important implications for the use of hematologic growth factors as adjuvant therapy in the treatment of chronic hepatitis C, as has recently been advocated.<sup>20</sup> A more detailed evaluation of the impact that reducing peginterferon and ribavirin has on both virologic response and SVR is therefore warranted.

Although treatment with peginterferon and ribavirin has dramatically improved the outcome for patients with HCV,<sup>1,2</sup> over half of all patients with genotype 1 infection fail to achieve SVR. Nonresponders with advanced fibrosis or cirrhosis remain at increased risk for fibrosis progression, decompensation, and hepatocellular carcinoma and may require liver transplantation.<sup>11-13</sup> A previous study has suggested that continuing interferon as maintenance therapy in these nonresponders may reduce the rate of fibrosis progression.<sup>21</sup> The HALT-C Trial is a prospective, randomized, controlled study designed to determine whether continuing peginterferon alfa-2a as maintenance therapy for an additional 3.5 years can significantly delay fibrosis progression and reduce the risk for hepatic decompensation and hepatocellular carcinoma and the need for liver transplantation. Nearly all patients who failed to achieve an SVR during the "lead-in" phase of the HALT-C Trial, described in this report, have been randomized to continue peginterferon alfa-2a at a dose of  $90 \mu\text{g}/\text{week}$  or to be followed in an untreated control group. The merits of maintenance interferon therapy will not become apparent until the completion of this trial.

In conclusion, the results from the "lead-in" phase of the HALT-C Trial have provided valuable insight into

the management of patients with chronic hepatitis C infection. Even though the SVR in this nonresponder population was low, several factors that increased the likelihood of an SVR were identified. These factors included previous treatment with only interferon monotherapy, HCV genotypes 2 or 3, and serum HCV RNA levels of less than  $1.5 \times 10^6$  IU/mL. In addition, because reducing the dose of peginterferon appeared to have little effect on SVR, the initial response to treatment-induced neutropenia or thrombocytopenia should be to reduce the interferon dose, rather than to initiate growth factor support. In contrast, SVR was adversely affected by reducing the dose of ribavirin during the first 20 weeks of therapy. Studies to determine whether virologic response rates could be improved by utilizing erythropoietic growth factors during this time period, as opposed to reducing the ribavirin dose, should be undertaken in this difficult to treat patient population.

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