Impact of Disease Severity on Outcome of Antiviral Therapy for Chronic Hepatitis C: Lessons From the HALT-C Trial

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In patients with chronic hepatitis C, advanced fibrosis and cirrhosis are associated with lower rates of sustained virologic response (SVR) to interferon (IFN)-based therapy. In this study, we assessed virologic response to retreatment with peginterferon alfa-2a and ribavirin (RBV), as a function of the baseline fibrosis score (Ishak staging) and platelet count, in 1,046 patients enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial. All patients had failed prior treatment with IFN or peginterferon ± RBV and had Ishak fibrosis scores ≥ 3. Four groups of patients with increasingly severe liver disease were compared: (A) bridging fibrosis (Ishak 3 and 4) with platelet counts >125,000/mm^3 (n = 559); (B) bridging fibrosis with platelet counts ≤125,000/mm^3 (n = 96); (C) cirrhosis (Ishak 5 and 6) with platelet counts >125,000/mm^3 (n = 198); and (D) cirrhosis with platelet counts ≤125,000/mm^3 (n = 193). SVR rates were 23%, 17%, 10%, and 9% in groups A, B, C, and D, respectively ($P < .0001$ for trend). Reduction in SVR as a function of increasingly severe disease was independent of age, percent African American, HCV genotype, HCV level, and type of prior therapy. Dose reduction lowered SVR frequencies, but to a lesser extent than disease severity. By logistic regression, cirrhosis ($P < .0001$) was the major determinant that impaired virologic response, independent of dose reduction or platelet count. In conclusion, disease severity is a major independent determinant of rate of SVR in patients with advanced chronic hepatitis C. New strategies are needed to optimize antiviral therapy in these "difficult-to-cure" patients. (HEPATOLOGY 2006;44:1675-1684.)

Abbreviations: HCV, hepatitis C virus; RBV, ribavirin; SVR, sustained virologic response; PEG-IFN, pegylated interferon; INR, international normalized ratio.

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Currently, more than 2.7 million persons living in the United States are actively infected with the hepatitis C virus (HCV), and an estimated 8,000 to 10,000 deaths each year are attributable to complications of chronic hepatitis C.[1-3] Modeling, based on the age-stratified prevalence of HCV infection and the known natural history of chronic hepatitis C, suggests that the number of persons infected for 20 or more years will continue to rise and peak in 2015.[4] As a consequence, cases who decompensate, advance to hepatocellular carcinoma, and need liver transplantation will increase dramatically over the ensuing decade.[5-10]

Antiviral therapy of chronic hepatitis C has improved substantially[11]; however, virologic responses are lower in patients with advanced hepatic fibrosis or cirrhosis. Results of trials involving pegylated interferons-alfa 2a or 2b in combination with ribavirin (RBV) showed that sustained virologic response (SVR) rates ranged from 41% to 44% in patients with bridging fibrosis or cirrhosis, compared with an SVR of up to 65% in those with less advanced hepatic fibrosis.[12-14] All of these studies involved patients not previously treated and included persons with compensated cirrhosis who were clinically and biochemically stable. Reasons for diminished virologic responses in patients with cirrhosis are incompletely defined.

The ongoing Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial is examining the impact of treatment in persons with chronic hepatitis C and advanced hepatic fibrosis.[15] Persons eligible for this trial had to have histologically documented bridging fibrosis or cirrhosis and to have failed to respond to prior antiviral treatment. Eligible patients were treated during a lead-in phase with pegylated interferon (PEG-IFN) alfa-2a plus RBV. In this report, we analyze the relationship between the severity of liver disease at baseline and the virologic response to treatment during the lead-in phase of the trial.

Patients and Methods

The HALT-C Trial is being conducted at 10 clinical centers in the United States; details of the study design and entry criteria have been reported previously.[15] The study protocol was approved by the institutional review board at each participating center, and written consent was obtained from all patients.

Patient Population. Study patients had detectable HCV RNA in serum and histological evidence of either bridging fibrosis (Ishak score 3 or 4) or cirrhosis (Ishak score 5 or 6) within 12 months of enrollment. Patients were also required to have evidence of nonresponse to their most recent course of treatment with a minimum of 12 weeks of standard interferon, 3 MU thrice weekly, with or without RBV. A small number of nonresponders to PEG-IFN monotherapy (n = 38) or PEG-IFN/RBV (n = 61) were enrolled. Exclusions to enrollment were other co-existent liver disorders, a liver biopsy displaying 3 or 4+ stainable iron (Prussian blue stain),[16] a Child-Turcotte-Pugh score ≥ 7; human immunodeficiency virus positivity; or a history of variceal hemorrhage, ascites, or hepatic encephalopathy. Baseline laboratory values that excluded patients from enrollment included a serum creatinine >1.5 mg/dL, absolute neutrophil count $<1{,}000/mm^3$, platelet count $<50{,}000/mm^3$, or hemoglobin level <11.0 g/dL. A total of 1,145 patients entered the HALT-C trial, but only patients with HCV RNA results at week 20 on treatment and at week 72 during follow-up (n = 1,046) were included in this analysis.

Defining Severity of Liver Disease. Severity of liver disease was categorized, a priori, according to the Ishak fibrosis score on baseline liver biopsy and platelet count. The platelet count was included in our model of disease severity to detect two sets of patients not readily definable by other means: those with presumed cirrhosis but whose liver biopsy demonstrated only fibrosis due to sampling error, and those who truly lacked histological cirrhosis but who had advanced fibrosis and portal hypertension.

Both Ishak fibrosis score and platelet count correlated strongly with serum bilirubin and albumin, prothrombin time/international normalized ratio (INR), endoscopic findings of portal hypertensive gastropathy or varices, and ultrasonographic evidence of splenomegaly ($P < .0001$ for all). The cutoff we chose for platelet count was defined by the median platelet count of trial patients with cirrhosis, which was $125{,}000/mm^3$. Two histological groups, showing either fibrosis (Ishak score 3 or 4) or cirrhosis (Ishak score 5 or 6), were further subdivided into those with platelet counts of $>$ or $\leq 125{,}000/mm^3$, yielding group A, patients with fibrosis and platelet counts $>125{,}000/mm^3$; group B, patients with fibrosis and platelet counts $\leq 125{,}000/mm^3$; group C, patients with cirrhosis and platelet counts $>125{,}000/mm^3$; and group D, patients with cirrhosis and platelet counts $\leq 125{,}000/mm^3$.

Study Design. Patients were treated with PEG-IFN (Pegasys, Roche Laboratories, Nutley, NJ) and RBV (Copegus, Roche Laboratories, Nutley, NJ). Twelve of the 1,046 patients were intolerant of RBV during previous therapy and did not receive RBV, and 15 additional patients were started on lower doses of RBV. During treatment, patients were monitored monthly for side effects and changes in serum tests of liver chemistry, complete blood counts, and serum HCV RNA levels.

Definitions of Response. Hepatitis C virus RNA was considered undetectable based on a value of <100 IU/mL

by the Roche COBAS Amplicor HCV Test, v. 2.0. To provide sufficient time for completion of virologic testing and randomization into the maintenance phase of the HALT-C Trial by week 24, we defined on-treatment response as negative serum HCV RNA at week 20 (VR20).[15] SVR was defined as the absence of detectable serum HCV RNA at week 72, 24 weeks after discontinuation of treatment.

Dose Reduction

According to protocol, the dose of PEG-IFN was reduced stepwise from 180 to 135 to 90 and then to 45 μg/week if the neutrophil count declined to $<750/mm^3$ or the platelet count to $<50{,}000/mm^3$. Ribavirin was reduced from 1,000 or 1,200 to 600 mg/d if the hemoglobin declined to 10 g/dL or by more than 4 g/dL from the pretreatment baseline. Investigators managing the patient could reduce doses or discontinue one or both drugs for other clinical reasons. Prior doses of PEG-IFN and RBV could be reinstituted if adverse events or cytopenias resolved.

The doses of both PEG-IFN and RBV actually taken by each patient were evaluated by reviewing nursing records and patient diaries.[15] The amounts taken by each patient during the first 20 weeks were expressed as a percentage of the target doses. The target doses were 180 μg/wk PEG-IFN and 1,000 or 1,200 mg/d RBV. Dose discontinuation was defined as permanently stopping RBV by week 16. In patients who did not discontinue therapy, the actual amounts received were categorized as full doses if they exceeded 80% of the target doses of both PEG-IFN and RBV and as reduced doses if they were less than 80% of the target doses.

Liver Histology. Biopsy specimens were reviewed by a team of pathologists representing each of the clinical centers participating in this trial. Length and fragmentation were determined, and all biopsies were assigned an inflammatory and fibrosis score based on the criteria of Ishak.[17] The degree of steatosis and intensity of iron staining were quantified.[16,18]

Assessment of HCV RNA

All serum samples were frozen at $-70°C$ and shipped to the virology core laboratory at the University of Washington for analysis.[15] Samples negative by quantitative COBAS Amplicor HCV Monitor test v.2.0 (Roche Molecular Systems, Branchburg, NJ) were retested with the qualitative COBAS Amplicor HCV Test, v. 2.0 assay (Roche Molecular Systems, Branchburg, NJ), which has a sensitivity of 100 IU/mL.

Statistical Analyses

Chi-square and ANOVA were used to identify variables that were significantly different among the four patient groups, A through D. Predictors of virologic response were assessed with chi-square tests and *t* tests. Predictors that were related to response in univariate analyses were entered into multivariate logistic regression to assess their relative importance. The linear relationship between response and the four groups was assessed by a logistic regression with the four groups coded 1 to 4. Analyses were performed with the Statistical Analysis System version 9.1.

Results

Characterization of Study Groups

Patient characteristics of the four study groups are shown in Table 1. Mean age, ethnicity, type of prior therapy, percentage of patients with a history of drinking alcohol or of smoking, and use of nearly all medications were similar among the four groups. Body mass index was slightly higher in the groups with cirrhosis ($P < .04$ for linear trend).

The lifetime number of alcoholic drinks increased from groups A to D ($P < .03$), but the proportion of patients using alcohol at baseline was greatest in group A, the group with the least severe disease $P < .004$). Thus, no consistent relationship was apparent between alcohol exposure and severity of liver disease. Highly significant linear increases were found in the Beck Depression Index (6.7-8.3) and use of nonselective β-blockers (2%-8%) for treatment of portal hypertension from groups A to D ($P = .0081$ and $P = .0004$, respectively).

Baseline laboratory, histologic, ultrasonographic, and endoscopic results are given in Table 2. Fewer patients in group B were infected with HCV genotype 1 ($P = .02$). HCV RNA levels linearly declined from groups A to D ($P < .0001$). Patients in groups B and D had lower mean white blood counts (WBC, $P < .0001$), absolute neutrophil counts ($P < .0001$), hemoglobin levels ($P = .0016$), and platelet counts. Linear regression analysis demonstrated that the serum bilirubin, INR, and aspartate aminotransferase:alanine aminotransferase ratio increased while serum albumin decreased from group A to group D ($P < .0001$ for all); however, results of these standard tests were very similar between groups B and C. The proportion of patients with a history of diabetes or glucose > 126 mg/dL ($P = .02$) and the mean homeostasis model assessment score ($P = .01$) were both lower in group A than in other groups.

Ishak inflammation score ($P < .0001$) and Ishak fibrosis score increased from groups A to D, whereas the grade of hepatic iron was similar among the four groups. Pa-

Table 1. Selected Baseline and Clinical Features of Study Groups

∴	Group A Fibrosis Plt. > 125K	Group B Fibrosis Plt. ≤ 125K	Group C Cirrhosis Plt. > 125K	Group D Cirrhosis Plt.≤ 125K	P^1	P^2
Number of patients	559	96	198	193		
Demographics						
Age, years	49.5	50.5	50.5	50.2	.28	.33
Female	28%	25%	34%	21%	.03	.31
Black	18%	8%	15%	13%	.08	.11
Body Mass Index	29.4	29.4	30.2	30.2	.19	.04
Prior treatment						
Previous combination therapy	72%	72%	75%	69%	.56	.99
ETOH						
Ever drank	83%	83%	84%	87%	.74	.33
Total number of drinks in lifetime	16,324	18,986	19,379	22,593	.10	.01
Drinking at baseline	22%	11%	9%	19%	.0006	.03
Smoking history						
Ever smoked	77%	67%	79%	75%	.13	.79
Smoke cigarettes now	31%	21%	30%	33%	.20	.73
Pack-years of cigarettes	15.1	11.7	14.3	13.0	.18	.14
Depression						
Beck BDI Depression score	6.7	7.2	7.9	8.3	.04	.004
Medications at Baseline						
NSAID	8%	4%	9%	6%	.33	.34
Cox2 Inhibitors	4%	2%	4%	4%	.86	.99
Any anti-hypertensive	29%	38%	34%	38%	.09	.02
Selective β-blocker	7%	10%	10%	13%	.03	.004
Nonselective β-blocker	2%	4%	4%	8%	.003	.0004
ACE inhibitors	9%	14%	16%	13%	.06	.03
Thiazide diuretics	13%	16%	15%	17%	.67	.23
Hypoglycemics	11%	15%	15%	15%	.36	.11
Antidepressants/anxiolytics	30%	29%	31%	33%	.92	.50
Anxiolytic	11%	14%	12%	12%	.95	.81
SSRI antidepressant	18%	15%	16%	18%	.87	.81
Non-SSRI antidepressant	9%	6%	10%	9%	.75	.74

NOTE. The values listed in this table are means or percentages.

[1]*P*-values for differences in variables among the four groups were determined by *t* tests for means and chi-square tests for percentages.

[2]*P* values for trends in variables from groups A through D were determined by regression analysis.

tients in groups B and C had more hepatic steatosis ($P = .04$). Splenomegaly and esophageal varices were more common in patients with platelet counts ≤125,000/mm^3 (Table 2, $P < .0001$ for both). Frequencies of esophageal varices and portal hypertensive gastropathy increased from groups A to D ($P < .0001$ for both trends, Table 2).

Fifteen percent of patients with fibrosis without histological evidence of cirrhosis had platelet counts ≤125,000/mm^3 (group B). Despite the apparent lack of histological cirrhosis in either groups A or B, patients in group B had higher frequencies of splenomegaly, varices, and portal hypertensive gastropathy—features suggestive of portal hypertension—compared with patients in group A (Table 2). Patients in group B had similar biochemical impairment, similar frequencies of varices and portal hypertensive gastropathy, and a higher frequency of splenomegaly compared with the patients in group C, whose liver biopsies showed cirrhosis (Table 2). Patients in group D had more biochemical impairment and higher frequencies of varices, portal hypertensive gastropathy, and splenomegaly compared with patients in groups A, B, and C (Table 2). Thus, the combination of platelet count with the Ishak fibrosis score establishes a spectrum of increasingly severe liver disease.

Virologic Response

Virologic responses at week 20 (VR20) declined from a high of 41% in group A to a low of 18% for group D (Fig. 1A). The decline in VR20 from groups A to D was 36% to 16% for patients infected with HCV genotype 1 and 80% to 35% for patients infected with non-1 genotypes. SVR declined from 23% in group A to 9% in group D (Fig. 1B). The decline in SVR from groups A to D was 18% to 8% for patients infected with HCV genotype 1, and 64% to 25% for patients infected with non-1 genotypes. Logistic regression analysis showed that the trendlines for diminished virologic responses with increasing disease severity from group A to group D were highly significant for both VR20 and SVR ($P < .0001$).

Factors associated with diminished responsiveness to PEG-IFN/RBV therapy have included HCV genotype-1, high HCV RNA levels, African American heritage, and

Table 2. Laboratory, Histologic, Ultrasonographic, and Endoscopic Characteristics of the Four Study Groups

∴	Group A Fibrosis Plt. > 125K	Group B Fibrosis Plt.≤ 125K	Group C Cirrhosis Plt. > 125K	Group D Cirrhosis Plt.≤ 125K	P^1	P^2
Number of patients	559	96	198	193		
WBC × 1,000/mm^3	6.23	4.60	6.42	4.96	<.0001	<.0001
Neutrophils × 1,000/mm^3	3.41	2.48	3.44	2.64	<.0001	.0001
Hemoglobin, g/dL	15.2	14.8	15.1	14.85	.002	.02
Platelets × 1,000/mm^3	204	101	179	93	<.0001	<.0001
Total bilirubin, mg/dL	0.69	0.97	0.78	1.03	<.0001	<.0001
Albumin, g/dL	4.01	3.79	3.89	3.64	<.0001	<.0001
Prothrombin time,INR	1.00	1.07	1.05	1.11	<.0001	<.0001
AST/ALT	0.77	0.90	0.87	0.99	<.0001	<.0001
ALT ratio to ULN	2.16	2.77	2.34	2.52	.003	.01
History of diabetes or fasting						
Glucose ≥ 126 mg/dL	19%	27%	28%	28%	.02	.004
HOMA[3]	13.2	19.2	18.4	17.1	.01	.11
Log HCV RNA (IU/mL)	6.49	6.44	6.41	6.27	<.0001	<.0001
Genotype 1 no/yes	90%	81%	93%	90%	.02	.78
Liver histology						
Ishak inflammation score	7.10	7.51	7.87	7.92	<.0001	<.0001
Fibrosis-Ishak score	3.12	3.41	5.38	5.56	<.0001	<.0001
Hepatocellular iron grade	0.49	0.49	0.53	0.51	.91	.52
Steatosis (0-4)[4]	1.26	1.40	1.46	1.28	.04	.16
Ultrasonography						
Frequency of splenomegaly	18%	52%	24%	66%	<.0001	<.0001
Endoscopy[5]						
Frequency of gastropathy	26%	39%	44%	57%	<.0001	<.0001
Frequency of esophogeal varices	11%	33%	28%	54%	<.0001	<.0001

NOTE. The values listed in this table are means or percentages.

[1]*P*-values for differences in variables among the four groups were determined by *t* tests for means and chi-square tests for percentages.

[2]*P*-values for trends in variables from groups A through D were determined by regression analysis.

[3]HOMA is homeostasis model assessment; fasting insulin (μU/mlL × fasting glucose (mmol/L)/22.5.

[4]Steatosis scores were: 0: none, 1: 5%, 2: 6%–34%, 3: 35%–64%, and 4: 64%. [5]Endoscopy was only performed in the patients who entered the randomized phase of HALT-C.

obesity, hepatic steatosis, and excess stainable hepatic iron. In a multiple logistic regression analysis, we found that none of these variables accounted for the decline in either VR20 or SVR from groups A to D.

Rates of VR20 were 47%, 53%, 28%, and 21%, and rates of SVR were 27%, 34%, 13%, and 11% in patients whose prior therapy was interferon, PEG-IFN, interferon/RBV, and PEG-IFN/RBV, respectively. However, by multiple logistic regression analysis, type of prior treatment did not account for the decline in either VR20 or SVR from groups A to D.

Rates of VR20 and SVR were examined in relation to four quartiles of platelet counts: 426,000 to 211,000/mm^3 (n = 261 patients), 210,000 to 165,000/mm^3 (n = 256 patients), 164,000 to 121,000/mm^3 (n = 265 patients), and 120,000 to 39,000/mm^3 (n = 263 patients). Respective rates for VR20 were 42%, 35%, 35%, and 20%, and respective rates of SVR were 21%, 20%, 17%, and 11%. Baseline platelet counts ≤120,000/mm^3 were associated with the lowest rates of VR20 and SVR.

Rates of VR20 and SVR were also evaluated according to the following Ishak fibrosis scores: 3 (n = 461 patients), 4 (n = 193 patients), 5 (n = 206), and 6 (n = 185). Respective rates for VR20 were 41%, 36%, 25%, and 22%, and respective rates for SVR were 24%, 17%, 10%, and 10%. Rates for VR20 and SVR were approximately 50% lower in the patients with Ishak fibrosis scores of 5 or 6.

Dose Reduction and Discontinuation

In a prior detailed analysis of our patients,[19] only 3 of 80 patients who had discontinued RBV within the first 20 weeks achieved SVR. The SVR in those who continued treatment with both PEG-IFN and RBV was compromised by dose reductions, primarily of PEG-IFN. For these reasons, in this study we examined the frequency of discontinuation of RBV and analyzed the impact of dose reductions on VR20 and SVR.

Patients in groups B, C, and D discontinued RBV (11%, 8%, and 10%) more frequently than did the patients in group A (6%) (Fig. 2, $P = .02$). Frequencies of dose reductions were higher in groups B and D (50% and 47%), the groups with lower platelet counts, compared with groups A and C (32% and 36%, Fig. 2, $P < .0001$).

The magnitude of the decline in SVR from group A to D was similar between patients who took full doses of PEG-

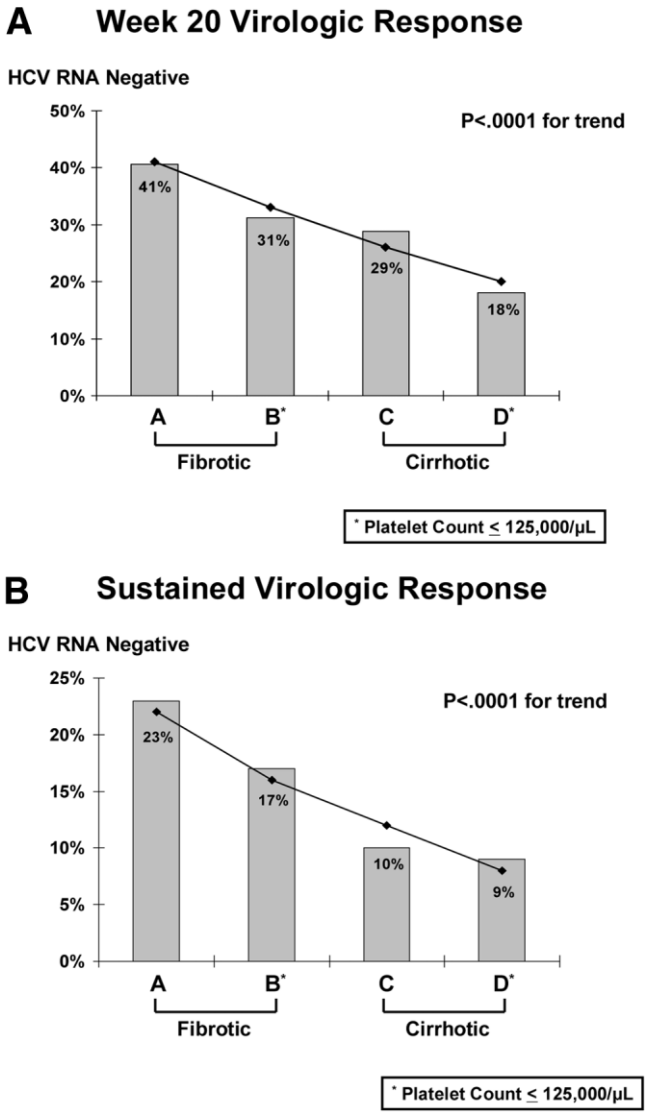

Fig. 1. Bars represent means and trend lines derived from logistic regression. (A) Mean virologic response at week 20 of therapy is highest in patients with fibrosis and platelet counts >125,000/mm^3 (group A). Patients with cirrhosis with platelet counts ≤125,000/mm^3 were least likely to respond (group D). (B) Sustained virologic response is lowest in patients with cirrhosis (groups C and D).

IFN/RBV and those who had dose reductions (Fig. 3). Decline in SVR due to dose reduction was only significant in this linear trend analysis in patients with cirrhosis, groups C and D ($P = .044$), but was modest compared with the decline in SVR based on disease severity ($P < .0001$).

Relative Influence of Disease Severity, Dose Reduction, and Platelet Count on SVR

The relative effect of dose reduction or increase in disease severity on attenuation of SVR is shown in Fig. 4A. The impact of dose reduction is marginally significant ($P = .046$), whereas both groups C and D had lower SVR than group A ($P = .0005$ and .0006). Because both the

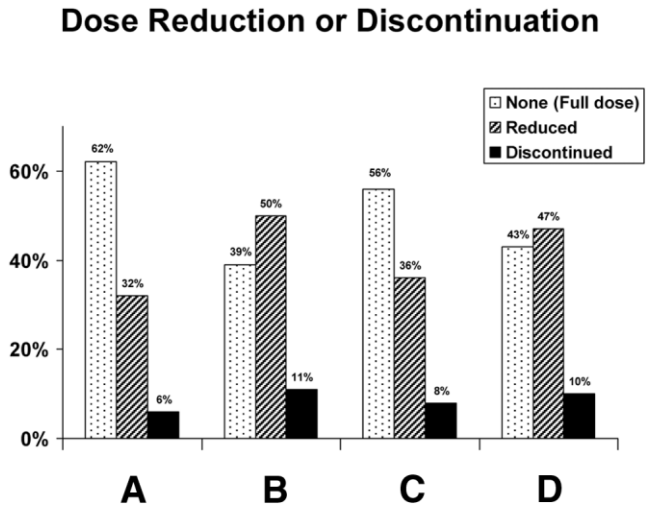

Fig. 2. Treatment was discontinued more frequently in groups B, C, and D. Dose reductions were more frequent in patients with platelet counts ≤125,000/mm^3 (groups B and D compared with A and C, $P <$ .0001).

increase in Ishak fibrosis score and the decrement in platelet count correlated with disease severity, we examined the relative contributions of dose reduction, cirrhosis, and platelet count ≤ 125,000/mm^3 on impairment of SVR (Fig. 4B). Cirrhosis was the most influential factor contributing to reduction in SVR ($P < .0001$).

Management Issues

Liver Biopsy. The mean ± SD of length of liver biopsies was 1.83 ± 0.89 cm, and 24% of biopsies were fragmented. Sixty-four percent of biopsies were greater than 1.5 cm in length, and 91% were greater than 1.0 cm in length. The means (±SDs) and ranges for length of

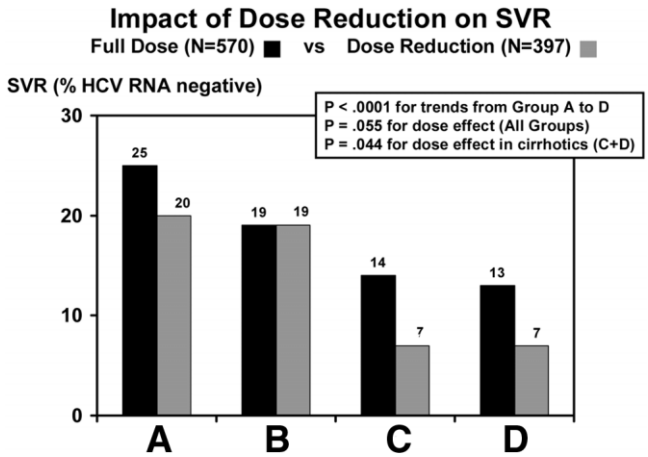

Fig. 3. Bars represent means. SVR was lower in patients who dose reduced (P </> = .055), especially in patients with cirrhosis (groups C and D) (P </> = .044). Dose reduction had less effect in patients with fibrosis without cirrhosis (groups A and B, P </> = .19). Patients who discontinued ribavirin are not included in this analysis.

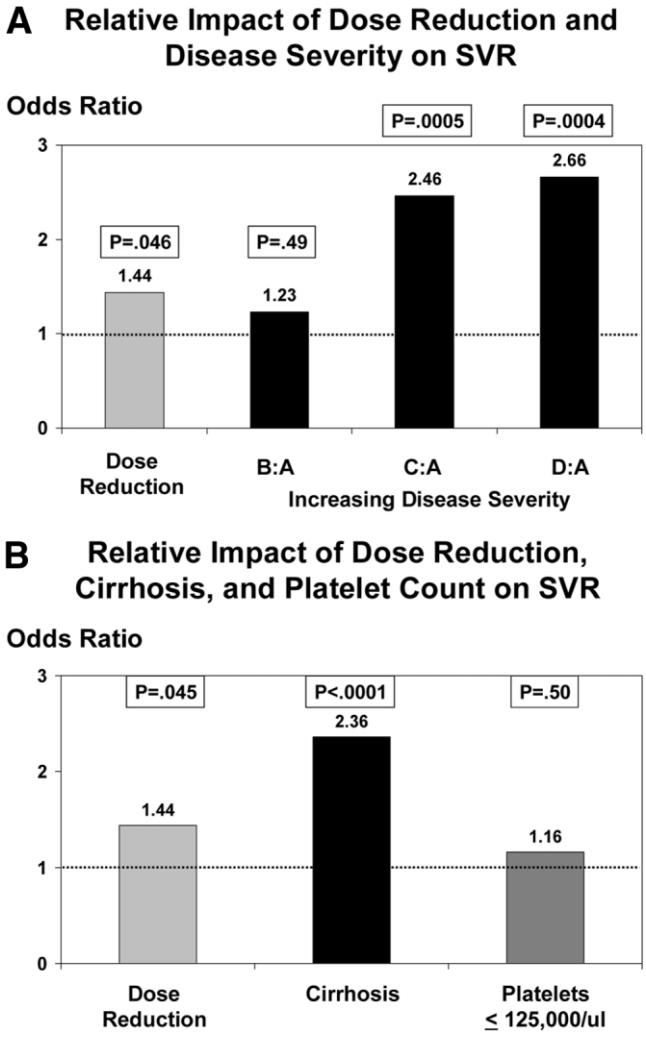

Fig. 4. (A) Disease severity had a more significant impact on SVR than dose reduction. (B) Cirrhosis is the variable with the most significant impact on SVR. Patients who discontinued ribavirin are not included in this analysis.

liver biopsies and percentages of patients with biopsies of length less that 1.0 or 1.5 cm were not significantly different among groups A through D. Biopsy-related complications occurred in 2.8% and included pain (n = 20), bruising (n = 1), dehydration (n = 1), hematoma (n = 1), and hypotension (n = 1). Hospitalization for observation was required in 1.1%. Biopsy-related complications, including hospitalization, were similar among groups A through D.

Side Effects of Treatment. Side effects were encountered commonly during therapy (Table 3). Flu-like symptoms (fatigue, arthralgia, anorexia, fever, and headache) were common, and the frequencies were similar across groups. Anxiety, mood swings, depression, insomnia, and mental confusion were also commonly encountered, with similar frequencies across groups. Alopecia was more frequent in groups A and C ($P = .034$); anemia was more frequent in groups B, C, and D ($P = .007$); and neutropenia ($P = .0002$) and thrombocytopenia ($P < .0001$) were more frequent in groups B and D.

Discussion

HALT-C Trial patients are characterized by histological evidence of advanced fibrosis or cirrhosis and by nonresponse to prior interferon-based therapy. In the first 604 HALT-C Trial patients,[20] we reported rates of SVR of 11% in the subset of patients with biopsy-proven cirrhosis (n = 233), and 23% in those without cirrhosis (n = 371) ($P = .0005$). Herein we report the results for all patients enrolled in the lead-in phase of the HALT-C Trial, and examine, in detail, the contribution of disease severity to the impairment of virologic response. The 1,046 patients were assigned to one of four groups, A through D, with increasing disease severity as defined, *a priori*, by histological stage of fibrosis and platelet count. Clinical, laboratory, endoscopic, and ultrasonographic features were compared among the four groups.

The key finding of our study was profound impairment of virologic response with progressively more severe liver disease. Rates of SVR plummeted from 23% in the group with the least severe disease (group A) to 9% in the group with most severe disease (group D). This 61% relative reduction in SVR was much higher than the approximately 10% to 30% relative reductions attributable to advanced fibrosis or cirrhosis reported in trials of treatment-naive patients.[11-14,21] The principal reasons for this difference are that all of our patients had either advanced fibrosis (62%) or cirrhosis (38%), and all of them were nonresponders to prior interferon-based therapy. In the trials of treatment-naive patients, only 10% to 25% had advanced fibrosis or cirrhosis. In addition, the entry criteria for the HALT-C Trial allowed inclusion of patients with more severe disease (platelet count $\geq 50{,}000/mm^3$), patients that would have been excluded from entry into the treatment-naive trials. All of these factors magnified the impairment in virologic response and the effect of disease severity.

In our study, SVR progressively declined from group A to group D regardless of HCV genotype. The rate of SVR in patients infected with HCV genotype 1 in group A was 18%, compared with 8% in patients in group D. The rate of SVR in persons with non-1 HCV genotypes in group A was 64%, compared with 25% in patients in group D. Data from trials of PEG-IFN/RBV therapy in treatment-naive patients have yielded comparable results. In the study of Hadziyannis and co-workers, the SVR rate among patients infected with HCV genotype 1 who had advanced fibrosis or cirrhosis was 41%, compared with an SVR rate of 57% in those without significant fibrosis.[14]

Table 3. Frequency of Selected Side Effects and Adverse Events

∴	Group A Fibrosis Plt. >125K	Group B Fibrosis Plt.≤ 125K	Group C Cirrhosis Plt. >125K	Group D Cirrhosis Plt.≤ 125K	*P*
Number of patients	559	96	198	193	
Abdominal pain	26%	20%	21%	24%	.36
Alopecia	11%	7%	13%	5%	.04
Anemia	22%	31%	29%	34%	.004
Anorexia	19%	17%	23%	21%	.54
Anxiety, mood swings	40%	41%	35%	35%	.45
Arthralgias	62%	65%	64%	60%	.80
Confusion, memory loss	16%	13%	15%	19%	.57
Depression	20%	16%	22%	26%	.15
Diaphoresis	9%	15%	8%	7%	.19
Dizziness	16%	13%	18%	8%	.02
Dry skin	8%	20%	11%	6%	.001
Fatigue	71%	72%	72%	70%	.97
Fever, URI, Flu	26%	26%	29%	27%	.90
Headache	49%	41%	47%	44%	.32
Infection (not URI, flu)	14%	19%	14%	16%	.63
Injection site bruising, redness	22%	13%	18%	16%	.08
Insomnia	35%	32%	37%	37%	.77
Nausea or vomiting	42%	44%	43%	41%	.95
Paresthesia	7%	5%	8%	6%	.71
Rash or pruritus	51%	47%	56%	55%	.36
Respiratory symptoms	35%	31%	32%	30%	.52
Sinusitis	6%	5%	9%	8%	.33
Neutropenia	23%	43%	29%	40%	<.0001
Thrombocytopenia	3%	27%	4%	44%	<.0001

The rate of SVR in patients infected with HCV genotypes 2 and 3 who had advanced fibrosis or cirrhosis was 73%, compared with an SVR of 84% in those without significant fibrosis.[14]

In the current study, the percentages of patients infected with HCV genotype 1 was similar and mean serum levels of HCV RNA level lower from group A to group D. Thus, in regression analysis, neither HCV genotype nor blood level of HCV RNA accounted for the reduction in SVR that occurred with increasing disease severity from groups A to D.

Alternative explanations for diminished SVR in patients with the more advanced liver disease include an increase in the prevalence of other established predictors of poor response, or a high frequency of dose reductions. We did analyze the impact of age, sex, the proportion with African American heritage, hepatic iron, body mass index, hepatic steatosis, and the type of prior therapy (IFN or PEG-IFN ± RBV) and found that none accounted for the reduction in SVR from group A to group D.

Another well-established predictor of SVR is adherence to prescribed doses of antiviral therapy.[22] Patients with more advanced liver disease would be more likely to discontinue or reduce doses of medication due to cytopenias and increased side effects during treatment. Indeed, we found that patients with more advanced disease (groups B, C, and D compared with group A) were more likely to discontinue treatment, and patients with lower platelet counts (groups B and D compared with groups A and C) were more likely to experience dose reductions. Not surprisingly, we also found that dose reductions diminished virologic responses, primarily in patients with cirrhosis. However, compared with disease severity, the effect of dose reduction on impairment of virologic response was modest (Fig. 4B).

Three treatment trials suggest further that attenuation of doses of treatment impairs virologic response, particularly in patients with the most advanced liver disease. In a study by one of us (G.T.E.), 124 patients with decompensated liver disease were treated with low, accelerating doses of interferon alfa-2b and RBV.[23] Although overall SVR was 24%, patients infected with HCV genotype 1, who tolerated neither full doses nor full duration of treatment, had an SVR rate of 0%. Forns et al. treated 30 patients with hepatitis C and cirrhosis before liver transplantation.[24] Side effects were frequent; 63% required dose reductions, and only 20% remained free of HCV infection after transplantation. Crippin and colleagues[25] treated 15 patients who had severely decompensated cirrhosis awaiting liver transplantation (mean ± SD Child-Turcotte-Pugh score 11.9 ± 1.2) with low doses of interferon or interferon/RBV, and none achieved SVR.[25] Thus, patients with cirrhosis, especially those with the most advanced liver disease, represent a population that is "difficult-to-treat" and "difficult-to-cure." The American Association for the Study of Liver Disease has suggested

that only experienced clinicians, using vigilant monitoring for adverse events, treat these patients.[26]

Maintaining the dose of antiviral therapy, particularly in patients with cirrhosis, may be crucial to achieving optimal virologic responses. Because dose reductions for cytopenias were dictated by our study protocol, we could potentially have achieved higher rates of SVR had we maintained lower cell-count thresholds for dose reductions or relied on growth factors to counteract cytopenias. The safety and efficacy of these approaches, however, have been neither evaluated nor confirmed by properly controlled trials.

In patients with functioning spleens, thrombocytopenia may be a reliable and inexpensive laboratory marker of advanced disease and likelihood of SVR. In a previous report from the HALT-C Trial, Lok et al.[27] described a model based on standard laboratory tests (bilirubin, aspartate aminotransferase:alanine aminotransferase, INR, and platelet count) that was highly predictive of the presence of cirrhosis.[27] In that model, the most influential variable was platelet count. Furthermore, in the current study, patients without cirrhosis who had low platelet counts (group B) had more severe liver disease than patients without cirrhosis who had normal platelet counts (group A) but had liver disease of similar severity to that of patients with cirrhosis and normal platelet counts (group C). We also found that the rate of SVR in our patients with platelet count $\leq$120,000/mm^3 was only 11%, similar to the SVR rate of patients with histologic cirrhosis. The probability that thrombocytopenia is a faithful marker of advanced disease in patients classified histologically as having fibrosis but lacking cirrhosis is supported by our findings that, among the individuals in group B, 33% had varices, 39% had portal hypertensive gastropathy, and 52% had splenomegaly.

We conclude that more advanced liver disease, especially cirrhosis, independently impairs the response to interferon-based antiviral therapy. Although mechanisms were not defined by—and are well beyond the scope of—our study, potential factors in more advanced disease that could diminish response might include microcirculatory alteration by extensive fibrosis, impaired uptake or metabolism of antiviral medications, interference with immune mechanisms of viral clearance by cytokines or other factors mediating fibrosis, and refractoriness to the interferon signaling pathway. Improvement of responses to currently available therapy in patients with advanced fibrosis and cirrhosis will require a better understanding of the mechanisms underlying the inhibitory effect of disease severity on virologic response. Our results also emphasize the urgent need for new and better drugs to eradicate HCV in those most in need of effective treatment, namely, the patients with advanced liver disease.

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