Maintenance Therapy With Ribavirin in Patients With Chronic Hepatitis C Who Fail to Respond to Combination Therapy With Interferon Alfa and Ribavirin

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To assess the efficacy and safety of maintenance therapy with ribavirin alone in chronic hepatitis C, 108 patients were treated with the combination of interferon alfa and ribavirin for 24 weeks; those who failed to have a virologic response were offered enrollment in a randomized, double-blind, controlled trial of ribavirin (1,000-1,200 mg daily) versus placebo for the subsequent 48 weeks. Patients were monitored at regular intervals with symptom questionnaires, serum aminotransferase levels, hepatitis C virus (HCV) RNA levels, and complete blood counts and underwent liver biopsy at the completion of therapy. Among 108 patients, 50 were still HCV RNA positive after 24 weeks of treatment, of whom 34 agreed to be randomized to continue either ribavirin monotherapy or placebo. Among 17 patients who received placebo, there was no overall improvement in symptoms, serum alanine aminotransferase (ALT) levels, HCV RNA levels, or hepatic histology. Among the 17 patients who received ribavirin, serum ALT levels and necroinflammatory features of liver histology were improved, whereas symptoms, HCV RNA levels, and hepatic fibrosis scores were not changed significantly from baseline. Responses to ribavirin seemed to be categorical, such that 8 patients (47%) had definite improvement in liver histology. Patients with improved histology had improvements in serum ALT levels both on combination therapy and after switching to ribavirin monotherapy. In conclusion, continuation of ribavirin monotherapy may maintain serum biochemical improvements that occur during interferon-ribavirin combination therapy in some patients and that these improvements are often associated with decreases in necroinflammatory changes in the liver. Whether these improvements will ultimately result in prevention of progression of hepatitis C requires further study. (HEPATOLOGY **2003;38:66-74.**)

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Combination therapy using interferon alfa and ribavirin induces a sustained virologic response in as many as one half of patients with typical chronic hepatitis C.[1-3] Loss of detectable hepatitis C virus (HCV) RNA during therapy that persists for at least 6 months after stopping treatment is associated with long-term improvement in symptoms, serum biochemical abnormalities, and liver histology. Indeed, long-term follow-up on sustained virologic responders has shown that liver histology returns to normal with resolution of hepatic fibrosis in a high proportion of patients.[4-6]

Unfortunately, sustained responses to combination therapy occur in only 40% to 50% of patients, with the remaining patients either experiencing a relapse when therapy is stopped (relapsers) or never becoming HCV RNA negative even with prolonged and high doses of therapy (nonresponders). A somewhat higher response rate of 54% to 56% has recently been reported using the combination of pegylated interferon alfa and ribavirin, but at least 40% of patients still do not have a sustained response.[7-9] Although patients who relapse or fail to respond may have temporary benefit from a course of ther-

Abbreviations: HCV, hepatitis C virus; ALT, alanine aminotransferase; HAI, histologic activity index.

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apy, it is doubtful that treatment has a long-lasting effect on the natural history of this disease, which is typically insidious and slowly progressive.[10,11] Options for nonresponders include monitoring on no therapy while awaiting further advances in treatment or attempts to ameliorate progression of disease by long-term or continuous therapy with interferon alfa or ribavirin (or both). Interferon therapy is associated with many adverse effects, making long-term maintenance therapy difficult. Nevertheless, long-term treatment of patients with advanced chronic hepatitis C using a pegylated form of interferon alfa is now the focus of a large, multicenter trial in the United States (HALT-C).[12] Continuous, long-term therapy with ribavirin has been assessed in small studies[13-18] and can be accompanied by improvements in serum alanine aminotransferase (ALT) levels and, in some instances, improvement in liver histology. We have assessed whether continuation of ribavirin monotherapy is beneficial in patients who have failed to have a virologic response to a course of combination therapy. The hypothesis tested was whether continuous ribavirin monotherapy has a role in amelioration of disease in patients with chronic hepatitis C who fail to respond to combination antiviral treatment.

Patients and Methods

Study Design. Patients with chronic hepatitis C of at least moderate severity were enrolled. Patients were required to have HCV RNA in serum, increased serum aminotransferase levels, and liver histology showing chronic necroinflammatory disease consistent with chronic viral hepatitis and with a total histology score (combining the inflammatory histologic activity index [HAI] and the fibrosis score) of at least 6 (of a maximum of 24).[19,20] Patients had to be older than 18 years and to have no specific contraindications to therapy. Exclusion criteria included previous therapy with the combination of interferon alfa and ribavirin, but patients who had previously received interferon alone without a sustained virologic response were eligible (both relapsers and nonresponders). Other exclusion criteria included symptomatic coronary or cerebrovascular disease, serious autoimmune disease, renal insufficiency, hemolysis or anemia (hematocrit $<32\%$), and severe neuropsychiatric disease. All patients underwent a pretreatment evaluation including blood and urine tests, abdominal ultrasonography, and percutaneous liver biopsy (if not performed in the previous year). Patients who qualified for the trial were then started in the first of 2 phases of treatment. Phase 1 was the then-current standard therapy for chronic hepatitis C, which consisted of combination therapy with interferon alfa and ribavirin. Phase 2 was limited to patients who did not become HCV RNA negative during the first 24 weeks of therapy. Eligible nonresponder patients were randomized to continue therapy with either ribavirin or placebo alone, with interferon alfa discontinued in both groups.

Phase 1. After completion of pre-evaluation, all patients were started on combination therapy using interferon alfa (interferon alfa-2b, Intron-A; Schering-Plough Corp., Kenilworth, NJ) subcutaneously at a dosage of 3 million units 3 times weekly and ribavirin (Rebetol; kindly provided by Schering-Plough Corp.) by mouth at a dosage of 1,000 mg (if body weight was <75 kg) or 1,200 mg (if body weight was ≥ 75 kg) daily in 2 divided doses. Combination therapy was continued for at least 24 weeks. During therapy, patients were seen, filled out symptom and adverse effect questionnaires, and had blood tests performed at 2, 4, 6, 8, 12, 16, 20, and 24 weeks. Blood was tested for routine liver tests (ALT, aspartate aminotransferase, bilirubin, and albumin), complete blood count, reticulocyte count, and HCV RNA by polymerase chain reaction. Patients who were HCV RNA negative at 24 weeks were continued on combination therapy for a total of 48 weeks. These patients were seen every 8 weeks on therapy and at 4, 8, 16, and 24 weeks after stopping treatment. At the end of the 72-week period, patients underwent re-evaluation including liver biopsy.

Phase 2. Patients who remained HCV RNA positive after 24 weeks of combination therapy were eligible to be randomized into the second phase of the study. These patients stopped combination therapy at week 26 (the 2-week delay allowed for HCV RNA testing to be completed) and were randomized to receive either ribavirin monotherapy or identical-appearing placebo tablets at the dose level given during combination treatment (based on initial body weight and any dose reduction because of adverse effects). Patients were seen and had blood taken at 8-week intervals for the next 48 weeks. At the end of the 48-week period of ribavirin or placebo therapy, patients underwent re-evaluation including a battery of blood and urine tests, abdominal ultrasonography, and liver biopsy.

All patients gave written informed consent, and all details of the protocol and consent form were approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases of the Clinical Center of the National Institutes of Health. This study was conducted under an investigational new drug application for the use of ribavirin (IND 54,311) held by the investigators.

Symptom Scores. Patients were asked to fill out a questionnaire regarding symptoms and adverse effects at

each outpatient visit. The questionnaire consisted of a visual analogue scale; patients were asked to make a mark on a 10-cm line from none (or best ever) to worst ever that best described their degree of symptoms (including fatigue, nausea, poor appetite, itching, irritability, sadness, and general well-being) during the previous week. The distance of the mark from the origin of the line was measured in millimeters and used as a score for each symptom, thus ranging from 0 to 100.

Virologic Testing. Serial serum samples were tested for HCV RNA using the Amplicor qualitative HCV RNA assay (Roche Diagnostics, Branchburg, NJ), which has a lower limit of sensitivity of 100 copies/mL. Samples taken before treatment and after 24, 48, and 72 weeks were also tested for HCV RNA level by Superquant competitive polymerase chain reaction assay (National Genetics Institute, Los Angeles, CA). HCV genotyping was performed by Lipa assay (Innogenetics, Ghent, Belgium).

Histologic Analyses. Liver biopsy histology was read under code by a hepatic pathologist (D.E.K.) using a modification of the HAI for inflammatory scores[19,20] and the Ishak index[21] for fibrosis scores. Inflammatory scores included readings for periportal inflammation and necrosis (0-10), lobular inflammation and necrosis (0-4), and portal inflammation (0-4). Fibrosis scores ranged from 0 (none) to 1 to 2 (portal fibrosis only), 3 to 4 (bridging fibrosis), and 5 to 6 (early and complete cirrhosis). A *post-hoc* analysis was performed on patients with a sustained virologic response to determine an algorithm that would define a histologic response that could be applied to patients randomized to the placebo or ribavirin arms. Using a combination of total inflammatory score (from 0 to 18) and improvement in score from pretreatment liver biopsy, a histologic response was defined by the minimal decrease and highest final total HAI score that was achieved by all sustained responders (see following text).

Statistical Analyses. Group means were compared by standard and paired *t* tests. Dichotomous results were analyzed using Fisher's exact test or χ^2 analysis. In assessing serial results of symptom scores, results were censored for patients who stopped therapy early and carried forward in those with missing results. Values for serum aminotransferase levels were logarithmically transformed for calculation of means and statistical comparisons.

Results

A total of 108 patients were enrolled into the first phase and 34 into the second phase of the study. The demographic and clinical features of the patient populations are shown in Table 1. Twenty-eight patients had received interferon alfa therapy previously, 13 of whom were reported to be virologic nonresponders and 15 relapsers.

Table 1. Demographic Features of Patients Enrolled to Receive Combination Therapy (Phase 1) and Patients Enrolled Into the Randomized Study (Phase 2)

Feature	Phase 1 (n = 108)	Phase 2 (n = 34)
Age (y)	47.1 ± 0.9	47.6 ± 1.4
Male sex (%)	68 (63)	25 (74)
Race (%)		
White	84 (78)	25 (74)
Asian	8 (7)	2 (6)
Black	16 (15)	7 (20)
Previous therapy (%)	28 (26)	11 (32)
Serum ALT (IU/L)	90 ± 7	89 ± 9
Serum aspartate aminotransferase (IU/L)	62 ± 5	62 ± 7
Serum bilirubin (mg%)	0.8 ± 0.1	0.8 ± 0.1
Serum albumin (gm%)	4.3 ± 0.1	4.3 ± 0.1
HCV RNA level (10^6 copies/mL)	3.118 ± 0.180	4.052 ± 0.223
Genotype (%)		
1	79 (73)	33 (97)
2	12 (11)	0
3	10 (9)	1 (3)
4	2 (2)	0
Mixed	5 (5)	0
HAI scores		
Periportal necrosis	3.5 ± 1.4	3.4 ± 0.5
Lobular inflammation	3.7 ± 0.5	3.6 ± 0.1
Portal inflammation	2.4 ± 1.0	2.2 ± 0.2
Fibrosis (0-6)	2.7 ± 1.7	2.9 ± 0.3
Cirrhosis (%)	16 (15)	5 (15)

NOTE. Results are expressed as mean ± SEM unless otherwise noted.

Liver histology showed that 16 patients (15%) had cirrhosis (Ishak fibrosis score of 5 or 6), but none had hepatic decompensation. One patient had a history of hepatocellular carcinoma that had been resected 6 months before enrollment.

Phase 1. During combination therapy, 58 of the 108 patients (54%) became HCV RNA negative and remained negative at 24 weeks (Fig. 1). These patients were eligible to continue therapy for a full 48 weeks. Among these initial responders, 41 (38%) had a sustained virologic response and were HCV RNA negative at least 6 months after stopping therapy (72 weeks). Sustained responses occurred in 79% (19 of 24) of patients with non-1 genotypes (2, 3, or 4) but in only 26% (22 of 84) of those with genotype 1 (or mixed) infection. In sustained responders, serum ALT levels decreased from an average of 105 IU/L before therapy to 21 IU/L at 72 weeks ($P < .0001$), at which time ALT levels were normal in 38 and minimally elevated (46, 46, and 61 IU/L; normal, ≤41 IU/L) in the remaining 3 patients. Among the 41 responders, 36 (88%) agreed to have a repeat liver biopsy that showed improvement in histologic scores of necrosis and inflammation in all (mean HAI score before therapy, 9.8; mean HAI score after therapy, 2.6; $P < .0001$) and improvement in fibrosis scores in 20 (mean Ishak score before therapy, 2.1; mean Ishak score after therapy, 1.5;

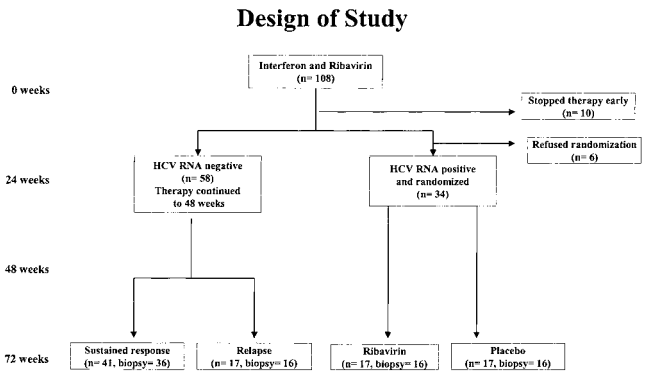

Fig. 1. Study design. A total of 108 patients were initially treated with interferon alfa and ribavirin combination therapy, of which 58 (54%) became HCV RNA negative and were continued on treatment for a total of 48 weeks. Among 50 patients who did not achieve a 24-week virologic response, 10 stopped therapy early, 6 refused randomization, and 34 were randomized to receive either ribavirin or placebo for another 48 weeks.

$P < .0002$). The results of the pretreatment and posttreatment HAI scores from the 36 responders are shown in Fig. 2. All except 3 patients with a sustained response had a final necroinflammatory HAI score of 3 points or less; each of these 3 patients had a 5-point or more decrease in HAI score. These findings were used to define criteria for a histologic response.

Seventeen patients (16%) had a virologic response at 24 weeks but experienced a relapse once therapy was stopped (Fig. 1). At follow-up, mean serum aminotransferase levels were not different (mean ALT level before therapy, 76 IU/L; mean ALT level after therapy, 79 IU/L)

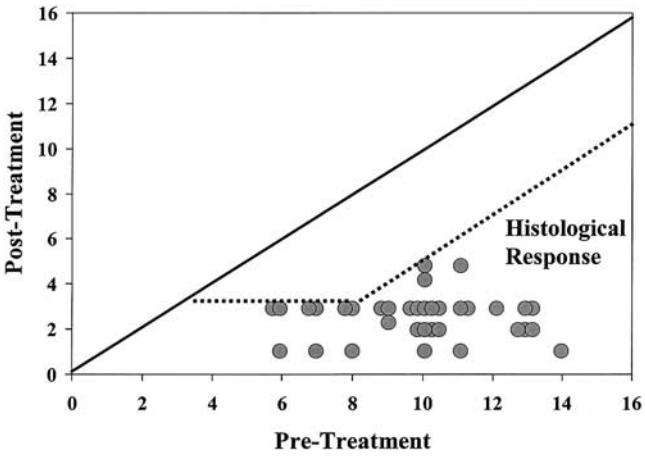

Fig. 2. Pretreatment and posttreatment (72 weeks after enrollment) total necroinflammatory HAI scores for 36 patients who had a sustained virologic response to combination therapy and a repeat liver biopsy after treatment. Among the 36 patients, HAI scores decreased to a total of 3 points or less in 33 and decreased by 5 points or more in 32 patients. Thus, all 36 had either a decrease to a total score of 3 or less and/or a decrease of 5 points or more. Scores to the right and below the dotted line meet the criteria for a histologic response.

Table 2. Demographic Features of Patients Enrolled in the Randomized Phase of the Trial

Feature	Ribavirin (n = 17)	Placebo (n = 17)	*P*
Age (y)	47.7 ± 2.7	47.4 ± 1.2	.87
Male sex (%)	14 (82)	11 (65)	.44
Race (%)			
White	11 (65)	14 (82)	
Asian	1 (6)	1 (6)	.44
Black	5 (29)	2 (12)	
Previous therapy (%)	5 (29)	6 (35)	1.00
Genotype (%)			
1	16	15	
2	0	0	1.00
3	0	1	
Mixed	1	1	
Cirrhosis (%)	1 (6)	4 (23)	.34

and average symptom scores were not different from baseline in these 17 patients. Among 16 relapsers who underwent repeat liver biopsy, the average necroinflammatory scores improved (mean HAI score before therapy, 10.0; mean HAI score after therapy, 8.2; $P = .01$) but fibrosis scores worsened slightly (mean Ishak score before therapy, 3.0; mean Ishak score after therapy, 3.4; $P = .16$).

The remaining 50 patients (45%) did not achieve a 24-week virologic response. Ten patients stopped therapy before the 24-week point, either because of intolerable adverse effects (8 patients) or because they were lost to follow-up (2 patients). Of the 40 patients who were nonresponders at 24 weeks and were still on therapy, 6 elected not to participate in the randomized, double-blind phase of the trial, leaving 34 patients who were randomized and received either ribavirin or placebo starting at week 26 (Fig. 1).

Phase 2. Compared with the 108 patients enrolled in the first phase of the study, the 34 patients entering the randomized, second phase were more likely to have genotype 1 infection and have higher initial levels of HCV RNA; these are features that are known to correlate with nonresponse to interferon-based therapies (Table 1).[1-3] Among 34 patients randomized, 17 received ribavirin and 17 received placebo. The 2 groups were well matched in regard to age, sex distribution, pretreatment values for serum ALT and aspartate aminotransferase, HCV RNA levels, and liver histology scores (Tables 2-4). All except one patient had genotype 1.

Serum Aminotransferase Levels. Serial mean serum ALT levels for the 17 ribavirin and 17 placebo recipients are shown in Fig. 3. For comparison, mean ALT levels for the 41 sustained virologic responders are also shown. Serum ALT levels decreased in most patients during the initial 24 weeks of combination therapy, becoming normal in 93% of sustained responders and 52% and 58% of

Table 3. Clinical Features in Patients Before and at the End of Therapy or Follow-up

Feature	SVR (n = 41)	Ribavirin (n = 17)	Placebo (n = 17)	P*
ALT (IU/L) (normal, <41 IU/L)				
Initial	105	92	85	
Final	21†	56‡	78	.057
AST (IU/L) (normal, <32 IU/L)				
Initial	61	60	64	
Final	22†	44§	60	.310
Bilirubin (mg %)				
Initial	0.7	0.7	0.9	
Final	0.6	1.1‡	0.9	.001
Hematocrit (%)				
Initial	43.9	45.9	44.6	
Final	43.8	42.7‡	44.5	.005
Platelet count (/mm^3)				
Initial	216	198	196	
Final	215	220§	192	.025
HCV RNA level (10^6/mL)				
Initial	2.8	4.157	3.947	
Final	0	4.241	4.142	.796
Fatigue score (0–100)				
Initial	33	35	29	
Final	13‡	26	27	.230
Well-being score (0–100)				
Initial	20	29	21	.423
Final	15	31	21	

NOTE. Values shown are means.

Abbreviations: SVR, sustained virologic response; AST, aspartate aminotransferase.

*t test comparing changes between initial and final values in ribavirin vs. placebo recipients.

§$P < .05$, ‡$P < .01$, †$P < .001$ in paired t tests comparing initial with final values.

Table 4. Histologic Features in Patients Before and at the End of Therapy or Follow-up

Feature	Scale	SVR (n = 36)	Ribavirin (n = 16)	Placebo (n = 16)	P*
Periportal necrosis (0–10)					
Initial		3.3	3.3	3.6	.098
Final		0.7†	1.6‡	2.8	
Lobular inflammation (0–4)					
Initial		3.3	3.6	3.6	.027
Final		1.2†	2.7§	3.6	
Portal inflammation (0–4)					
Initial		2.6	2.4	2.0	.031
Final		0.7†	1.1‡	1.6	
Total HAI (0–18)					
Initial		9.8	9.2	9.2	.024
Final		2.6†	5.4†	7.9§	
Fibrosis (0–6)					
Initial		2.1	2.6	3.2	.452
Final		1.5‡	2.6	3.5	
Histologic response (%)		100	47	0	.003
Iron concentration (μg/g dry wt)					
Initial		486	488	460	.016
Final		630	1,111§	430	

NOTE. Values shown are means.

Abbreviation: SVR, sustained virologic response.

*t test comparing change between initial and final value of ribavirin vs. placebo-treated patients except for histologic response, which was analyzed by Fisher's exact test comparing ribavirin and placebo recipients.

§$P < .05$, ‡$P < .01$, †$P < .001$ in paired t tests comparing initial with final values.

the nonresponders who continued on ribavirin or placebo. During the blinded phase of the study, mean serum ALT levels increased to pretreatment levels among placebo recipients but remained in the near-normal range in ribavirin recipients. At the 72-week point, mean ALT levels remained lower than baseline among ribavirin recipients (92 to 56 IU/L; $P < .01$) but not placebo recipients (85 to 78 IU/L; $P = .45$). The absolute change in ALT levels between ribavirin and placebo recipients was close to statistical significance (−37 vs. −7 IU/L; $P = .056$) (Table 3). Serum ALT levels were normal or near normal (within 1.5 times the upper limit of the normal range) in 11 ribavirin recipients (64%) but only 5 placebo recipients (29%).

Symptoms. Serial results of visual analogue scales for measurement of fatigue and general well-being are shown in Fig. 4A and B for nonresponders who received ribavirin or placebo and for sustained virologic responders. Fatigue increased and general well-being worsened during combination therapy to an equal degree in all 3 groups. At 26 weeks, when interferon alfa was stopped in nonresponder patients, fatigue and sense of well-being improved, and the improvements in each were similar among ribavirin and placebo recipients. Sustained responders had a gradual decrease in fatigue and improvement in well-being during the second 24 weeks of therapy, which was followed by a marked improvement in both scales once combination therapy was stopped. Symptom scores for fatigue

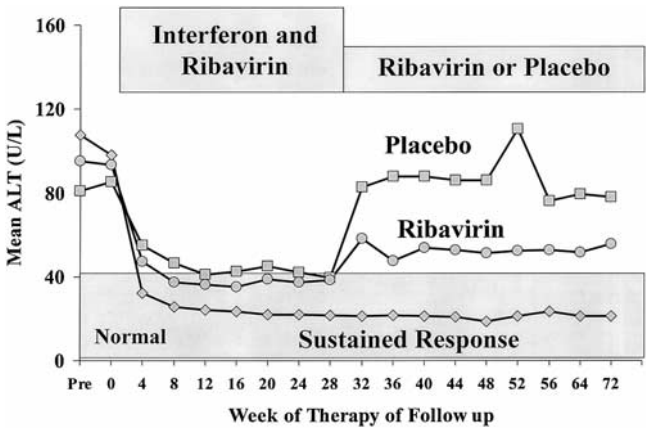

Fig. 3. Serial mean serum ALT levels in patients who were virologic nonresponders after 24 weeks of combination therapy and were continued on ribavirin alone (n = 17; **triangles**) or placebo (n= 17; **squares**) for the subsequent 48 weeks. For comparison, serial results from 41 patients who had a sustained virologic response to therapy are also shown (**diamonds**). ALT levels were geometrically transformed to calculate means.

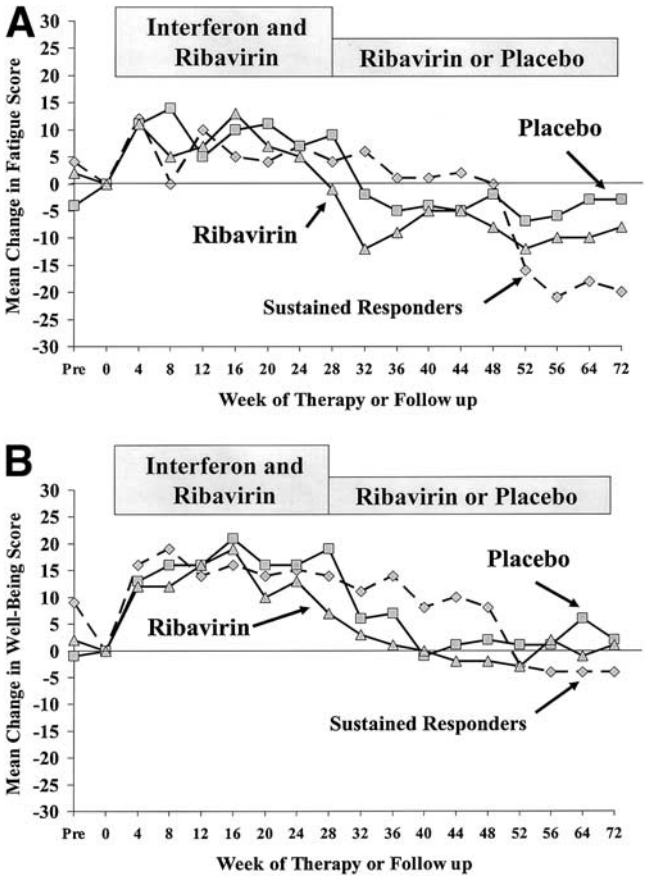

Fig. 4. Serial mean change from baseline of (A) fatigue and (B) general well-being visual analogue scores in patients who were virologic nonresponders after 24 weeks of combination therapy and were continued on ribavirin alone (n = 17; **triangles**) or placebo (n = 17; **squares**) for the subsequent 48 weeks. For comparison, results from patients who had a sustained virologic response (n = 41) are also shown (**diamonds** and **dashed lines**); these patients received interferon alfa and ribavirin for 48 weeks and were followed up for 24 weeks afterward on no therapy.

at the end of follow-up were significantly improved compared with baseline scores in sustained virologic responders ($P < .01$) but were not significantly changed in placebo and ribavirin recipients.

HCV RNA Levels. Among the 34 patients in the randomized phase of the study, HCV RNA levels increased after discontinuation of interferon alfa and all 34 patients remained HCV RNA positive. HCV RNA levels at the end of ribavirin therapy were similar to initial levels (mean levels before therapy, 4.157 million copies/mL; mean levels after therapy, 4.241 million copies/mL) and similar to those among placebo recipients (mean levels before therapy, 3.947 million copies; mean levels after therapy, 4.142 million copies).

Histologic Responses. Repeat liver biopsies at the end of follow-up were available for 16 ribavirin and 16 placebo recipients. One ribavirin recipient stopped therapy and refused follow-up, and one placebo recipient finished the full 48 weeks of therapy but refused repeat liver biopsy. Changes in the HAI necroinflammatory scores for each patient are shown in Fig. 5, and summary results of the individual components of the HAI and fibrosis scores are shown in Table 4. Necroinflammatory scores improved significantly in both groups but were numerically and significantly greater in the ribavirin- than placebo-treated patients. Fibrosis scores did not change in either group. In contrast, both necroinflammatory scores and fibrosis scores improved significantly among the sustained virologic responders.

Responses to ribavirin appeared to be categorical in that some patients had marked improvements in serum aminotransferase levels and liver histology whereas others (including the 3 who stopped therapy early) had little or no change. Using results from patients with a sustained virologic response (Fig. 2), criteria were developed to define a histologic response that was achieved by all 36 patients with a sustained response: (1) a decrease in HAI to a level of 3 or less or (2) a decrease in HAI inflammatory scores by 5 points or more. Using these criteria, 8 of 17 ribavirin recipients (47%) but none of 17 placebo recipients had a histologic response ($P = .003$) (Fig. 5). All 8 patients with a histologic response were receiving ribavirin, and 7 had either normal or near-normal ALT levels both at the end of combination therapy as well as at the end of ribavirin therapy. No other predictive factors clearly correlated with a histologic response among ribavirin

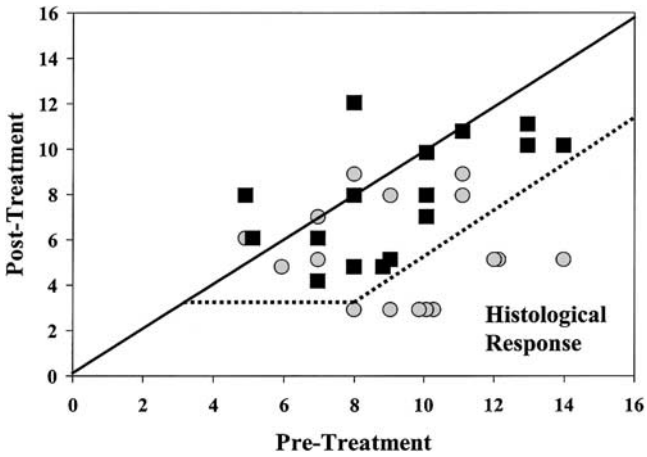

Fig. 5. Pretreatment and posttreatment total HAI inflammatory scores on liver biopsies from 16 patients who received ribavirin (Rbv; **circles**) and 16 who received placebo (**squares**) after failing to respond to a 24-week course of the combination of interferon alfa and ribavirin. Liver biopsies were performed during the last week of a 48-week course of ribavirin or placebo, approximately 72 weeks after enrollment. Mean improvement in inflammatory scores was greater in ribavirin than placebo recipients (−3.8 vs. −1.3; $P = .024$). Scores to the right and below the dotted line meet the criteria for a histologic response. Eight ribavirin recipients but no placebo recipients achieved a histologic response.

recipients (age, sex, initial ALT levels, HCV RNA levels, or initial histology; data not shown).

Side Effects and Adverse Events. Ribavirin and placebo were generally well tolerated during the blinded part of the study. Hematocrit and hemoglobin levels, which had decreased during combination therapy, increased thereafter but remained lower than baseline among ribavirin but not placebo recipients. By the end of therapy, hematocrit levels were minimally lower among ribavirin (42.7%) than placebo (44.5%) recipients and changes in hematocrit levels were significantly greater in ribavirin than placebo recipients ($P = .005$). Dose reductions were made in 3 patients, all of who were receiving ribavirin (one each for fatigue, anemia, and itching). Three patients discontinued therapy early, all of who were receiving ribavirin (one because of intractable itching despite dose reduction and 2 because they did not believe the medication was helpful [one patient continued to be followed up and the other refused further follow-up]). None of these 3 patients had normal ALT levels, and the 2 undergoing repeat liver biopsy did not have a histologic response. One patient on placebo had an acute variceal hemorrhage that was managed by esophageal variceal banding and transient discontinuation of the study medication.

Hepatic iron concentrations were determined on all liver biopsies from which adequate tissue was available (ribavirin recipients, 12 before and 15 at the end of therapy; placebo recipients, 9 before and 12 at the end of therapy). Mean hepatic iron concentrations increased 2-fold among ribavirin recipients but did not change significantly among placebo recipients (Table 4).

At the conclusion of participation, patients were asked whether they believed they were receiving ribavirin or placebo; 17 patients believed that they were receiving ribavirin (9 were correct) and 13 placebo (7 were correct), and 4 stated that they did not know (2 ribavirin, 2 placebo). Thus, correct responses were given by less than one half of patients, the proportion that would be expected to occur by chance.

Discussion

This randomized, double-blind, controlled trial focused on management of patients with chronic hepatitis C who did not respond to optimal antiviral therapy. Patients completing 24 weeks of combination therapy who remained positive for HCV RNA were assigned randomly to receive either ribavirin or placebo for the following 48 weeks. Serum aminotransferase levels were either normal or had decreased by more than one half in most patients receiving combination therapy, including 82% of those who did not become HCV RNA negative. By continuing treatment with ribavirin, the improvements in aminotransferase levels were maintained during the next 48 weeks; this improvement in biochemical tests was matched by improvements in necroinflammatory scores on liver histology. The histologic improvements associated with maintenance ribavirin therapy were not as marked as occurred in sustained virologic responders but were statistically different from changes in the control (placebo-treated) patients. Thus, improvements in hepatitis disease activity that occur on combination therapy may be maintained at least in part by continuation of ribavirin alone without interferon.

Ribavirin monotherapy was reasonably well tolerated and not associated with severe adverse events. However, it should be pointed out that patients with severe side effects from ribavirin would have been culled during the initial 24-week period of this study when they received combination therapy. Ribavirin causes a dose-dependent hemolysis and can induce symptomatic anemia in up to 15% of patients. Other important side effects of ribavirin include itching, skin rash, irritability, nasal congestion and cough, gallstones, and gout.[22-24] Itching and skin rash were problematic in one patient in this study and led to early discontinuation of therapy. In addition, there was accumulation of hepatic iron in many patients who were maintained on ribavirin, although in no case did liver iron levels approach those associated with hepatic injury. Otherwise, ribavirin seemed to cause few symptoms; indeed, results of symptom scales were similar between placebo and ribavirin recipients. Furthermore, a "test of the blind" at the end of the participation showed that most patients could not tell whether they were receiving placebo or ribavirin.

This study used a strict but *post-hoc* definition of a histologic response to therapy. In most trials of interferon-based therapy of hepatitis C, a 2-point improvement in the HAI has been used as a definition for "histologic improvement." This definition has never been shown to be clinically significant and can occur with changes in a single subcomponent of the HAI score. Using this definition, the 2 groups in this study had similar rates of histologic improvement: 10 of 16 (63%) ribavirin recipients and 9 of 16 (56%) placebo recipients ($P = $ NS). A categorical definition of histologic improvement would be preferable, such as a resolution of all necrosis and inflammation and normal histology. However, this standard may be too strict to apply to liver biopsies taken only 6 to 12 months after stopping therapy. Indeed, in long-term follow-up of patients with a sustained virologic response, liver histology does not always return to normal, with residual minor nonspecific inflammatory changes commonly found.[4-6] Similar, nonspecific changes have been described in patients with spontaneous resolution of

acute hepatitis C.[20,25] In this study, we used the changes in inflammatory scores that occurred in the patients who had a sustained virologic response to provide a definition of a histologic response. Among 36 patients who had cleared HCV RNA with therapy, 33 had total inflammatory scores of 3 or less; 3 had total scores of 4 or 5, but these represented a 5- to 8-point decrease from the initial biopsy. For this reason, we used a definition of a decrease in inflammatory scores to a level of 3 or less or by at least 5 points from baseline. Using this definition, 8 of the 16 ribavirin recipients who had a second liver biopsy had a histologic response. All 8 had normal or near-normal (<1.5 times the upper limit of the normal range) ALT levels during both combination and ribavirin monotherapy. These findings, while based on small numbers, suggest that the maintenance of a biochemical and histologic response with ribavirin alone can be achieved in patients who have a biochemical response to combination therapy.

Although maintenance therapy with ribavirin seemed to sustain biochemical and histologic improvements for 48 weeks after stopping combination therapy, it cannot be assumed that these improvements will be sustained indefinitely or that they will ultimately result in slower progression of disease to cirrhosis or hepatocellular carcinoma. Such clinical end points require years to decades to show, even in untreated patients. Long-term follow-up studies of patients with sustained virologic responses suggest that these clinical end points are avoided and that patients appear "cured" of their chronic viral infections.[4-6] Reports of hepatocellular carcinoma occurring in patients with sustained virologic response have been published, but the rate of development of cirrhosis and cancer appears significantly less than in patients with only a transient or no virologic response.[26-28] Extrapolating these findings to patients with a sustained biochemical or histologic response is difficult. In this regard, patients who completed this study have been offered enrollment in a long-term, open-label study of continuous ribavirin therapy (in decreasing doses) to assess if changes in aminotransferase levels and histology can be sustained and whether fibrosis scores improve with long-term therapy. Furthermore, the findings of this study need to be confirmed in larger numbers of patients using similar criteria for a histologic response.

Thus, ribavirin monotherapy can maintain biochemical and histologic improvements in a proportion of patients with chronic hepatitis C who have a biochemical but not a virologic response to interferon alfa/ribavirin combination therapy. Ribavirin does not significantly decrease HCV RNA levels, and its mechanism of action in amelioration of chronic hepatitis C is not well defined.[29,30] Importantly, the long-term safety and benefit of maintenance ribavirin therapy in preventing progression of disease in chronic hepatitis C have yet to be shown.

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