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## INTERFERON ALFA-2b ALONE OR IN COMBINATION WITH RIBAVIRIN AS INITIAL TREATMENT FOR CHRONIC HEPATITIS C

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### ABSTRACT

**Background** Only 15 to 20 percent of patients with chronic hepatitis C have a sustained virologic response to interferon therapy. We compared the efficacy and safety of recombinant interferon alfa-2b alone with those of a combination of interferon alfa-2b and ribavirin for the initial treatment of patients with chronic hepatitis C.

**Methods** We randomly assigned 912 patients with chronic hepatitis C to receive standard-dose interferon alfa-2b alone or in combination with ribavirin (1000 or 1200 mg orally per day, depending on body weight) for 24 or 48 weeks. Efficacy was assessed by measurements of serum hepatitis C virus (HCV) RNA and serum aminotransferases and by liver biopsy.

**Results** The rate of sustained virologic response (defined as an undetectable serum HCV RNA level 24 weeks after treatment was completed) was higher among patients who received combination therapy for either 24 weeks (70 of 228 patients, 31 percent) or 48 weeks (87 of 228 patients, 38 percent) than among patients who received interferon alone for either 24 weeks (13 of 231 patients, 6 percent) or 48 weeks (29 of 225 patients, 13 percent) ( $P < 0.001$  for the comparison of interferon alone with both 24 weeks and 48 weeks of combination treatment). Among patients with HCV genotype 1 infection, the best response occurred in those who were treated for 48 weeks with interferon and ribavirin. Histologic improvement was more common in patients who were treated with combination therapy for either 24 weeks (57 percent) or 48 weeks (61 percent) than in those who were treated with interferon alone for either 24 weeks (44 percent) or 48 weeks (41 percent). The drug doses had to be reduced and treatment discontinued more often in patients who were treated with combination therapy.

**Conclusions** In patients with chronic hepatitis C, initial therapy with interferon and ribavirin was more effective than treatment with interferon alone. (N Engl J Med 1998;339:1485-92.)

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CHRONIC hepatitis C infection is now recognized as an important health care problem.<sup>1</sup> Nearly 4 million Americans are estimated to be infected, and cirrhosis will eventually develop in at least 15 to 20 percent of them.<sup>2-5</sup> In the United States, infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease and the most common indication for liver transplantation.<sup>1,6</sup>

Until recently, interferon alfa was the only therapy available for patients with chronic hepatitis C. However, after 48 weeks of treatment, serum HCV RNA levels are undetectable in only 15 to 20 percent of patients.<sup>7-12</sup> Pilot studies of patients who have relapsed and of previously untreated patients suggest that combining interferon with ribavirin is more effective than using interferon alone,<sup>13,14</sup> and in a small, placebo-controlled study of previously untreated patients, treatment with interferon and ribavirin for six months was more effective than interferon alone.<sup>15</sup>

The aims of this study were to compare the safety and efficacy of interferon alone and in combination with ribavirin for the initial treatment of chronic hepatitis C and to determine the optimal duration of combination therapy.

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## METHODS

## Selection of Patients

Adult patients were eligible for the study if they were seropositive for HCV RNA on testing with the polymerase chain reaction, had undergone a liver biopsy within one year before entry whose results were consistent with a diagnosis of chronic hepatitis, and had had elevated serum alanine aminotransferase values (more than the upper limit of normal values) for at least six months. Patients with decompensated cirrhosis,<sup>16</sup> serum alpha-fetoprotein concentrations of more than 50 ng per milliliter, anemia (hemoglobin concentration, less than 12 g per deciliter in women and less than 13 g per deciliter in men), human immunodeficiency virus infection, psychiatric conditions, seizure disorders, cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, or autoimmune diseases were excluded, as were those who had undergone organ transplantation and those who were unable to practice contraception.

## Study Design and Organization

This double-blind, placebo-controlled trial was conducted at 44 centers in the United States. The study was approved by the institutional review board at each center, and all the patients provided written informed consent. We screened 1337 patients, of whom 404 did not meet the inclusion criteria. The remaining 933 patients were randomly assigned to one of four treatment groups, which were balanced for the presence or absence of cirrhosis, pretreatment serum HCV RNA level, and HCV genotype. The analysis was based on the 912 patients who received at least

one dose of medicine (21 patients were randomly assigned to a treatment group but did not receive therapy: 13 did not wish to continue, 5 did not meet the entry criteria, and 3 had adverse events before the initiation of therapy). Enrollment began in April 1996, and the trial was completed in March 1998.

The patients were randomly assigned to a treatment group as follows: recombinant interferon alfa-2b (Intron A, Schering-Plough, Kenilworth, N.J.) plus placebo for 24 weeks in the case of 231 patients and for 48 weeks in the case of 225 patients, and the combination of interferon alfa-2b and ribavirin (Rebetron, Schering-Plough) for 24 weeks in the case of 228 patients and for 48 weeks in the case of 228 patients. Interferon alfa-2b was given subcutaneously in a dose of 3 million units three times per week, and ribavirin (or matched placebo) was administered orally twice a day at a total daily dose of 1000 mg for patients who weighed 75 kg or less and 1200 mg for those who weighed more than 75 kg. Both drugs were started and stopped at the same time.

The severity of adverse events was graded as mild, moderate, severe, or life-threatening<sup>17</sup>; therapy was discontinued after life-threatening events. For severe adverse events other than anemia, the dose of interferon alfa-2b was reduced to 1.5 million units three times a week and the dose of ribavirin was reduced to 600 mg per day. The full dose could be resumed after the event or discontinued if the effect persisted. The dose of ribavirin was reduced to 600 mg per day in patients whose hemoglobin concentrations fell below 10 g per deciliter, and it was discontinued if the concentration fell below 8.5 g per deciliter.

The patients were evaluated as outpatients at weeks 1, 2, 4, 6, and 8 and then every 4 weeks during treatment and 4, 8, 12, and

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 wk (N=231)	48 wk (N=225)	24 wk (N=228)	48 wk (N=228)
Age — yr	45±7	44±8	44±8	44±8
Sex — M/F	154/77	150/75	148/80	152/76
Weight — kg	83.9±17.0	83.3±16.3	83.7±18.1	80.8±17.9
Serum alanine aminotransferase — no. of times upper limit of normal	4.0±2.9	3.7±2.5	4.1±2.8	3.7±2.3
Serum aspartate aminotransferase — no. of times upper limit of normal	2.9±2.3	2.7±1.7	2.9±2.2	2.7±1.7
Serum HCV RNA				
No. of copies/ml — ×10 <sup>-6</sup>	5.0±5.0	4.8±4.6	5.1±5.8	5.7±7.5
>2×10 <sup>6</sup> copies/ml — no. (%)	157 (68)	162 (72)	166 (73)	152 (67)
Estimated duration of infection — yr†	18.5±9.1	18.8±9.5	18.9±9.8	19.6±9.6
Source or type of infection — no. (%)				
Transfusion	41 (18)	54 (24)	55 (24)	49 (21)
Intravenous drug use	124 (54)	115 (51)	106 (46)	127 (56)
Sporadic or unknown	66 (29)	56 (25)	67 (29)	52 (23)
Genotype — no. (%)				
1	167 (72)	162 (72)	164 (72)	166 (73)
2	38 (16)	43 (19)	29 (13)	37 (16)
3	24 (10)	19 (8)	28 (12)	23 (10)
Other	2 (1)	1 (0.4)	7 (3)	2 (1)
Knodell score‡	7.4±2.7	7.6±2.6	7.5±2.5	7.3±2.8
Cirrhosis — no. (%)	15 (6)	10 (4)	9 (4)	15 (7)
Bridging fibrosis — no. (%)	50 (22)	61 (27)	50 (22)	40 (18)

\*Plus-minus values are means ±SD. Because of rounding, percentages may not total 100. None of the differences among the groups were significant.

†The duration of infection was estimated from the date of transfusion or initial exposure to other parenteral sources, and it could not be calculated for patients with sporadic infection or those in whom the source of infection was unknown.

‡Scores could range from 0 to 18, with higher scores indicating more severe abnormalities.

24 weeks after therapy. Biochemical and hematologic testing was performed by a central laboratory. Serum HCV RNA levels were determined before treatment; during treatment at weeks 4, 12, and 24; at 36 and 48 weeks in the patients who were treated for 48 weeks; and after therapy at weeks 12 and 24. Serum HCV RNA was measured by a reverse-transcription-polymerase-chain-reaction assay with a sensitivity of 100 copies per milliliter (National Genetics Institute, Los Angeles).<sup>18</sup> HCV genotyping was performed as previously described.<sup>19</sup> Liver biopsy was performed 24 weeks after the end of treatment, and the specimens were analyzed by a single pathologist who was unaware of the patients' identification, treatment regimen, and response and of the timing of the biopsy in relation to treatment.

**Assessment of Efficacy**

The primary end point was a sustained virologic response, defined as the absence of serum HCV RNA 24 weeks after treatment was completed. Secondary end points were normalization of the serum alanine aminotransferase concentration and histologic improvement. The degree of hepatic inflammation and fibrosis was graded with a modified Knodell Histologic Activity Index.<sup>20</sup> The inflammation score was obtained by combining the scores for the first three components of this index: portal, periportal, and lobular inflammation. The scores could range from 0 to 18, with higher scores indicating more severe abnormalities. The degree of fibrosis was graded as 0, no fibrosis; 1, portal fibrosis; 3, bridging fibrosis; or 4, cirrhosis. Histologic improvement was defined as a decrease of at least two points in the inflammation score, as compared with the score for the pretreatment biopsy specimen. The biochemical response and the sustained combined biochemical and virologic response were also assessed.<sup>1</sup>

**Statistical Analysis**

The study was designed to have 220 patients per group in order to have a power of 89 percent to detect a difference of 15 percentage points between the rates of sustained virologic response (30 percent vs. 45 percent), at a 5 percent level of significance (with two-sided tests). The treatment responses were compared with the use of Fisher's exact test.<sup>21</sup> Changes in the liver-biopsy score within each group were compared with the use of Student's t-tests.<sup>21</sup> The relation between pretreatment variables and treatment response was examined by stepwise logistic-regression analysis.<sup>22</sup> All P values are two-tailed.

**RESULTS**

**Characteristics of the Patients**

The base-line characteristics of the patients in the four groups were similar (Table 1). The proportion of patients with HCV genotype 1 (72 percent) was similar to the proportions in prior reports from the United States.<sup>23,24</sup>

**Virologic Response**

At the end of follow-up, the rates of virologic response were higher among the patients who had been treated with interferon and ribavirin for 24 weeks (31 percent) or 48 weeks (38 percent) than among those who had received interferon alone for 48 weeks (13 percent, P<0.001) (Table 2). Increasing the duration of combination therapy from 24 weeks

**TABLE 2. VIROLOGIC AND BIOCHEMICAL RESPONSES AT THE END OF TREATMENT AND FOLLOW-UP.\***

RESPONSE	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK	48 WK	24 WK	48 WK
<b>Virologic response</b>				
End of treatment				
No. with response/ total no. treated	66/231	54/225	121/228	115/228
Percent (95% CI)	29 (23-34)	24 (18-30)	53 (47-60)†	50 (44-57)†
End of follow-up				
No. with response/ total no. treated	13/231	29/225	70/228	87/228
Percent (95% CI)	6 (3-9)	13 (9-17)	31 (25-37)†	38 (32-45)†‡
<b>Biochemical response</b>				
End of treatment				
No. with response/ total no. treated	56/231	62/225	133/228	149/228
Percent (95% CI)	24 (19-30)	28 (22-33)	58 (52-65)†	65 (54-67)†
End of follow-up				
No. with response/ total no. treated	25/231	35/225	72/228	83/228
Percent (95% CI)	11 (7-15)	16 (11-20)	32 (25-38)†	36 (30-43)†

\*A virologic response was defined as the absence of serum HCV RNA (limit of detection, 100 copies per milliliter), and a biochemical response was defined as a normalization of the serum alanine aminotransferase concentration. Responses were assessed in the last week of treatment and 24 weeks later. CI denotes confidence interval.

†P<0.001 for the comparison with either interferon group.

‡P=0.05 for the comparison with 24 weeks of interferon and ribavirin.

to 48 weeks increased the rate of virologic response from 31 percent to 38 percent ( $P=0.05$ ). The rates of response at the completion of 24 weeks of therapy were almost twice as high in the combination-therapy group as in the interferon-alone group (53 percent vs. 29 percent,  $P<0.001$ ), and the respective rates after 48 weeks of therapy were more than twice as high (50 percent vs. 24 percent,  $P<0.001$ ). Relapse after therapy was less frequent with combination therapy (42 percent at 24 weeks and 24 percent at 48 weeks) than with interferon alone (80 percent at 24 weeks and 46 percent at 48 weeks).

In patients who were treated with interferon alone, viral clearance at week 4 was associated with a sustained virologic response, as reported previously.<sup>25-27</sup> However, among 51 of the 87 patients (59 percent) who were treated with combination therapy for 48 weeks and who eventually had sustained responses, HCV RNA remained detectable in serum until week 12 or 24 of therapy. Late viral clearance with a subsequent sustained response was also observed in 50 percent of patients (35 of 70 patients) who were treated with interferon and ribavirin for 24 weeks, 23 percent of those (3 of 13 patients) who received interferon alone for 24 weeks, and 52 percent of those (15 of 29 patients) who received interferon alone for 48 weeks.

#### Biochemical Response

The rate of sustained biochemical response was higher among patients who received interferon and ribavirin for 24 or 48 weeks than among those who received interferon alone for 24 or 48 weeks (Table 2).

The combined rates of sustained biochemical and virologic responses in the groups given interferon and ribavirin were 26 percent (60 of 228 patients) in the group treated for 24 weeks and 34 percent (77 of 228 patients) in the group treated for 48 weeks, as compared with 5 percent (12 of 231 patients,  $P<0.001$ ) in the group treated with interferon for 24 weeks and 12 percent (27 of 225 patients,  $P<0.001$ ) in the group treated with interferon for 48 weeks.

Normalization of serum alanine aminotransferase values was associated with undetectable levels of serum HCV RNA in most patients who had sustained virologic responses. Of 199 patients who had a sustained virologic response, 176 (88 percent) had persistently normal serum alanine aminotransferase concentrations. The mean ( $\pm$ SD) elevations of serum alanine aminotransferase after therapy in the remaining 23 patients (12 percent) was  $1.6\pm 0.1$  times the upper limit of the normal value. Eighteen percent of patients (39 of 215) with a sustained biochemical response had persistently detectable serum HCV RNA. The proportion of patients who had sustained virologic responses among those with a sustained biochemical response was higher in the combination-therapy group as a whole (137 of 155 patients, 88

percent) than in the interferon group as a whole (39 of 60 patients, 65 percent).

#### Histologic Response

Pretreatment and post-treatment liver-biopsy specimens were available from 670 patients (73 percent). Histologic improvement occurred in all four groups, but it was more common in either combination-therapy group than in the interferon group that was treated for 48 weeks ( $P<0.001$ ) (Table 3). The degree of histologic improvement, defined as a decrease in the inflammatory score of at least two points, was greatest in the group given interferon and ribavirin for 48 weeks. Of the 165 patients who had a sustained virologic response and who had pretreatment and post-treatment biopsy specimens available, 142 (86 percent) had a decrease in hepatic inflammation regardless of the treatment regimen. Inflammation also decreased in 194 of 497 patients (39 percent) who had persistent viremia at follow-up. Treatment had no effect on fibrosis.

TABLE 3. RATES OF HISTOLOGIC RESPONSE.\*

VARIABLE	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK (N=176)	48 WK (N=158)	24 WK (N=179)	48 WK (N=157)
<b>Change in inflammation score†</b>				
All patients				
Percent with improvement	44	41	57	61
Mean change	-0.6	-1.0	-1.8‡	-2.4§
Patients with a response				
Percent with improvement	89	78	88	86
Mean change	-3.8	-5.2	-4.4	-4.5
Patients with a relapse or no response				
Percent with improvement	41	35	41	39
Mean change	-0.4	-0.3	-0.6	-0.5
<b>Change in fibrosis score¶</b>				
All patients				
Percent with improvement	11	17	16	14
Mean change	0.1	-0.1	0.0	0.0
Patients with a response				
Percent with improvement	11	26	24	16
Mean change	-0.2	-0.2	-0.2	-0.1
Patients with a relapse or no response				
Percent with improvement	11	16	12	12
Mean change	0.1	0.0	0.2	0.2

\*The numbers of patients are the numbers with pretreatment and post-treatment biopsy specimens.

†Scores could range from 0 to 18, with higher scores indicating more severe abnormalities. Improvement was defined as a decrease in the inflammation score of at least two points, no change as an increase or decrease of one point, and worsening as an increase of at least two points.

‡ $P=0.005$  for the comparison with 48 weeks of treatment with interferon alone.

§ $P<0.001$  for the comparison with 48 weeks of treatment with interferon alone.

¶Scores could range from 0 (no fibrosis) to 4 (cirrhosis). Improvement was defined as a decrease of at least one point in the score.

**Variables Associated with a Response**

Treatment with interferon and ribavirin was the strongest predictor of a response. Sustained virologic response was unrelated to age, sex, body weight, or the estimated duration of disease. The response rates for pretreatment variables known to influence the response to treatment are shown in Table 4. Among patients with HCV genotype 1 infection who were treated for 48 weeks, the rate of sustained response for patients who were treated with interferon and ribavirin was four times as high as that in patients who were treated with interferon alone for 48 weeks. Among patients with this genotype, 48 weeks of combination therapy was more beneficial than 24 weeks of combination therapy (46 of 166 patients [28 percent] had a response, as compared with 26 of 164 patients [16 percent];  $P=0.01$ ). The response rates for patients with HCV genotype 1a infections and those with genotype 1b infections were similar. Among patients with other HCV genotypes who were treated with combination therapy, the response rates did not vary significantly as a function of the duration of therapy. The results in patients with HCV genotype 2 were similar to those in patients with HCV genotype 3.

Regardless of the viral load at base line or the presence of cirrhosis or bridging fibrosis at base line, the response was better in patients who were treated with interferon and ribavirin. Among patients with a high viral load or fibrosis at base line, the response rates were two to five times as high in those who were treated with interferon and ribavirin for either 24 or 48 weeks as in those who were treated with interfer-

on alone for 48 weeks. The response of patients with HCV genotypes other than 1 who were treated with 24 or 48 weeks of combination therapy were similar irrespective of the base-line viral load, whereas the response of patients with HCV genotype 1 and high pretreatment viral loads was better among those who received 48 weeks of combination therapy than among those who received 24 weeks of therapy.

Stepwise logistic-regression analyses revealed that greater efficacy was associated with HCV genotypes other than 1 ( $P<0.001$ ), a base-line viral load of  $2 \times 10^6$  copies per milliliter or less ( $P<0.001$ ), the absence of cirrhosis at base line ( $P=0.04$ ), and female sex ( $P=0.05$ ), in addition to combination treatment ( $P<0.001$ ) and 48 weeks of therapy ( $P=0.002$ ).

**Safety**

Hemoglobin concentrations decreased to less than 10 g per deciliter, necessitating a reduction in the dose of ribavirin, in 8 percent of the patients who were treated with combination therapy (Table 5). The mean maximal decrease from base line was 3.1 g per deciliter (range of changes,  $-7.0$  to  $+0.2$ ) after four weeks of therapy, and this was associated with compensatory reticulocytosis. A reduction in the dose resulted in an increase in hemoglobin concentrations of 1 to 1.5 g per deciliter, and the concentrations were subsequently stable throughout treatment. Both hemoglobin concentrations and reticulocyte counts returned to base line within 4 to 8 weeks after treatment was discontinued at 24 or 48 weeks. The longer duration of therapy was not associated with a significantly higher incidence of reductions in

**TABLE 4. RATES OF SUSTAINED VIROLOGIC RESPONSE ACCORDING TO PRETREATMENT VARIABLES AND TREATMENT GROUP.**

VARIABLE	NO. OF PATIENTS	INTERFERON		INTERFERON AND RIBAVIRIN	
		24 WK	48 WK	24 WK	48 WK
no./total no. of patients (%)					
Genotype					
1	659	3/167 (2)	11/162 (7)	26/164 (16)*	46/166 (28)†
Other	253	10/64 (16)	18/63 (29)	44/64 (69)‡	41/61 (66)‡
Base-line serum HCV RNA level					
$>2 \times 10^6$ copies/ml	637	6/157 (4)	11/162 (7)	44/166 (27)†	54/152 (36)†
$\leq 2 \times 10^6$ copies/ml	275	7/74 (9)	18/63 (29)	26/62 (42)‡	33/76 (43)§
Degree of fibrosis at base line¶					
Cirrhosis or bridging fibrosis	250	3/65 (5)	9/71 (13)	17/59 (29)*	21/55 (38)†
Minimal or no fibrosis	608	7/154 (5)	18/136 (13)	51/159 (32)†	62/159 (39)†

\* $P=0.01$  for the comparison with interferon alone for 48 weeks.

† $P<0.001$  for the comparison with interferon alone for 48 weeks.

‡ $P=0.06$  for the comparison with interferon alone for 48 weeks.

§ $P=0.04$  for the comparison with interferon alone for 48 weeks.

¶Fibrosis was defined as a score of 3, and cirrhosis as a score of 4. The degree of fibrosis could not be adequately evaluated in the pretreatment biopsy specimens of 54 patients.

**TABLE 5.** RATES OF DISCONTINUATION OF TREATMENT, DOSE REDUCTIONS, AND OTHER ADVERSE EVENTS DURING TREATMENT.\*

ADVERSE EVENT	INTERFERON		INTERFERON AND RIBAVIRIN	
	24 WK (N=231)	48 WK (N=225)	24 WK (N=228)	48 WK (N=228)
	percent			
Discontinuation of treatment for any severe event	9	14	8	21
Dose reduction				
Due to anemia†	0	0	7	9
Due to other adverse events‡	12	9	13	17
Influenza-like symptoms				
Headache	63	67	63	66
Fatigue	62	72	68	70
Malaise	7	5	4	11
Myalgia	57	63	61	64
Arthralgia	27	36	30	33
Musculoskeletal pain	26	32	20	28
Fever	35	40	37	41
Gastrointestinal symptoms				
Anorexia	16	19	27	25
Dyspepsia	6	9	14	16
Vomiting	10	13	11	9
Nausea	35	33	38	46
Diarrhea	22	26	18	22
Abdominal pain	17	20	15	14
Psychiatric symptoms				
Anxiety	9	13	10	18
Impaired concentration	14	14	11	14
Depression	25	37	32	36
Emotional lability	6	8	7	11
Insomnia	27	30	39	39
Irritability	19	27	23	32
Respiratory tract symptoms				
Cough	5	9	15	14
Dyspnea	9	10	19	18
Pharyngitis	9	10	11	20
Sinusitis	7	14	9	10
Dermatologic symptoms				
Alopecia	27	28	28	32
Pruritus	9	8	21	19
Rash	9	8	20	28
Dry skin	4	8	8	15
Inflammation at injection site	10	14	13	12

\*Only events that occurred in at least 10 percent of patients are included.

†The daily dose of ribavirin was reduced to 600 mg for patients with hemoglobin values below 10 g per deciliter, and treatment with ribavirin was discontinued in patients with hemoglobin values below 8.5 g per deciliter.

‡In the case of other severe events, the dose of interferon was decreased to 1.5 million units three times a week and the dose of ribavirin was decreased to 600 mg per day.

the dose of ribavirin due to anemia. Discontinuation of therapy and transfusion were necessary in one patient with a hemoglobin concentration of less than 10 g per deciliter. Reductions in the dose of ribavirin and subsequent completion of treatment did not affect the rate of sustained response. Leukocyte counts decreased in all groups during therapy, but the mean value remained within the normal range. The mean platelet counts were similar at base line and during

therapy, remaining above  $100 \times 10^3$  per cubic millimeter in 95 to 98 percent of all patients.

Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than with interferon alone (Table 5). The incidence of side effects was higher after 48 weeks of treatment than after 24 weeks of treatment, regardless of the type of therapy.

The drug doses were reduced because of adverse events other than anemia in 13 percent of patients who were given interferon and ribavirin for 24 weeks and in 17 percent of those who were treated for 48 weeks. Among the patients who were given interferon alone, the dose was reduced in 12 percent of those who were treated for 24 weeks and in 9 percent of those who were treated for 48 weeks. The most frequent reason for the discontinuation of therapy in all groups was emotional disturbance — mainly depression; the frequency of cessation of treatment for depression ranged from 2 to 9 percent in the four groups.

## DISCUSSION

The currently approved initial therapy for patients with chronic HCV infection consists of treatment with interferon for at least 48 weeks. The rates of sustained virologic response with this regimen are approximately 15 to 20 percent.<sup>7-12</sup> Our results confirm this low response rate.

We found that combination therapy with interferon and ribavirin for either 24 or 48 weeks was superior to therapy with interferon alone with respect to virologic, biochemical, and histologic end points. The higher rates of sustained virologic response were the result of higher rates of response at the end of treatment and, subsequently, lower rates of relapse. Recent reports suggest that similar sustained virologic responses are usually long-lasting (5 to 10 years) and are accompanied by progressive histologic improvement.<sup>28,29</sup> In our study, late clearance of HCV RNA from serum during combination therapy was also frequently associated with a sustained response. This phenomenon is uncommon in patients who are treated with interferon alone, which suggests that stopping therapy at week 12 because of persistent viremia, as recently suggested,<sup>1,18,30</sup> may not be appropriate in the case of therapy with interferon and ribavirin.

The beneficial effect of combination therapy also extended to subgroups of patients in whom treatment has historically been unsuccessful, such as patients with HCV genotype 1 infection, high pretreatment viral burdens, or advanced fibrosis or cirrhosis. Approximately 70 percent of U.S. patients with chronic HCV have genotype 1 infection, and such patients derived the greatest benefit from combination therapy for 48 weeks, suggesting that HCV genotyping should be considered before treatment is initiated.

Ribavirin, a synthetic guanosine analogue, has actions *in vitro* against a range of RNA and DNA viruses.<sup>31</sup> When given alone to patients with chronic hepatitis C, ribavirin decreases serum aminotransferase concentrations but has no antiviral effect.<sup>32-34</sup> Ribavirin has been postulated to inhibit viral-dependent RNA polymerase, the capping structure of viral messenger RNA, and inosine monophosphate dehydrogenase.<sup>31</sup> Other immunomodulatory actions may also contribute to the drug's beneficial effects.<sup>35</sup> Despite these potential actions, the exact mechanism responsible for the improved response that occurs when ribavirin is combined with interferon is unknown.

Combination therapy was relatively safe, but modifications in the dose and discontinuation of treatment were required more often in patients who received interferon and ribavirin than in those who were treated with interferon alone. Reversible, hemolytic anemia due to ribavirin occurred, as has been previously reported when this drug was given alone.<sup>32-34</sup> Patients who are treated with ribavirin should therefore be monitored closely (hemoglobin should be measured two and four weeks after therapy is begun and then as clinically indicated). The symptoms related to treatment with interferon and ribavirin have been reported previously, and there were no synergistic effects. Cough, pruritus, rash, and insomnia, all of which have been associated with the use of other, similar nucleoside analogues, were more common in the patients who received combination therapy.

In summary, in patients with chronic hepatitis C, therapy with interferon and ribavirin is more effective than interferon alone in inducing virologic and histologic improvement, and the combination may therefore be indicated as initial therapy in such patients.

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## APPENDIX

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