

# Treatment of Chronic Hepatitis C With Consensus Interferon: A Multicenter, Randomized, Controlled Trial

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This multicenter, randomized, controlled, double-blind, phase III study in 704 patients with chronic hepatitis C infection compared treatment with consensus interferon (CIFN), a non-natural recombinant type-1 interferon, with a standard regimen of recombinant interferon alfa-2b (IFN- $\alpha$ 2b). Patients were randomized to receive CIFN at doses of 3  $\mu$ g or 9  $\mu$ g, or 15  $\mu$ g IFN- $\alpha$ 2b (3 million units), subcutaneously three times weekly for 24 weeks, followed by 24 weeks of observa-

tion. Efficacy was assessed by normalization of serum alanine transaminase (ALT) concentration and decrease in serum hepatitis C virus (HCV) RNA concentration below the limit of detection by reverse-transcription polymerase chain reaction (RT-PCR) (100 copies/mL). The beneficial effect of CIFN was greater with the 9- $\mu$ g dose than the 3- $\mu$ g dose. The sustained ALT and HCV RNA response rates were 20.3% and 12.1%, respectively, in the 9- $\mu$ g CIFN cohort and 19.6% and 11.3%, respectively, in the 15- $\mu$ g IFN- $\alpha$ 2b cohort. However, patients receiving 9  $\mu$ g of CIFN had a greater reduction in serum HCV RNA concentrations compared with patients receiving 15  $\mu$ g IFN- $\alpha$ 2b over the course of treatment ( $P < .01$ ). Similarly, analysis of patients infected with HCV genotype 1 showed a greater reduction in serum HCV RNA concentration over the course of treatment for the 9- $\mu$ g CIFN group when compared with the 15- $\mu$ g IFN- $\alpha$ 2b group ( $P < .01$ ). In addition, a greater percentage of patients infected with HCV genotype 1 treated with 9  $\mu$ g CIFN had undetectable HCV RNA concentrations when compared with patients in the 15- $\mu$ g IFN- $\alpha$ 2b cohort at the end of treatment (24% vs. 15%;  $P = .04$ ). Improvements in liver histology were noted in all three treatment groups; 52% to 55% of the patients in the three cohorts had at least a 2-unit improvement in the Knodell score at the end of the posttreatment period. The adverse-events profiles were characteristic of treatment with type-1 interferon, and the incidences of anti-interferon antibody formation did not significantly differ among the three treatment groups. These results show that administration of 9  $\mu$ g CIFN three times weekly for 6 months is safe and is effective in reducing serum HCV RNA concentration. (HEPATOLOGY 1997;26:747-754.)

Hepatitis C virus (HCV) is a heterogeneous group of positive-stranded RNA viruses of the *Flaviviridae* family.<sup>1</sup> Before the implementation of blood screening for HCV, it was the most common cause of posttransfusion non-A, non-B hepatitis in the Western world. Currently, intravenous drug abuse is the most frequently cited source of HCV exposure.<sup>2</sup> As estimated by healthy blood donors in the United States with anti-HCV antibodies, the prevalence of HCV infection varies from 0.3% to 1.5%.<sup>3</sup> The clinical manifestations of acute hepatitis C are insidious, but a large proportion of patients develop chronic hepatitis that may progress to cirrhosis and hepatocellular carcinoma.<sup>3</sup> Extrahepatic clinical manifestations are uncommon, but may include skin rashes, glomerulonephritis, and cryoglobulinemia.<sup>4-7</sup> In patients with chronic hepatitis C, the serum bilirubin is usually normal, but serum

Abbreviations: HCV, hepatitis C virus; RT-PCR, reverse-transcription polymerase chain reaction; CIFN, consensus interferon; IFN- $\alpha$ 2b, recombinant interferon alfa-2b; ALT, alanine transaminase; HAI, histological activity index.

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Received March 25, 1997; accepted April 29, 1997.

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Funded by Amgen Inc., Thousand Oaks, CA.

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0270-9139/97/2603-0031\$3.00/0

aminotransferases may fluctuate for many years with levels in the range of 100 to 200 IU/L.<sup>8</sup>

Alfa interferons are currently the only therapies approved for treatment of HCV infection. The standard regimen is 3 million units administered subcutaneously three times per week for 6 to 12 months. However, approximately half of the patients do not respond to the standard regimen, and, of those who do show a response, 50% to 80% will relapse within 6 months of discontinuation of therapy.<sup>9,10</sup> Thus, the overall long-term response rate is low. In many of the early trials, the definition of a response was an improvement or normalization of serum aminotransferases. However, with the development of the reverse-transcription polymerase chain reaction (RT-PCR), it has become apparent that HCV RNA is a better indicator of response than surrogate markers such as serum aminotransferases.<sup>11</sup> HCV RNA was detected in 10% to 40% of patients with normalized serum aminotransferase levels after treatment with interferon.<sup>12,13</sup> Thus, serum HCV RNA may be a more relevant determinant of treatment efficacy than serum aminotransferases. In addition, pretreatment HCV RNA levels appear to be a better prognostic predictor of response to interferon therapy than serum aminotransferases.<sup>14</sup>

Consensus interferon (CIFN) (Amgen Inc., Thousand Oaks, CA) is a non-natural, synthetic, recombinant type-1 interferon derived by aligning the sequences of the then-known interferon alfa (IFN- $\alpha$ ) nonallelic subtypes, and assigning the most commonly observed amino acid in each position.<sup>15,16</sup> The biological activities of CIFN have been compared with other recombinant type-1 interferons (IFN- $\alpha$ 2a and IFN- $\alpha$ 2b) on an equal mass basis, and the results have shown that CIFN has significantly greater natural killer cell activation, antiviral, antiproliferative, and gene-induction activities.<sup>17,18</sup> This may be due to the increased affinity of CIFN for type I interferon receptors relative to other alpha interferons.<sup>15</sup> The following report describes a multicenter phase 3 study that was conducted to: 1) evaluate the safety and the efficacy of two dose levels of CIFN in chronic HCV-infected patients, as measured by changes in serum alanine transaminase (ALT) and HCV RNA concentrations; and 2) compare the response to treatment with CIFN with the response to a standard regimen of IFN- $\alpha$ 2b (Schering Corp., Kenilworth, NJ).

## PATIENTS AND METHODS

**Patient Population.** From February 19, 1993, through December 14, 1993, 821 patients were enrolled under protocol at 41 centers, including 34 in the United States and 7 in Canada. To be eligible for enrollment, patients had to meet the following criteria: positive for HCV RNA as measured by RT-PCR assay; serologically documented HCV infection by enzyme-linked immunoassay; liver biopsy within 12 months of enrollment confirming a diagnosis of chronic hepatitis; serum ALT concentrations at least 1.5 times the upper limit of normal within 4 weeks of enrollment; and documentation of elevated ALT concentrations for a minimum of 3 months before study enrollment. In addition, all causes of chronic liver disease other than HCV had to be excluded by appropriate clinical and/or laboratory evaluation. Patients were excluded from this study if there was a history (previous 5 years) of malignancy or depression; human immunodeficiency virus infection; evidence of decompensated liver disease; prior use of interferon preparation, chemotherapy, or other agents that could influence treatment outcomes; and thyroid abnormality in which normal thyroid function cannot be maintained by medication.

Of the 821 patients (728 U.S., 93 Canada) who were enrolled in the 12-week pretreatment observation period, 704 were randomized into the double-blind treatment study. Seventy-four of the 117 patients (63.2%) who were not randomized into the study were withdrawn because of failure to satisfy the eligibility criteria. There were 232, 232, and 240 patients randomized into the 3- $\mu$ g CIFN, 9- $\mu$ g CIFN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively. Six hundred thirty-two patients (89.8%) completed 24 weeks of treatment, and 591 patients (83.9%) completed the 24-week posttreatment observation period. Each patient gave written informed consent to participate in the study. The protocol, protocol amendments, and informed consent forms were approved by the Institutional Review Board of each study center. The Declaration of Helsinki on experimentation in humans was observed in all aspects of this study.

**Study Design.** This was a multicenter, double-blind, randomized, parallel-group study in patients with chronic HCV infection. After a 12-week pretreatment observation period, patients were randomly assigned to one of three treatment cohorts: 3  $\mu$ g CIFN, 9  $\mu$ g CIFN, or 15  $\mu$ g IFN- $\alpha$ 2b (approximately equivalent to 3 MU).<sup>19</sup> Therapy was administered subcutaneously three times per day (at least 48 hours apart) for a total of 24 weeks. At the end of the treatment period, patients entered a 24-week posttreatment observation period to evaluate the duration of response. During the study, patients maintained a daily journal that included the doses of blinded study drug administered, concomitant medications taken, and any adverse events experienced. Data presented herein are for the end of the treatment period and for the end of the observation period.

**Identification of Genotypes.** The patients' HCV genotypes and subtypes were identified at baseline through a modification of the specific line probe assay (Inno-LiPA system Innogenetics NV, Zwijnaarde, Belgium), as described by Stuyver et al.<sup>20</sup> Briefly, primers complementary to the conserved sequences of the 5' untranslated region of the different HCV genotypes were used in the RT-PCR reactions. HCV RNA was extracted from patients' sera and amplified by RT-PCR with the incorporation of biotinylated dUTP. Oligonucleotide probes (16-mers), specific for the different HCV genotypes and subtypes, were immobilized as parallel lines on membrane strips and then hybridized with the patients' amplified viral complementary DNA. After hybridization, streptavidin labeled with alkaline phosphatase was added. Incubation with nitro-blue tetrazolium/x phosphate/5-bromo-4-chloro-3-indolyl-phosphate-4-toluidine salt powder chromogen resulted in a purple-brown precipitate. The HCV genotypes were designated according to the nomenclature proposed by Simmonds et al.<sup>21</sup>

**Assessment of Efficacy.** The primary efficacy endpoint in this study was measured by changes in serum ALT, while secondary efficacy endpoints included serum HCV RNA, liver histology, differences in response rates between the two interferons, and ALT and HCV RNA responses by HCV genotype. All of the endpoints with the exception of the latter were defined prospectively.

**Serum ALT.** Patients' baseline serum ALT concentrations were calculated as the average of the four ALT concentrations determined during the screening and pretreatment observation periods. Serum ALT concentrations measured at the end of the 24-week treatment and posttreatment observation periods were used to determine response. Response to therapy was determined both quantitatively (reduction in serum ALT) and qualitatively (proportion of patients with normalization of serum ALT). The latter was defined as a decrease in serum ALT concentration to  $\leq$ 48 U/L.

**Serum HCV RNA.** The baseline serum HCV RNA concentration for each patient was calculated as the mean of the HCV RNA concentrations determined at weeks -12 and 0. In addition, serum HCV RNA concentrations were determined at weeks 12, 20, 24, 36, 44, and 48. Response to therapy was determined both quantitatively (reduction in serum HCV RNA) and qualitatively (proportion of patients with serum HCV RNA that are below the limits of detection). Serum HCV RNA was determined by a quantitative multicycle RT-PCR method (National Genetics Institute, Culver City, CA), which has a lower limit of sensitivity of 100 copies/mL. Briefly,

RNA was extracted from serum using guanidium thiocyanate/phenol/chloroform mixture, followed by ethanol/ammonium precipitation. Reverse transcription was initiated using random hexadeoxyribonucleotide primers that were allowed to anneal to the RNA templates, followed by reverse transcription using Moloney-Murine leukemia virus reverse transcriptase. The complementary DNA was then amplified in four separate PCRs for 25, 30, 35, or 40 cycles, each of which were subjected to gel electrophoresis and Southern blotting. The Southern blot membranes were scanned and quantitated by densitometry and compared with a standard curve. The assays were performed at the National Genetics Institute (Culver City, CA) by technicians who were blinded to the patients' study treatment.

**Liver Histology.** Liver biopsy specimens were obtained within the 12 months before enrollment and at the end of the posttreatment observation period (week 48). Pre- and posttreatment liver biopsies were performed on 697 patients. However, only 594 and 487 of the pre- and posttreatment biopsies, respectively, were adequate for evaluation. Thus, there were a total of 426 patients with pre- and posttreatment liver biopsies that were evaluable. Pre- and posttreatment biopsy specimens were reviewed by a single pathologist (Dr. J. Craig), who was blinded with respect to treatment group, patient identification, and the chronological order of the biopsies in each pair. A liver biopsy was judged adequate for evaluation if the specimen was  $\geq 1$  cm in length and contained at least three portal areas. Biopsy specimens were diagnosed as chronic hepatitis C, cirrhosis, or nonspecific changes. The latter category included diagnoses of minimal changes, fatty liver, and mononucleosis pattern. In addition, biopsy specimens were graded with respect to the degree of periportal necrosis, intralobular necrosis, portal inflammation, and fibrosis according to the histological activity index (HAI) devised for asymptomatic chronic active hepatitis, as described by Knodell et al.<sup>22</sup> The distribution of the pretreatment Knodell scores was comparable among the treatment groups.

**Assessment of Safety.** All adverse events, serious adverse events, dose-limiting toxicities, vital signs, physical findings, and laboratory test results were evaluated for safety. All adverse events that occurred during the study and were observed by the investigator or reported by the patient were recorded and graded for severity according to the World Health Organization criteria. Patients were withdrawn from the study if there was an unacceptable toxicity, a greater than 14-day dose interruption, or greater than two dose reductions of study drug, noncompliance, and/or evidence of hepatic decompensation.

**Detection of Anti-Interferon Antibodies.** All serum samples were assayed in both an Amgen radioimmunoassay specifically developed to detect antibodies to C1FN, as well as by a commercially available assay (ANAWA Laboratorien AG, Zurich, Switzerland) designed to detect antibodies to IFN- $\alpha$ 2b. Both of these assays were performed at a commercial laboratory (CEDRA Corp., Austin, TX).

**Statistical Analysis.** All patients who were randomized to the double-blind treatment period were included in the intention-to-treat analysis, while patients who received at least one dose of study medication were included in the safety evaluation. All hypothesis tests were two-tailed, and statistical significance was assessed at the 0.05 level, unless otherwise noted. The significance level for the primary comparison between 3  $\mu$ g C1FN and 9  $\mu$ g C1FN each, with 15  $\mu$ g IFN- $\alpha$ 2b, was adjusted using the Bonferroni method.

Data were summarized using descriptive statistics, and patient data listings were provided. Means and standard deviations were computed for continuous data. Categorical data were summarized using frequency and incidence rates, and 95% confidence intervals around point estimates were provided.<sup>23</sup> Response classifications of outcome data (ALT and HCV RNA) were tabulated and analyzed by treatment group using a  $\chi^2$  test of association. Multivariate repeated-measures ANCOVAs, controlled for baseline values, were conducted on the quantitative changes in log-transformed HCV RNA concentration over the course of treatment and over the entire study (treatment period combined with the observation period).

Statistical tests were conducted first, without including center or treatment-by-center interactions. If subsequent analyses revealed no statistically significant treatment-by-center interactions exhibiting differences in the direction of the treatment response, centers were pooled for point estimates and confidence intervals. *P* values were provided for treatment main effects without treatment-by-center interactions in the model.

## RESULTS

### Patient Population

The baseline characteristics in the three treatment groups are summarized in Table 1. The mean age of the patients at entry into the study was 43 years, and the majority of patients were male (>70%) and white (>80%). Intravenous drug abuse (43.4%) and transfusion (23.7%) were the most frequent suspected modes of HCV acquisition. The mode of HCV acquisition was not determined in 21.6% of the patients. Evaluable liver biopsies were available from 594 of the 704 randomized patients (84.4%) before the administration of study drug. The majority of the patients had chronic hepatitis C (73.9%), and 16.5% had cirrhosis. The distribution of histological diagnoses within the three treatment cohorts is presented in Table 2. More patients with a histological diagnosis of cirrhosis were randomized to the 3- $\mu$ g (20.2%) and 9- $\mu$ g (17.6%) C1FN cohorts than to the 15- $\mu$ g IFN- $\alpha$ 2b cohort (11.9%).

There were no significant differences between the three treatment groups in baseline serum ALT, albumin, bilirubin concentration, and other laboratory parameters (prothrombin time) judged to be clinically relevant in staging the severity of liver disease (Table 1).

### Genotype

The distribution of HCV genotypes among patients in this study showed a predominance of infection with genotype 1 (67.9%). The remaining genotypes were, in order of decreasing frequency, 3a (12.6%), 2b (10.4%), 6 (0.3%), 2a (5.5%), and others (0.9%). Thirteen patients (1.8%) were infected with more than one genotype. The genotype could not be determined in 4 patients (0.4%). The HCV genotypes were evenly distributed within the three treatment groups.

### Assessment of Efficacy

**Serum ALT Response.** At baseline, the mean serum ALT concentrations were  $140 \pm 61$ ,  $147 \pm 63$ , and  $151 \pm 70$  U/L in the 3- $\mu$ g C1FN, 9- $\mu$ g C1FN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively. The mean serum ALT concentrations decreased to  $118 \pm 106$ ,  $84 \pm 82$ , and  $84 \pm 73$  U/L at the end of the 24-week treatment period, but increased to  $124 \pm 81$ ,  $107 \pm 74$ , and  $108 \pm 76$  at the end of the 24-week posttreatment observation period in the 3- $\mu$ g C1FN, 9- $\mu$ g C1FN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively (Fig. 1). Qualitatively, 16.8%, 42.2%, and 36.7% of the patients in the 3- $\mu$ g C1FN, 9- $\mu$ g C1FN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively, had normalization of their serum ALT concentrations at the end of the 24-week treatment period. However, by the end of the 24-week posttreatment observation period, 6.5% of patients treated with 3  $\mu$ g C1FN, 20.3% of patients treated with 9  $\mu$ g C1FN, and 19.6% of patients treated with 15  $\mu$ g IFN- $\alpha$ 2b had serum ALT concentrations that were within the normal range.

There was a significant difference in the distribution of ALT response rates by genotype at the end of the 24-week

TABLE 1. Patient Characteristics at Baseline

	CIFN 3 $\mu$ g (n = 232)	CIFN 9 $\mu$ g (n = 232)	IFN- $\alpha$ 2b 15 $\mu$ g (n = 240)	P
Age (yr)*	43.4 $\pm$ 10.3	42.7 $\pm$ 10.1	42.8 $\pm$ 8.9	.669†
Race				
White	193 (83.2%)	186 (80.2%)	194 (80.8%)	.935‡
Black	18 (7.8%)	17 (7.3%)	23 (9.6%)	
Hispanic	15 (6.5%)	23 (9.9%)	17 (7.1%)	
Asian	5 (2.2%)	5 (2.2%)	5 (2.1%)	
Other	1 (0.4%)	1 (0.4%)	1 (0.4%)	
Sex				
Male	168 (72.4%)	167 (72.0%)	173 (72.1%)	.994‡
Female	64 (27.6%)	65 (28.0%)	67 (27.9%)	
Mode of HCV Acquisition				
Intravenous drug use	94 (40.5%)	106 (45.7%)	106 (44.2%)	.698‡
Transfusion	62 (26.7%)	52 (22.4%)	53 (22.1%)	
Health care worker	12 (5.2%)	8 (3.5%)	13 (5.4%)	
Other	16 (7.0%)	15 (6.5%)	15 (6.3%)	
Unknown	48 (20.7%)	51 (22.0%)	53 (22.1%)	
Laboratory measures (units)*				
Albumin (g/L)	40 $\pm$ 4	41 $\pm$ 3	41 $\pm$ 3	.101†
Alkaline phosphatase (U/L)	92 $\pm$ 37	85 $\pm$ 36	85 $\pm$ 31	.024†
ALT (U/L)	140.3 $\pm$ 60.7	146.7 $\pm$ 63.0	150.5 $\pm$ 69.9	.228†
Bilirubin (mmol/L)	14 $\pm$ 6	14 $\pm$ 6	13 $\pm$ 6	.465†
PT (sec)	13 $\pm$ 1	13 $\pm$ 1	13 $\pm$ 1	.717†
PTT (sec)‡	30 $\pm$ 4	30 $\pm$ 4	30 $\pm$ 4	.709†

\* Mean  $\pm$  SD.

† Comparison among treatment groups analyzed using ANOVA methods.

‡ Comparison of the distribution of patients among treatment groups analyzed using the  $\chi^2$  test for homogeneity.

treatment period. Higher response rates were observed for those patients infected with genotypes 2 (54%) and 3 (55%) than for those infected with genotype 1 (23%) ( $P < .001$ ). At the end of the posttreatment observation period, the ALT response rates were 16% and 18% for patients infected with genotypes 2 and 3, respectively, and 10% for patients infected with genotype 1 ( $P < .001$ ). This difference was independent of the treatment group. Table 3 summarizes the ALT response rates (percent of patients with normal serum ALT concentrations) by genotype for the three treatment groups at the end of the treatment and posttreatment observation periods.

**HCV RNA Response.** The mean serum HCV RNA concentrations in the 3- $\mu$ g CIFN cohort decreased 26% from  $2.88 \pm 1.69 \times 10^6$  copies/mL at baseline to  $2.13 \pm 2.12 \times 10^6$  copies/mL following 24 weeks of therapy. The decrease in the mean serum HCV RNA concentration was greater in the 9- $\mu$ g CIFN dose cohort, decreasing 56% from  $2.93 \pm 1.76 \times 10^6$  copies/mL to  $1.28 \pm 1.94 \times 10^6$  copies/mL after 24 weeks of treatment (Fig. 2). By comparison, the mean serum HCV RNA

concentration decreased 49% from  $2.79 \pm 1.78 \times 10^6$  copies/mL to  $1.41 \pm 1.93 \times 10^6$  copies/mL in the 15- $\mu$ g IFN- $\alpha$ 2b cohort (Fig. 2). Multivariate repeated-measures ANOVA, controlled for baseline viral load, revealed statistically significantly greater reductions in log-transformed HCV RNA concentration for the 9- $\mu$ g CIFN group than for the 15- $\mu$ g IFN- $\alpha$ 2b group over the course of treatment ( $P < .01$ ), and over the course of the entire study ( $P < .01$ ).

TABLE 2. Histological Diagnosis

Diagnosis	CIFN 3 $\mu$ g (n = 232)	CIFN 9 $\mu$ g (n = 232)	IFN- $\alpha$ 2b 15 $\mu$ g (n = 240)
Not evaluable	35 (15.1%)	32 (13.8%)	36 (15.0%)
Evaluable	193 (83.2%)	199 (85.8%)	202 (84.2%)
Not available	4 (1.7%)	1 (0.4%)	2 (0.8%)
Nonspecific changes	15 (7.8%)	18 (9.0%)	16 (7.9%)
Chronic hepatitis C	138 (71.5%)	143 (71.9%)	158 (78.2%)
Cirrhosis	39 (20.2%)	35 (17.6%)	24 (11.9%)
Other	1 (0.5%)	3 (1.5%)	3 (1.5%)
Missing	0 (0.0%)	0 (0.0%)	1 (0.5%)

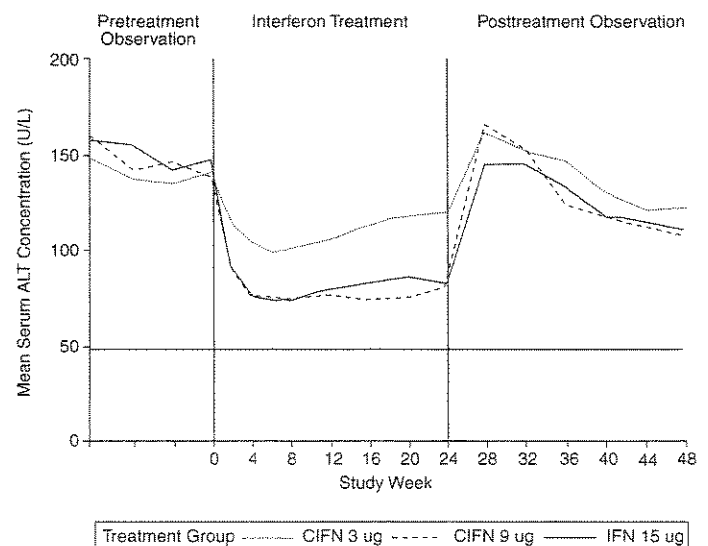


FIG. 1. Mean Serum ALT concentrations. Changes in serum ALT concentrations (U/L) in patients with chronic HCV during the pretreatment observation and posttreatment observation periods. Patients were treated with 3  $\mu$ g CIFN, 9  $\mu$ g CIFN, or 15  $\mu$ g IFN- $\alpha$ 2b for 24 weeks.

TABLE 3. Percentage of Patients With Normal ALT Levels by Genotype

	CIFN 3 $\mu$ g	CIFN 9 $\mu$ g	IFN- $\alpha$ 2b 15 $\mu$ g
End of Treatment*			
Genotype 1 (n = 478)	11%	30%	28%
Genotype 2 (n = 112)	31%	74%	54%
Genotype 3 (n = 89)	37%	69%	58%
End of posttreatment observation*			
Genotype 1 (n = 478)	2%	14%	14%
Genotype 2 (n = 112)	17%	39%	36%
Genotype 3 (n = 89)	22%	27%	25%

\* Data presented exclude 2 patients with genotype 6; 13 patients with mixed genotype; 6 patients with genotypes other than 1, 2, 3, or 6; and 4 patients who were unable to be genotyped.

The percentage of patients with serum HCV RNA less than 100 copies/mL was determined to define responders to therapy at the end of the 24-week treatment and at the end of the 24-week posttreatment observation periods. At the end of the treatment period, 6.5% of patients treated with 3  $\mu$ g CIFN, 34.9% of patients treated with 9  $\mu$ g CIFN, and 27.1% of patients treated with 15  $\mu$ g IFN- $\alpha$ 2b had serum HCV RNA concentrations below the limits of detection of the RT-PCR assay. However, by the end of the posttreatment observation period, 2.6%, 12.1%, and 11.3% of the patients in the 3- $\mu$ g CIFN, 9- $\mu$ g CIFN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively, had serum HCV RNA concentrations below the limits of detection of the RT-PCR assay.

There were significantly higher response rates in patients infected with HCV genotypes 2 (39%) and 3 (48%), compared with those infected with genotype 1 (14%) at the end of the treatment period ( $P < .001$ ), independent of the treatment group (Table 4). Differences of the same magnitude were noted at the end of the posttreatment observation period (data not shown). Furthermore, analysis of HCV RNA concentrations showed differences in the response to CIFN or IFN- $\alpha$ 2b among patients infected with genotype 1. For patients infected with HCV genotype 1, there was a statistically

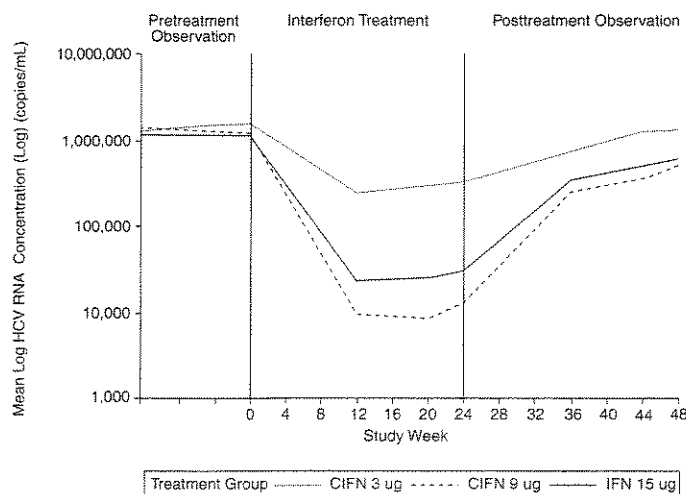


FIG. 2. Mean log HCV RNA concentrations. Changes in log serum HCV RNA concentrations (copies/mL) in patients with chronic HCV during the pretreatment observation, treatment, and posttreatment observation periods. Patients were treated with 3  $\mu$ g CIFN, 9  $\mu$ g CIFN, or 15  $\mu$ g IFN- $\alpha$ 2b for 24 weeks.

TABLE 4. Percentage of Patients With Undetectable HCV RNA by Genotype

	CIFN 3 $\mu$ g	CIFN 9 $\mu$ g	IFN- $\alpha$ 2b 15 $\mu$ g
End of treatment*			
Genotype 1 (n = 478)	4%	24%	15%
Genotype 2 (n = 112)	6%	63%	46%
Genotype 3 (n = 89)	22%	58%	61%
End of posttreatment observation*			
Genotype 1 (n = 478)	2%	8%	4%
Genotype 2 (n = 112)	3%	21%	23%
Genotype 3 (n = 89)	7%	15%	28%

\* Data presented exclude 2 patients with genotype 6; 13 patients with mixed genotype; 6 patients with genotypes other than 1, 2, 3, or 6; and 4 patients who were unable to be genotyped.

significantly greater number of responders at the end of the treatment period in the 9- $\mu$ g CIFN cohort than in patients treated with 15  $\mu$ g IFN- $\alpha$ 2b (24% vs. 15%;  $P = .04$ ). The percentage of HCV genotype 1 patients with complete virological responses at the end of posttreatment observation was 8% for patients treated with 9  $\mu$ g CIFN and 4% for patients treated with IFN- $\alpha$ 2b. In addition, multivariate repeated-measures ANCOVAs revealed a statistically significantly greater reduction in the change of the log-transformed HCV RNA concentrations in the 9- $\mu$ g CIFN group for patients infected with HCV genotype 1, compared with the 15- $\mu$ g IFN- $\alpha$ 2b group over the course of treatment ( $P < .01$ ), and over the course of the entire study ( $P < .01$ ).

#### Liver Histology

There were a total of 426 patients with pre- and posttreatment liver biopsies that were evaluable. The mean change in the Knodell HAI score among all patients (cirrhotic and noncirrhotic) was -1.73, -2.01, and -2.03 units for the 3- $\mu$ g CIFN, 9- $\mu$ g CIFN, and 15- $\mu$ g IFN- $\alpha$ 2b groups, respectively. The change in the HAI score was attributed primarily to reductions in inflammation (periportal necrosis, intralobular degeneration, and portal inflammation). The inflammatory component of the Knodell HAI score decreased 1.71, 1.76, and 2.03 units in the 3- $\mu$ g CIFN, 9- $\mu$ g CIFN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively. There was at least a 2-unit improvement in the HAI score at the end of the posttreatment period in 52% to 55% of the patients in the three cohorts. There were no statistically significant differences among the three treatment groups (Table 5). Although the 3- $\mu$ g CIFN treatment dose was not as efficacious as the 9- $\mu$ g CIFN dose in suppressing serum HCV RNA and ALT, there were no differences in the improvement in the Knodell HAI score between the two groups.

#### Relationship of ALT and HCV Responses to Liver Histology

The relationship between HAI scores and serum ALT and HCV RNA response rates was examined using ANCOVAs with adjustments made for baseline HAI score (Table 6). Treatment group, serum ALT or HCV RNA response at the end of the posttreatment observation period, and the presence or absence of cirrhosis were included in these analyses. Patients who were responders by the ALT or HCV RNA criteria had statistically significantly greater improvements in HAI scores, compared with patients who were not ALT

TABLE 5. Improvement in Knodell HAI Scores

$\Delta$ 2 units	CIFN 3 $\mu$ g		CIFN 9 $\mu$ g		IFN- $\alpha$ 2b 15 $\mu$ g	
	No. Improved/ No. Evaluable*	% Improved	No. Improved/ No. Evaluable*	% Improved	No. Improved/ No. Evaluable*	% Improved
All patients*	71/136	52.2%	78/143	54.6%	80/147	54.4%
Noncirrhotics	58/109	53.2%	62/117	53.0%	71/131	54.2%
Cirrhotics	13/27	48.2%	16/26	61.5%	9/16	56.3%

\* Patients with evaluable biopsies both pretreatment and posttreatment.

or HCV RNA responders ( $P < .001$  for both comparisons). Thus, normalization of serum ALT concentration and reduction of HCV RNA to below-detectable levels correlates with improved liver histology.

#### Anti-Interferon Antibody Formation

The percentages of patients who developed binding antibodies to interferon were similar in the 9- $\mu$ g CIFN (11.4%) and 15- $\mu$ g IFN- $\alpha$ 2b (14.7%) cohorts. However, the antibody responses were transient, and less than 4% of the patients in either cohort developed neutralizing antibodies. The presence of these antibodies did not affect efficacy (data not shown).

#### Adverse Events

Of the 704 randomized patients, 697 patients who received at least one dose of study drug were included in the safety evaluation group. The adverse events most frequently associated with interferon administration were constitutional "flu-like" symptoms (fatigue, fever, rigors, arthralgia, myalgia, headache, or diaphoresis), which were reported in 94%, 97%, and 99% of patients in the 3- $\mu$ g CIFN, 9- $\mu$ g CIFN, and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, respectively. The vast majority of these complaints occurred early in treatment and diminished with time. Other adverse events that were reported in  $\leq 25\%$  of patients in the 9- $\mu$ g CIFN cohort included pharyngitis, back pain, diarrhea, abdominal pain, nausea, insomnia, depression, and nervousness. The majority of the adverse events was reported by the investigators as mild to moderate in severity, and similar types of adverse events and frequency of occurrence were seen in all treatment groups.

Psychiatric adverse events, particularly nervousness and depression, were reported at least once during the follow-up visits in approximately 50% of patients in the three treatment groups. However, these infrequently resulted in the institution of anti-depressant therapy (7% to 10%), dose reductions

(3% to 6%), or withdrawal from the study (1% to 4%), and were comparable across the treatment groups. Nonetheless, psychiatric adverse events were the most common cause leading to withdrawal from the study, accounting for 46.7% of the 45 patients withdrawn from the study. In the 9- $\mu$ g CIFN and 15- $\mu$ g IFN- $\alpha$ 2b cohorts, 9 of the 16 patients in each group (56%) who were withdrawn from the study were withdrawn for psychiatric adverse events. In contrast, only 3 of the 13 patients (23.1%) who were withdrawn from the study in the 3- $\mu$ g CIFN cohort were withdrawn for psychiatric adverse events, suggesting that these events may be dose-related.

Laboratory abnormalities associated with CIFN therapy included decreases in erythrocyte, white blood cell, and platelet production. However, only decreases in the absolute neutrophil ( $< 500 \text{ mm}^3$ ) and platelet ( $< 50,000 \text{ mm}^3$ ) counts necessitated dose reductions. A dose reduction for neutropenia occurred in two patients, one each in the 9- $\mu$ g CIFN and 15- $\mu$ g IFN- $\alpha$ 2b cohorts. By comparison, 1% of patients treated with 3  $\mu$ g CIFN and 3% of patients treated with either 9  $\mu$ g CIFN or 15  $\mu$ g IFN- $\alpha$ 2b had thrombocytopenia that required dose reductions. However, these laboratory abnormalities did not result in infectious complications or clinically important bleeding. Alterations in thyroid function were also reported in 4% to 9% of the patients in the three cohorts. Hypothyroidism occurred in 1% to 4% of the patients, while hyperthyroidism occurred in 1% to 3% of the patients. Thyroid abnormalities rarely necessitated dose reduction (one patient) or withdrawal from the study (two patients).

#### DISCUSSION

Chronic hepatitis C is an insidious infection that may progress to cirrhosis in approximately 25% of patients with chronic HCV infection.<sup>24</sup> Underscoring the morbidity and mortality associated with chronic HCV infection, 15% to 30% of the liver transplantations performed in the United States are for complications associated with chronic hepatitis C.<sup>10</sup> Therefore, improvements in the medical therapy of chronic HCV infection would clearly be beneficial in this patient population. The current approved therapy for chronic hepatitis C is alpha interferons. The results from this randomized, double-blind trial show that CIFN is safe and effective therapy in the treatment of chronic HCV infection.

Historically, the normalization of serum ALT concentrations has been regarded as the most clinically relevant parameter in assessing the efficacy of antiviral therapy. The data from this study showed that CIFN induced a rapid decrease in serum ALT concentrations following the initiation of therapy in both the 3- $\mu$ g and 9- $\mu$ g CIFN cohorts. The mean serum ALT reached a nadir 6 weeks after the initiation of CIFN therapy at 99 U/L and 73 U/L in the 3- $\mu$ g and 9- $\mu$ g

TABLE 6. Mean Changes in HAI Score From Baseline by ALT and HCV RNA Responses

	Mean Change in HAI Score From Baseline		
	CIFN 3 $\mu$ g	CIFN 9 $\mu$ g	IFN $\alpha$ -2b 15 $\mu$ g
HCV RNA responders (n = 28)*†	-4.67	-5.18	-4.29
HCV RNA nonresponders (n = 398)	-1.66	-1.74	-1.80
ALT responders (n = 56)*†	-5.17	-4.13	-4.35
ALT nonresponders (n = 370)	-1.57	-1.58	-1.54

\* Response at end of posttreatment observation period (week 60).

†  $P < .001$  for responders vs. nonresponders in all 3 cohorts.

CIFN cohorts, respectively. Similarly, a nadir in serum ALT concentration was noted in patients treated with 15  $\mu$ g IFN- $\alpha$ 2b (74 U/L) at 8 weeks. Because the efficacy of the 3- $\mu$ g CIFN dose was less than that observed in the 9- $\mu$ g CIFN cohort, only the data from the latter group will be used for comparison with the IFN- $\alpha$ 2b cohort. At the conclusion of the 24-week treatment period, 42.2% of patients treated with 9  $\mu$ g CIFN had normal serum ALT concentrations, compared with 36.7% of patients in the 15- $\mu$ g IFN- $\alpha$ 2b cohort. However, serum ALT is only a surrogate marker for efficacy, because it does not directly assess the presence and replication of the etiologic agent of this disease.<sup>25</sup> Conversely, HCV RNA has been shown to be an independent factor for predicting response to interferon therapy.<sup>14</sup> Therefore, a direct measure of HCV, such as quantitation of serum HCV RNA concentration, may be a better determinant of efficacy than serum ALT concentration.

Recent advances in molecular biology now enable the direct measurement of HCV RNA concentrations by the RT-PCR assay. The data from this study represent the first time the impact of interferon therapy on HCV RNA concentrations has been examined in a large, prospective, randomized, double-blind study. CIFN caused a dramatic decrease in HCV RNA concentrations. By multivariate repeated-measures ANCOVA, the 9- $\mu$ g CIFN cohort showed a statistically significantly greater decrease in log-transformed HCV RNA concentrations, as compared with patients in the 15- $\mu$ g IFN- $\alpha$ 2b cohort over the treatment period ( $P < .01$ ). These data indicate that CIFN treatment significantly reduces HCV RNA when compared with treatment with IFN- $\alpha$ 2b. Although the quantitative assessment of HCV RNA suggests that CIFN reduces HCV RNA to a greater extent than IFN- $\alpha$ 2b, the number of patients with undetectable HCV RNA at the end of the observation period was not different. Thus, 34.9% of the patients treated with 9  $\mu$ g CIFN had undetectable levels of HCV RNA at the end of the 24-week treatment period versus 27.1% for IFN- $\alpha$ 2b, and 12.1% had undetectable levels of HCV RNA at the end of the posttreatment observation period compared with 11.3% for patients treated with IFN- $\alpha$ 2b. These data, coupled with the observation that the responses at the end of treatment are better than posttreatment, may indicate that longer treatment or the use of higher concentrations of interferon may improve the sustained response. In addition, studies are currently in progress to address the efficacy of re-treating patients who have relapsed with higher doses of CIFN therapy.

The natural history and response to interferon therapy of chronic HCV infection has been shown by many studies to be influenced by a variety of host, viral, and other factors. Among viral factors, HCV RNA level and genotype have been identified as being useful in predicting the success of treatment with IFN- $\alpha$ 2b.<sup>14</sup> In patients with low levels of HCV RNA, response rates are comparably good, regardless of genotype.<sup>26</sup> However, high viral loads, such as those present in HCV genotype 1, have resulted in poor therapeutic responses, as measured by ALT normalization and reduction in serum HCV RNA.<sup>27-29</sup> The lower response rates for therapy with both CIFN and IFN- $\alpha$ 2b in patients with genotype 1 are in accord with similar findings in other studies of type 1 IFN therapy.<sup>27,30-32</sup> This has significant clinical implications, because the majority of the patients in the United States are infected with HCV genotype 1.<sup>33,34</sup> However, the present data show for the first time that there was a statistically signifi-

cantly greater number of genotype 1 patients responding to 9  $\mu$ g CIFN when compared with genotype 1 patients receiving 15  $\mu$ g IFN- $\alpha$ 2b for 24 weeks (24% vs. 15%;  $P = .04$ ). Although not statistically significant at the end of posttreatment observation, the trend in HCV RNA response rates in genotype 1 patients treated with 9  $\mu$ g CIFN (8%) versus 15  $\mu$ g IFN- $\alpha$ 2b (4%) may have important clinical implications, especially if higher doses and/or a longer period of therapy with CIFN results in a higher proportion of hepatitis C patients responding to interferon therapy, as has been shown in other studies.<sup>35,36</sup>

In addition to biochemical and virological markers, CIFN also improved liver histology, which, like HCV RNA, has been suggested to be another direct assessment of the efficacy of interferon therapy.<sup>37</sup> In this study, 53.2% and 54.6% of patients treated with 3 and 9  $\mu$ g CIFN, respectively, showed at least a 2-unit improvement in the Knodell HAI score at the end of the posttreatment observation period. Similarly, 54.4% of the patients treated with 15  $\mu$ g IFN- $\alpha$ 2b had at least a 2-unit decrease in the Knodell HAI score. A decline in the Knodell HAI score was noted in both the cirrhotic and noncirrhotic patients. The improvement in the Knodell HAI score was attributed primarily to improvements in the inflammatory components, i.e., portal inflammation, periportal necrosis, and intralobular degeneration. The greater percentage of patients with improvement in liver histology relative to those with a biochemical or virological response (as defined by serum ALT and HCV RNA concentrations) suggests that alpha interferons may exert a beneficial effect upon the liver, even in patients who are incomplete responders.

An important observation with respect to patient management is the positive correlation found between biochemical and virological parameters of treatment efficacy and improvement in liver histology with interferon therapy. These data indicate that ALT normalization and reduction in HCV RNA to below-detectable limits may both be reliable predictors for histological liver improvement. The greatest improvements in HAI scores were observed in patients who had normalized serum ALT concentrations or who became HCV RNA-negative. Because ALT concentrations and HCV RNA are readily measured from serum, a second liver biopsy with its attendant morbidity and potential mortality may not be necessary in the management of chronic HCV patients treated with interferons.

Therapy with CIFN was well tolerated, although adverse events were frequently reported. The adverse-effects profile of CIFN and the frequency of occurrence were similar to that reported for the 15- $\mu$ g IFN- $\alpha$ 2b group. Flu-like symptoms were reported in greater than 94% of the patients in the three treatment regimens, usually during the first month of therapy. However, these symptoms were mild to moderate in severity, and the patients were treated symptomatically with analgesics such as aspirin and acetaminophen. Psychiatric symptoms, particularly depression, were the most common adverse events resulting in withdrawal from the study. The most common laboratory abnormalities were neutropenia, thrombocytopenia, and alterations in thyroid hormones. These adverse events and laboratory abnormalities are similar to what has been previously reported for type 1 interferon therapy.<sup>38,39</sup>

In conclusion, the results of this study show that CIFN provides a clinically important treatment that is safe and effective in patients with chronic HCV infection. Sustained

serum ALT and HCV RNA responses and improvements in liver histology were achieved with C1FN therapy. The data also indicate that C1FN may be more effective than IFN- $\alpha$ 2b in reducing HCV RNA after 24 weeks of therapy. More importantly, in patients infected with HCV genotype 1, 24 weeks of 9  $\mu$ g of C1FN therapy is more effective than a similar duration of IFN- $\alpha$ 2b in lowering serum HCV RNA concentrations. Thus, by providing a greater virological response without additional toxicity against the most prevalent HCV genotype, C1FN offers the potential for a beneficial alternative in the treatment of patients with chronic hepatitis C infection.

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