

# A Randomized, Controlled Trial of Maintenance Interferon Therapy for Patients With Chronic Hepatitis C Virus and Persistent Viremia

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**Background & Aims:** At least half of patients with chronic hepatitis C virus (HCV) fail to respond to interferon or interferon/ribavirin therapy. Histological improvement is observed in some nonresponders. We conducted a randomized, controlled trial to determine if maintenance interferon therapy could prevent histological progression in this subset of nonresponders. **Methods:** Fifty-three patients with chronic HCV were enrolled. All were HCV-RNA positive after 6 months of treatment with interferon alfa-2b but had a histological response. Twenty-seven of the patients were randomly assigned to continue interferon (3 MU 3 times weekly) for 24 months; 26 patients discontinued treatment and were observed prospectively. Alanine aminotransferase (ALT) level and HCV-RNA titer were monitored, and liver biopsy was repeated every 12 months. **Results:** Before interferon therapy, the 2 groups were well matched for all demographic factors, serum ALT ( $94.0 \pm 15.6$ ), log HCV-RNA titer ( $5.85 \pm 0.15$  copies/mL), histology score ( $9.5 \pm 0.2$ ), and percentage with cirrhosis (25%). After 6 months of treatment, significant reductions ( $P < 0.05$ ) in serum ALT level ( $62.6 \pm 9.6$ ), log HCV-RNA titer ( $4.79 \pm 0.13$  copies/mL), and hepatic inflammation ( $4.0 \pm 0.2$ ) were observed. These improvements were maintained in the patients randomized to continue interferon. Stopping treatment was associated with an increase in serum ALT, log HCV-RNA, and hepatic inflammation back to baseline. After 30 months of treatment, mean fibrosis score declined from 2.5 to 1.7 and 80% of patients had histological improvement ( $P < 0.03$ ). Discontinuation of interferon was associated with an increase in mean fibrosis score from 2.2 to 2.4 and worsening of hepatic histology in 30% of patients ( $P < 0.01$ ). **Conclusions:** These data support the hypothesis that maintenance interferon may prevent histological progression of chronic HCV in patients who remain viremic.

Treatment of chronic hepatitis C virus (HCV) with interferon is associated with 1 of 3 treatment outcomes: sustained virological response, end-of-treatment response with subsequent relapse, or nonresponse. The advent of combination interferon-ribavirin for either initial therapy or retreatment of previous relapse has significantly increased the number of patients who achieve a sustained response.<sup>1-4</sup> Despite treatment, at least half of all patients with chronic HCV remain viremic and continue to be classified as nonresponders.

Long-term sustained virological response after interferon therapy is associated with a persistent improvement in hepatic histology.<sup>5-7</sup> In recent years it has also become apparent that approximately 40% of nonresponders also have histological improvement in response to treatment with interferon or interferon/ribavirin combination therapy.<sup>1,5,8-14</sup> Interferon affects liver histopathology by reducing hepatic inflammation; our previous study suggested that this may be related to a reduction in HCV-RNA titer.<sup>14</sup> The rate at which patients with chronic HCV develop fibrosis and progress to cirrhosis is currently believed to be a function of hepatic inflammation.<sup>15-17</sup> It has therefore been hypothesized that continuous interferon therapy, by reducing hepatic inflammation, prevents or slows progression of chronic HCV even in the presence of persistent viremia. Recent studies also suggest that interferon directly inhibits hepatic fibrogenesis,<sup>18-20</sup> an effect that could provide additional benefit for this population.

The specific aim of this study was to test the hypothesis that continued maintenance interferon could prevent progression of chronic HCV in patients who remained viremic. We conducted a randomized controlled trial in which virological nonresponders who achieved a histological response after an initial 6-month interferon therapy

were either treated with maintenance interferon for an additional 2 years or observed prospectively without further treatment. The applicability of a maintenance treatment strategy in the management of patients with chronic HCV is discussed.

## Patients and Methods

### Patient Population

Entry criteria included the following: (1) well-documented chronic hepatitis C, defined by a history of increased serum alanine aminotransferase (ALT) levels above normal limits for at least 6 months, presence of anti-HCV in serum by second-generation enzyme-linked immunosorbent assay, HCV RNA in serum by quantitative polymerase chain reaction assay, and histological evidence of chronic hepatitis; (2) prior treatment with interferon alfa-2b (Intron-A; Schering-Plough, Kenilworth, NJ), 5 million units (MU) 3 times weekly for 6 months; (3) virological nonresponse to this prior course of therapy (HCV-RNA titer  $>500$  copies/mL at completion of therapy); and (4) histological response to this prior course of interferon therapy as previously defined by our group.<sup>14</sup> Patients with histological evidence of cirrhosis were eligible to enter the study. However, laboratory values for serum bilirubin, prothrombin time, albumin, and  $\alpha$ -fetoprotein had to be within the limits of normal; the platelet count had to be greater than  $90,000/\text{mm}^3$ ; and total white cell count had to be greater than  $1500/\text{mm}^3$  at entry. Patients with any other cause for chronic hepatitis were excluded from the study by appropriate serological testing and histological examination of liver tissue. All patients were negative for hepatitis B surface antigen, had either negative or insignificant elevations in serum titers of antinuclear antibody and anti-smooth muscle antibody, and had normal values for serum  $\alpha_1$ -antitrypsin and ceruloplasmin. Patients with increases in serum iron saturation and/or ferritin level had liver tissue analyzed for iron content. All patients with significant stainable iron within the histological specimen were excluded. Patients were also excluded from participation if they were known to be actively using intravenous drugs or consuming alcohol on a regular basis, were positive for human immunodeficiency virus, were pregnant, had chronic renal failure, or had received an organ transplant.

A total of 167 virological nonresponders underwent repeat liver biopsy within 2 weeks of completing a 6-month course of interferon. Sixty-five of these patients (39%) met the definition for histological response and were offered to participate in this clinical trial. Fifty-three patients agreed to enrollment and were randomly assigned to either discontinue treatment and be followed up prospectively or to continue treatment with a lower dose of interferon alfa-2b, 3 MU 3 times weekly, for an additional 24 months. The total duration of interferon treatment in the patients randomized to maintenance therapy was therefore 30 months. None of these patients were off interferon therapy for more than 4 weeks between the time they completed the first course of therapy and began treatment in

the maintenance arm of this protocol. During the 2-year study, patients were evaluated every 3 months. During each visit, serum ALT level, a complete blood count, platelet count, and quantitative HCV-RNA titer were determined. The cohort of patients evaluated and study design are summarized in Figure 1.

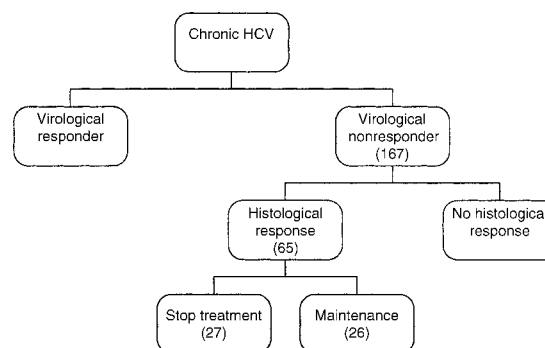
The study protocol was approved by the committee on the conduct of human investigations at the Medical College of Virginia Commonwealth University. Informed consent to participate was obtained after the initial course of interferon therapy but before randomization into this study.

### Liver Histology

Patients underwent liver biopsy within 6 months before the start of treatment and after 6 months of interferon therapy. The histological specimens were scored according to the histological activity index of Knodell et al.<sup>21</sup> by 2 pathologists (M.J.C. and A.S.M.) who were blinded to the timing of the biopsy and the patient's participation in this study. Histological response to interferon therapy was defined as a 50% or greater reduction in the sum of the inflammatory components of the Knodell score (piecemeal necrosis + lobular inflammation + portal inflammation) when the 2 biopsy specimens were compared.<sup>14</sup>

Only patients who remained viremic (virological nonresponders) and achieved histological response after the initial course of interferon therapy were eligible for enrollment to this randomized controlled trial. Both groups of patients (those treated with maintenance interferon and those followed up prospectively without treatment) underwent 2 additional liver biopsies 1 and 2 years after randomization. The decision to repeat the liver biopsy at 1 year was made to ensure that significant histological progression had not occurred in the patients randomized to discontinue interferon treatment. These patients were informed that they would have the option of retreatment with interferon if they developed significant worsening in hepatic histology during the year of observation. The liver biopsy specimens obtained after 1 and 2 years in the study were also scored in blinded fashion by the 2 pathologists according to the criteria of Knodell et al.<sup>21</sup>

Two patients randomized to maintenance therapy refused to



**Figure 1.** Flow diagram outlining the treatment protocol. Number in parenthesis indicates number of patients treated in each group.

undergo repeat liver biopsy after 1 year of treatment but did undergo the 2-year biopsy. Four liver biopsy specimens (1 at year 1 and 3 at year 2) were fragmented so that adequate scoring of hepatic inflammation and fibrosis could not be performed.

### HCV-RNA Analysis

Quantitative HCV-RNA titer was assessed by the Amplicor-Monitor quantitative polymerase chain reaction system (Roche Molecular, Nutley, NJ). The sensitivity, specificity, reproducibility coefficient of variance, and linearity of this assay system have been verified in our laboratory.<sup>22,23</sup> The assay, as set up in our laboratory, detects HCV RNA down to a titer of 500 copies/mL. Serum was obtained from all patients before the start of interferon therapy, 6 months after the start of interferon therapy (at the time patients were randomized to the present study), and at 3-month intervals thereafter. Serum was frozen at  $-70^{\circ}\text{C}$  within 30 minutes of collection. Specimens were thawed and assayed weekly. Results are presented as the log HCV-RNA titer.

### Statistical Analysis

The sample size for the study was calculated by assuming that 66% of patients randomized to maintenance interferon therapy would not have progression in histological severity and that 50% of patients in the control group, who stopped interferon therapy, would have histological progression. Based on these assumptions, it was calculated that 25 patients should be enrolled to each group for a significant difference to be detected.

Values for serum ALT level, Knodell score, and log HCV-RNA titer for each patient group are expressed as mean  $\pm$  SE. Differences in mean values between samples of each group were compared by the paired Student *t* test or the Wilcoxon rank sum test as appropriate. Differences between the 2 groups in demographic criteria, cirrhosis, and the number of patients who developed histological progression during the study were assessed by the  $\chi^2$  test. A *P* value of  $<0.05$  was considered significant.

## Results

### Characteristics of Study Population

A total of 167 nonresponders to interferon therapy were evaluated for inclusion to the study. Of the 65 patients who met entry criteria, 53 agreed to participate. No significant differences in mean age, sex, race, or mean values for serum ALT level, HCV-RNA titer, or Knodell score existed between patients enrolled to the study and the 12 patients who chose not to participate (data not shown).

All 53 patients enrolled to the study were virological nonresponders and therefore remained HCV RNA positive during and after their first course of interferon. Forty of these patients (75%) had participated in a previous

study that defined histological response to interferon treatment.<sup>14</sup> The characteristics of this patient population at baseline, before their initial course of interferon therapy, are summarized in Table 1. The mean age of the study population was 48.3 years (range, 29–75). Fifty-five percent of the patients were male and 87% were white. Mean serum ALT was  $94.0 \pm 15.6$  IU/L; mean log HCV-RNA titer was  $5.85 \pm 0.15$  copies/mL; and mean Knodell score was  $9.5 \pm 0.2$ . Twenty-five percent of the patients had cirrhosis. No significant differences in any of these parameters existed between the 2 study groups.

Table 2 summarizes the biochemical, virological, and histological characteristics of the 2 groups after the initial 6-month course of interferon therapy (5 MU 3 times weekly) and at the time patients were randomized to the study. The principal criterion to enter the study was histological response. As a result, all these patients had at least a 50% decline in the hepatic inflammatory score compared with their baseline pretreatment biopsy score. Thus, mean Knodell score ( $6.1 \pm 0.1$ ) was significantly less ( $P < 0.05$ ) than the pretreatment baseline score. In addition to the improvement in hepatic histology, mean serum ALT declined to  $62.6 \pm 9.6$  IU/L and mean log HCV-RNA titer to  $4.79 \pm 0.13$  copies/mL. Both values were significantly less ( $P < 0.05$ ) than those observed at baseline (Table 1).

The effects of either continuing maintenance interferon or stopping therapy on serum ALT level, HCV-RNA titer, and Knodell score in 2 representative patients from the study are shown in Figure 2. Both patients had a decline in serum ALT level, HCV-RNA titer, and Knodell score during the first 6 months of interferon therapy. The patient randomized to stop treatment had a rapid return in both serum ALT and HCV-RNA titer and an increase in Knodell score back to pretreatment baseline (Figure 2A). The patient on maintenance therapy

**Table 1.** Comparison of Patient Groups at Baseline

	Stop interferon	Maintenance interferon	<i>P</i> value
No. of patients	27	26	NS
Age (yr) <sup>a</sup>	$48.8 \pm 2.2$	$47.8 \pm 1.9$	NS
Sex (n, % male)	14 (52)	15 (58)	NS
Race (n, % white)	23 (85)	23 (88)	NS
Serum ALT (IU/L)	$99.9 \pm 17.9$	$87.6 \pm 10.6$	NS
Log HCV-RNA titer (copies/mL)	$5.62 \pm 0.21$	$6.16 \pm 0.43$	NS
Knodell score			
Inflammatory score <sup>b</sup>	$6.8 \pm 0.4$	$7.5 \pm 0.4$	NS
Fibrosis score	$2.2 \pm 0.3$	$2.5 \pm 0.3$	NS
Cirrhosis (n)	6	7	NS

<sup>a</sup>Values are given as mean  $\pm$  SE and represent baseline characteristics obtained before the initial course of interferon therapy.

<sup>b</sup>Inflammatory score represents the sum of piecemeal necrosis + lobular + portal inflammation as described previously.<sup>14</sup>

**Table 2.** Comparison of Patient Groups at Randomization

	Stop interferon	Maintenance interferon	<i>P</i> value
No. of patients	27	26	NS
Serum ALT (IU/L) <sup>a</sup>	64.6 ± 9.8	60.7 ± 7.5	NS
Log HCV-RNA titer (copies/mL)	4.57 ± 0.17	5.02 ± 0.18	NS
Knodell score			
Inflammatory score <sup>b</sup>	4.0 ± 0.4	3.9 ± 0.4	NS
Fibrosis score	1.8 ± 0.3	2.0 ± 0.3	NS

<sup>a</sup>Values are given as mean ± SE and represent characteristics obtained after 6 months of interferon therapy, at the time of randomization into the study.

<sup>b</sup>Inflammatory score represents the sum of piecemeal necrosis + lobular + portal inflammation as described previously.<sup>14</sup>

had continued decline in serum ALT and HCV-RNA titer with transient eradication of HCV RNA after 12 months of treatment (Figure 2B). Despite continuing interferon, HCV RNA reappeared and serum ALT fluctuated widely. However, Knodell score remained stable and did not return to its pretreatment baseline.

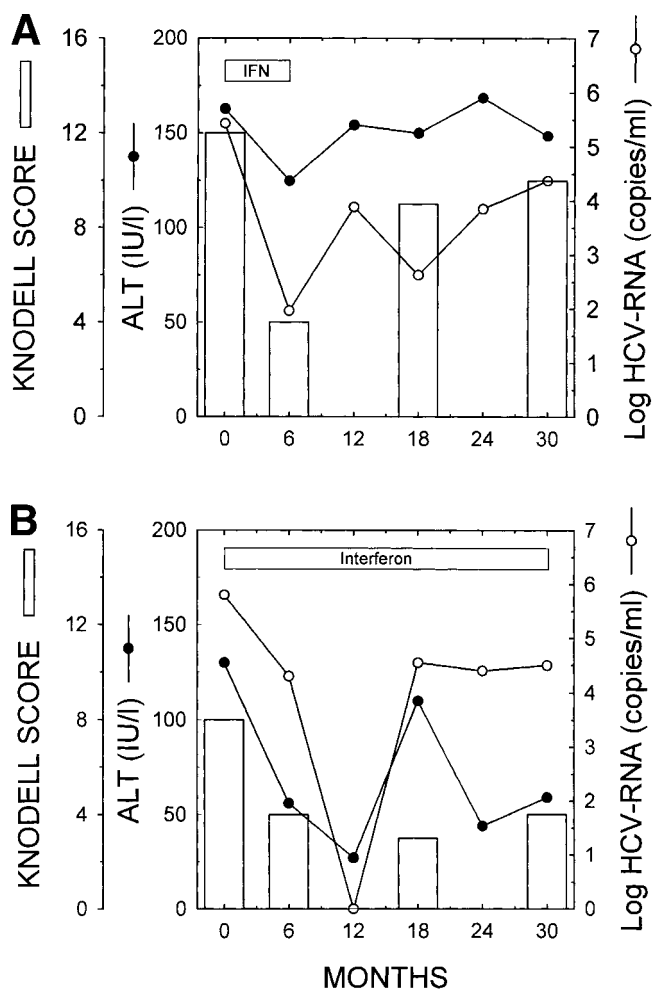
Five patients randomized to maintenance interferon therapy and 2 patients selected to stop treatment dropped out of the protocol after the 1-year liver biopsy. The principal reason given by these patients for discontinuing maintenance treatment was persistent interferon side effects, principally myalgias, arthralgias, fatigue, and headache. The 2 patients randomized to stop treatment withdrew from the protocol because the second liver biopsy showed increased fibrosis compared with pretreatment baseline. All data collected on these 7 patients, up until the time they dropped out, were included in the analysis.

### Effect on Serum ALT

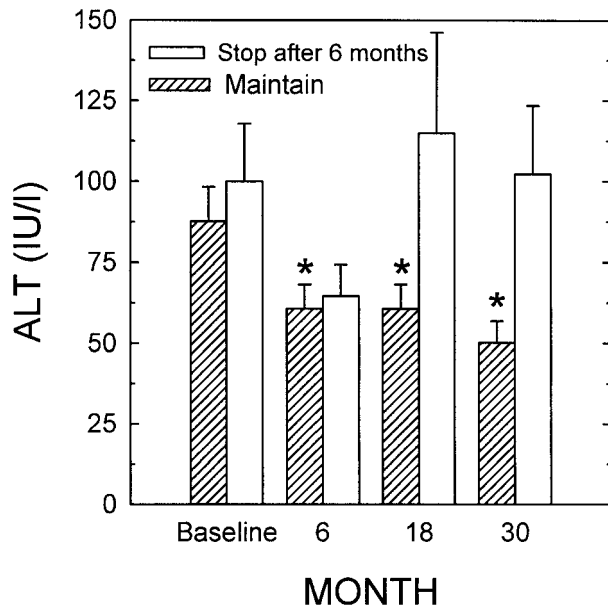
The effect of interferon treatment on serum ALT is shown in Figure 3. After 6 months of interferon treatment, mean serum ALT level declined significantly ( $P < 0.05$ ) in both patient groups (Table 2); 66% (35/53) had values within normal limits. The patients randomized to discontinue interferon treatment had an increase in serum ALT level (mean after 1 and 2 years,  $114.9 \pm 31.3$  and  $102.3 \pm 21.1$  IU/L, respectively) toward pretreatment baseline. During this 2-year period, 41% (11/27) of these patients continued to have serum ALT values that remained within normal limits. Patients randomized to continue interferon treatment had a mean serum ALT value ( $50.2 \pm 6.7$  IU/L after 2 years) that continued to be significantly ( $P < 0.05$ ) lower than pretreatment baseline value throughout the 2-year maintenance period. Sixty-two percent (16/26) of patients who remained on interferon therapy had a normal serum ALT value during the 2-year treatment.

### Effect on HCV-RNA Titer

The effect of interferon treatment on HCV-RNA titer is illustrated in Figure 4. After 6 months of interferon treatment, mean serum HCV-RNA titer declined significantly ( $P < 0.05$ ) in both patient groups (Table 2). Forty-nine percent (26/53) of patients had a decline in HCV-RNA titer of at least 1 log unit from baseline. The patients randomized to stop interferon had an increase in serum HCV-RNA titer (mean values at 1 and 2 years,  $5.49 \pm 0.09$  and  $5.68 \pm 0.09$  copies/mL) back to pretreatment baseline. In contrast, patients randomized to maintenance interferon continued to have an HCV-RNA titer (mean value after 2 years,  $4.90 \pm 0.26$  copies/mL) significantly ( $P < 0.05$ ) lower than baseline throughout the 2-year treatment period. Transient loss of HCV RNA occurred in 6 patients during the 2-year maintenance interferon treatment (see Figure 2B) and in 1 patient randomized to stop interferon therapy.



**Figure 2.** Effects of interferon therapy on serum ALT level, HCV-RNA titer, and Knodell score in 2 representative patients. (A) Patient randomized to discontinue interferon therapy after 6 months of initial treatment. (B) Patient randomized to maintenance interferon therapy at 6 months. See text for details.



**Figure 3.** Change in serum ALT level in patients randomized to stop or to continue interferon treatment with maintenance interferon for an additional 24 months. Both patient groups were treated with interferon for 6 months before randomization. \* $P < 0.05$  compared with baseline value.

### Effect on Liver Histology

The effect of interferon treatment on hepatic inflammation score is shown in Figure 5. After 6 months of interferon treatment, mean hepatic inflammatory score declined significantly ( $P < 0.05$ ) in both patient groups (Table 2). This was expected because histological response to the initial 6-month course of interferon therapy was part of the entrance criteria for enrollment into this study. The patients randomized to stop interferon had an increase in the hepatic inflammation score toward pretreatment baseline. Although the mean value for hepatic inflammation ( $5.2 \pm 0.5$  and  $5.4 \pm 0.6$  at 1 and 2 years, respectively) remained somewhat lower than pretreatment baseline ( $6.8 \pm 0.4$ ), this difference was no longer significant. Patients randomized to maintenance therapy continued to have significantly ( $P < 0.05$ ) lower values for hepatic inflammation score (mean value at 2 years,  $3.4 \pm 0.9$ ) compared with pretreatment baseline during the 2 years of interferon treatment.

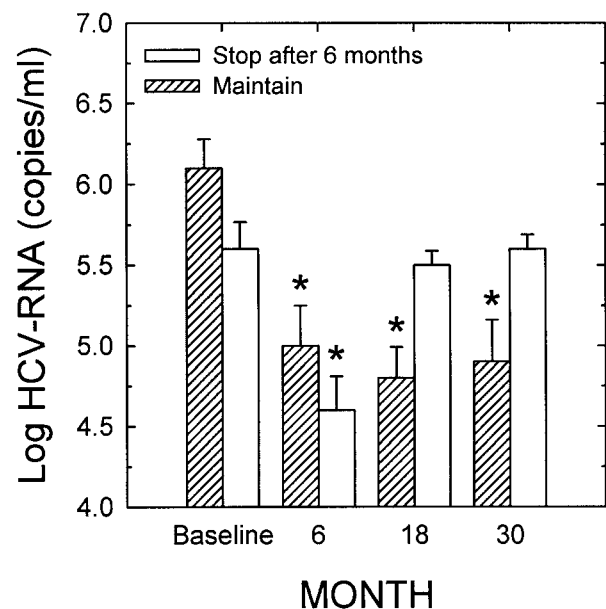
The effect of maintenance interferon therapy on hepatic fibrosis is shown in Figure 6. Hepatic fibrosis score increased in the patients randomized to stop interferon therapy from a baseline value of  $2.2 \pm 0.3$  before starting treatment to  $2.4 \pm 0.4$  ( $P = 0.11$ ) 2 years after stopping therapy. In contrast, after 30 consecutive months of therapy, hepatic fibrosis score declined in patients randomized to maintenance interferon from a baseline of  $2.5 \pm 0.3$  to  $1.7 \pm 0.4$  ( $P = 0.07$ ).

The effect of either stopping interferon or continuing

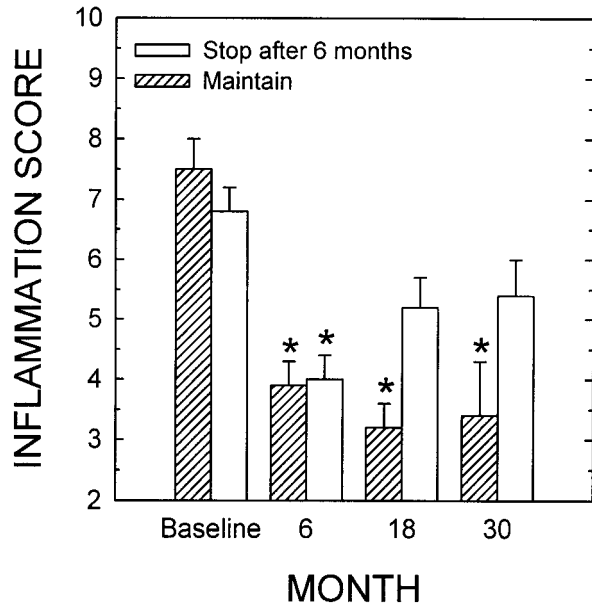
maintenance therapy on hepatic histology is further summarized in Table 3. After 2 years of follow-up, 35% of patients randomized to stop interferon therapy had a worsening in hepatic inflammation score of at least 2 points and 39% had an increase in fibrosis of at least 1 stage. In contrast, 85% of patients treated with interferon for 30 months had an improvement in hepatic inflammation score of at least 2 points and 55% had a reduction in fibrosis of at least 1 stage. Significantly more patients in the maintenance interferon group had histological improvement (a 2-point or more decline in Knodell score;  $P < 0.03$ ), whereas histological worsening (a 2-point or more increase in Knodell score) was significantly more common in the group randomized to stop treatment ( $P < 0.01$ ).

### Discussion

The primary goal of therapy in a patient with chronic HCV is to achieve a sustained virological response, complete resolution of chronic hepatitis, and a return to normal liver histology. To achieve this goal depends on viral characteristics (genotype and titer) and the specific therapy used.<sup>1-4,11,24</sup> Recent studies have clearly shown that the combination of interferon plus ribavirin is superior to interferon alone at achieving this primary goal, regardless of HCV genotype and titer for both initial therapy<sup>1,2,4</sup> and retreatment of patients who have a relapse after interferon monotherapy.<sup>3</sup> Patients infected with a non-type 1 genotype and low viral titer

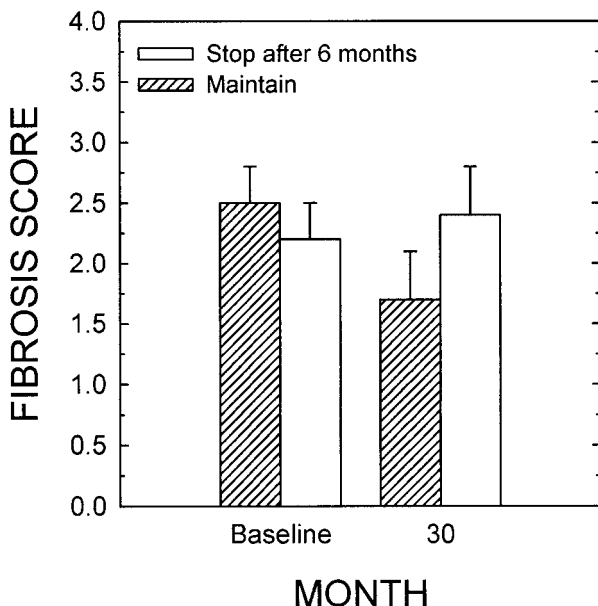


**Figure 4.** Change in HCV-RNA titer in patients randomized to stop interferon treatment or to continue treatment with maintenance interferon for an additional 24 months. Both patient groups were treated with interferon for 6 months before randomization. \* $P < 0.05$  compared with baseline value.



**Figure 5.** Change in hepatic inflammatory score (the sum of piecemeal necrosis + lobular + portal inflammation scores) in patients randomized to discontinue or to continue treatment with maintenance interferon for an additional 24 months. Both patient groups were treated with interferon for 6 months before randomization. \* $P < 0.05$  compared with baseline value.

have the greatest chance of achieving sustained virological response. In contrast, only a minority of patients with a high viral titer of HCV genotype 1 will achieve this goal, even with interferon/ribavirin combination therapy. In the United States, this most difficult to treat subgroup comprises more than half of the current HCV population.<sup>1,25</sup> As a result, most patients with chronic HCV still



**Figure 6.** Change in fibrosis score in patients randomized to stop or to continue interferon treatment with maintenance interferon for an additional 24 months.

**Table 3.** Number of Patients With Worsening or Improvement in Hepatic Histology

	Stop interferon (n = 23) <sup>a</sup>	Maintenance interferon (n = 20) <sup>a</sup>	P value
<b>Worsening in hepatic histology</b>			
≥2-point increase in inflammation score <sup>d</sup>	8 <sup>b</sup> (35%) <sup>c</sup>	0 (0%)	0.004
≥1-point increase in fibrosis stage <sup>e</sup>	9 (39%)	3 (15%)	NS
≥2-point increase in Knodell score	7 (30%)	0 (0%)	0.01
<b>Improvement in hepatic histology</b>			
≥2-point decline in inflammation score	9 (39%)	17 (85%)	0.004
≥1-point decline in fibrosis stage	7 (30%)	11 (55%)	NS
≥2-point decline in Knodell score	10 (43%)	16 (80%)	0.03

<sup>a</sup>Paired liver biopsy specimens from baseline and 30 months were only available in 23 patients randomized to stop interferon therapy and 20 patients in the maintenance treatment groups.

<sup>b</sup>Values are number of patients in each group.

<sup>c</sup>Number in parenthesis indicates percentage of patients in each group.

<sup>d</sup>Inflammation score represents the sum of piecemeal necrosis + lobular + portal inflammation scores.

<sup>e</sup>Stage represents the degree of fibrosis as follows: none, portal, bridging, or cirrhosis.

fail to respond to treatment, remain viremic, and are classified as nonresponders.

In the absence of viral eradication, it is important to consider the possibility that interferon therapy results in alternative benefits to patients with chronic HCV. One such benefit is histological improvement. Several studies have clearly shown that treatment with interferon improves liver histopathology not only in patients who achieve sustained virological response but in nonresponders as well.<sup>1,5,7-15,26,27</sup> Although criteria used to define histological response have varied considerably between studies, histological response has been consistently observed in approximately 80% of patients with end-of-treatment or sustained response and approximately 40% of patients classified as nonresponders.<sup>15</sup> Reevaluation of hepatic histology 2-5 years after discontinuation of treatment in patients with long-term sustained virological response has shown that this improvement in hepatic histology is either maintained or improved to an even greater degree.<sup>3-5</sup>

The goal of the present study was to determine if continuing interferon treatment long term could prevent histological progression in virological nonresponders and for how long histological improvement could be maintained in virological nonresponders after discontinuation of interferon therapy. The study was conducted in the subset of patients who achieved a histological response to

an initial 6-month course of interferon. Although several studies have defined histological response as a 2-point reduction in Knodell score,<sup>1-4,15</sup> histological response for this study was previously defined by our group as a 50% or greater decline in hepatic inflammation.<sup>14</sup> Patients who did not achieve a histological response, according our definition, were excluded from enrollment.

The results clearly show that continuous interferon therapy maintained the improvement in hepatic inflammation observed after short-term treatment and led to a decline in hepatic fibrosis and an improvement in hepatic histology score in 80% of the patients despite persistence of viremia (Figures 5 and 6; Table 3). The reduction in HCV-RNA titer observed during the initial 6-month course of interferon treatment was also maintained by continuous therapy and thereby served as a marker for the efficiency of maintenance therapy. In contrast, stopping interferon in patients who achieved an initial histological response was associated with a rapid return in mean HCV-RNA titer and hepatic inflammation back to their respective pretreatment baseline values, an increase in hepatic fibrosis, and an increase in hepatic histology score in 30% of patients (Figures 4-6; Table 3). The return of HCV-RNA titer and hepatic inflammation to pretreatment baseline value was complete within 3 and 12 months, respectively, the first time these parameters were assessed. Serum ALT appeared to be a poor marker for monitoring hepatic histology and response to interferon therapy in this population. Forty-one percent of patients continued to have a normal serum ALT value despite a worsening in hepatic histology after discontinuation of interferon therapy.

Forty-nine percent of patients enrolled in the trial had a decline in serum HCV-RNA titer of greater than 1 log unit from baseline during their initial course of interferon therapy. This observation and the results of our previous study<sup>14</sup> suggest that a reduction in HCV-RNA titer could be used to predict which patients achieve histological response and could be potential candidates for maintenance interferon therapy. It remains to be determined what minimum decline in HCV-RNA titer is necessary to achieve a histological response and/or if histological improvement can occur in the absence of a decline in HCV-RNA titer. Finally, it is unknown if maintenance interferon therapy could provide any benefit to the virological nonresponders who do not manifest histological response during their initial course of interferon therapy.

The hallmark of progressive liver disease is the development of fibrosis and cirrhosis. Inflammation and hepatocyte injury stimulate stellate cells to secrete type I collagen, the precursor of hepatic fibrosis and cirrho-

sis.<sup>28,29</sup> Any treatment that reduces hepatic inflammation has the ability to reduce the rate of disease progression. Interferon alfa and interferon gamma affect hepatic fibrogenesis by both reducing inflammation and by directly inhibiting collagen synthesis from hepatic stellate cells.<sup>16-18</sup> Morphometric studies showed that hepatic collagen is reduced after interferon treatment in both responders and nonresponders.<sup>30</sup> Recent studies showed that the serum concentration of collagen precursors is increased in patients with progressive liver disease, fibrosis, and cirrhosis<sup>31-34</sup> and is reduced in patients who achieve a sustained response after interferon therapy.<sup>35,36</sup> These observations suggest that interferon may alter progression of chronic HCV by either reducing hepatic inflammation and/or by acting as a direct antifibrotic agent. Whether monitoring serum markers of hepatic fibrosis could alleviate the need for repeated liver biopsy and histological analysis needs to be determined.

It has long been noted that the rate at which patients with chronic hepatitis progress to cirrhosis depends on the severity of hepatic inflammation.<sup>37-40</sup> The same seems to be true for chronic HCV.<sup>41,42</sup> The present study now shows that long-term maintenance interferon therapy can suppress hepatic inflammation over a prolonged period even in the presence of persistent viremia. This provides strong evidence to support the hypothesis that long-term interferon therapy could slow down or even prevent progression to worsening fibrosis or cirrhosis. Such treatment may be ideal for patients with advanced bridging fibrosis who are at increased risk for development of cirrhosis within the following 2-5 years. Such treatment may also benefit patients with stable cirrhosis by reducing the risk for development of decompensation and hepatocellular carcinoma.<sup>43-46</sup>

The secondary goals of interferon therapy—improving hepatic histology, reducing the rate of histological progression to cirrhosis, and reducing the risk for development of hepatocellular carcinoma—are especially important in the nonresponder population. A larger and longer randomized controlled trial is now necessary to confirm the observations made in this study and define the specific population of patients who could benefit from maintenance interferon therapy.

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