

# A Multicenter Study of Recombinant Human Interleukin 12 for the Treatment of Chronic Hepatitis C Virus Infection in Patients Nonresponsive to Previous Therapy

Paul J. Pockros,<sup>1</sup> Keyvr Patel,<sup>2</sup> Christopher O'Brien,<sup>2</sup> Myron Tong,<sup>3</sup> Coleman Smith,<sup>4</sup> Vinod Rustgi,<sup>5</sup> Robert L. Carithers,<sup>6</sup> John G. McHutchison,<sup>2</sup> Elizabeth Olek,<sup>7</sup> and Michael F. DeBruin<sup>7</sup>

Recombinant human interleukin 12 (IL-12) is an immunomodulatory cytokine that is active against several viruses. Treatment options in patients with chronic hepatitis C with nonresponse to interferon (IFN)-based therapy are limited. Prior dose-ranging studies have indicated drug tolerability and transient suppression of hepatitis C virus (HCV) RNA by IL-12. The aim of this study was to determine the safety and efficacy of prolonged IL-12 therapy in patients who have failed treatment with IFN- $\alpha$   $\pm$  ribavirin. A total of 225 patients at 21 U.S. sites who had a history of nonresponse to IFN- $\alpha$  or combination IFN- $\alpha$  plus ribavirin for treatment of HCV were randomized to 500 ng/kg IL-12 or placebo subcutaneously twice weekly for 12 weeks. The groups were then unblinded; patients receiving IL-12 continued for another 36 weeks, and the placebo group received 48 weeks of treatment with IL-12 in an open-label fashion. HCV RNA, serum alanine aminotransferase (ALT) level, and a repeat liver biopsy were assessed at 24 weeks following therapy. Approximately 1% (2 of 160) of nonresponsive patients enrolled for treatment had a sustained virologic response to IL-12 therapy, but 3% (7 of 225) developed severe adverse events probably related to treatment, resulting in early termination of the trial. Common adverse effects reported by most patients included chills, fever, fatigue, headache, and arthralgia. At termination of the study, 160 patients had received at least 8 weeks of treatment with IL-12. Paired liver biopsy specimens were available for evaluation in 54 patients, but there were no significant changes in Knodell fibrosis or histologic activity index (HAI) scores. In conclusion, IL-12 as monotherapy at the doses used in this trial for chronic hepatitis C has low efficacy, was poorly tolerated, and is unlikely to provide an alternative to conventional IFN-based therapy. (HEPATOLOGY 2003;37:1368-1374.)

**H**epatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States; it affects 3.8 million people, 2.7 million (70%) of whom have developed chronic HCV

infection characterized by variable degrees of liver inflammation and hepatocyte injury.<sup>1</sup> Chronic HCV infection is now the most frequent indication for liver transplantation in developed nations.<sup>2</sup> Predictions of disease burden over the next few years suggest that the incidence of HCV-related cirrhosis and hepatocellular carcinoma will increase by 60% to 70%, along with an approximate 2-fold increase in liver-related mortality.<sup>3</sup>

The most effective currently available therapy for chronic hepatitis C is the combination of pegylated interferon (IFN) and ribavirin, which results in a sustained viral response (defined as absence of serum HCV RNA 6 months after the end of treatment) in more than one half of treated patients.<sup>4,5</sup> However, therapy is costly, may be associated with significant adverse effects, and is not suitable for all patients. Thus, newer approaches to treatment are required.

An inadequate immune T-helper cell response may lead to persistent infection and the development of

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

From the <sup>1</sup>Division of Gastroenterology and Hepatology, Scripps Clinic, La Jolla, CA; <sup>2</sup>Duke Clinical Research Institute, Division of Gastroenterology and Hepatology, Duke University Medical Center, Durham, NC, and <sup>3</sup>Center for Liver Disease, University of Miami, Miami, FL; <sup>4</sup>Liver Center, Huntington Medical Research Institute, Pasadena, CA; <sup>5</sup>Minnesota Clinical Research Center, St. Paul, MN; <sup>6</sup>Metropolitan Research Group, Fairfax, VA; <sup>7</sup>Division of Gastroenterology and Hepatology, University of Washington Medical Center, Seattle, WA; and <sup>7</sup>Genetics Institute, Cambridge, MA.

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Address reprint requests to: Paul J. Pockros, M.D., Division of Gastroenterology and Hepatology, Scripps Clinic, 10666 North Torrey Pines Road, La Jolla, CA 92037. E-mail: ppockros@scrippsclinic.com; fax: 858-554-8065.

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chronic hepatitis C,<sup>6</sup> whereas a strong and polyclonal cytotoxic T-lymphocyte response is associated with lower levels of viremia in this disease.<sup>7</sup> Th1 cells stimulate cytotoxic T-lymphocyte responses by producing proinflammatory cytokines such as interleukin 2 (IL-2) and IFN- $\gamma$ . Th2 cells mediate humoral immunity through IL-4, IL-5, and IL-10 and may restrict cell-mediated responses.

Recombinant human IL-12 is a 70-kilodalton heterodimeric cytokine that facilitates a Th1 immune response, enhances cytotoxic T-lymphocyte and natural killer cell activity, and stimulates IFN- $\gamma$  production.<sup>8,9</sup> IL-12 secretion may be reduced in patients with chronic HCV with deficient cytotoxic T-lymphocyte responses, and administration of IL-12 to these patients has been associated with enhanced cellular immune responses to HCV antigens.<sup>10,11</sup>

A 12-week pilot trial of IL-12 in 24 nonresponders to IFN- $\alpha$  indicated that 3 of 6 patients randomized to the 300-ng/kg dosing regimen had complete loss of detectable HCV RNA during therapy.<sup>12</sup> However, all 3 patients experienced a relapse after treatment. The drug seemed to be well tolerated at doses of 30 to 300 ng/kg subcutaneously twice weekly in this study. Another dose-escalation phase 1/2 study using a different formulation of IL-12 (at 0.03-0.5  $\mu$ g/kg subcutaneously once per week for 10 weeks) indicated a greater than 50% decline from baseline HCV RNA in some patients but no loss of detectable virus.<sup>13</sup> Given the drawbacks and shortfalls of our current therapies as well as these preliminary findings, the investigators who designed and planned this study carefully discussed these issues and believed there was a sufficient need and rationale to proceed with this study. The pertinent negative results of this dose-escalation phase 1/2 trial were taken into account when the decision was made to prematurely terminate our study.

The aim of this study was to determine the safety and efficacy of a 48-week regimen of IL-12 in patients with chronic hepatitis C who had previously failed to respond to standard therapy with IFN- $\alpha$  alone or in combination with ribavirin.

## Patients and Methods

**Patients.** Patients aged 18 years or older who were infected with chronic hepatitis C and were nonresponders to previous treatment with standard IFN- $\alpha$  alone or in combination with ribavirin were eligible for this study. Chronic HCV infection was confirmed by the presence of serum HCV RNA greater than 10,000 copies/mL, elevation of alanine aminotransferase (ALT) level 1.25 times or greater above normal on at least 2 occasions within the

preceding 3 months (with the most recent value within 4 weeks of enrollment), and a liver biopsy specimen consistent with chronic hepatitis C within the preceding 12 months. Nonresponse was defined as detectable HCV RNA during standard therapy with IFN- $\alpha$  or IFN- $\alpha$  plus ribavirin therapy, which was at least 6 months before the first dose of IL-12. Patients should have received at least 12 weeks of IFN- $\alpha$  at 3 MIU or consensus IFN at 9 or 15  $\mu$ g thrice weekly with or without at least 1,000 mg/d of ribavirin before being considered nonresponders.

Patients were excluded if positive for hepatitis B surface antigen or human immunodeficiency virus or if there was any evidence of other causes of chronic liver disease. Other exclusion criteria included a comorbid illness such as clinically significant cardiovascular, neurologic, autoimmune, or thyroid disease. Patients were also required to have an absolute neutrophil count of 1,500/ $\mu$ L or greater, hemoglobin level 10 g/dL or greater, platelet count 90,000/ $\mu$ L or greater, serum bilirubin level 2 mg/dL or less, and serum albumin level, creatinine level, and prothrombin time within normal limits. Written informed consent was obtained from all patients, and the study protocol was approved by an institutional review board at each participating center.

**Study Design.** This study was a randomized, double-blind, placebo-controlled, multicenter trial. A total of 289 patients were screened at 21 centers in the United States; 225 patients were enrolled and randomized in a 1:1 ratio to receive either 500 ng/kg IL-12 or placebo subcutaneously twice weekly for 12 weeks. This dosage was chosen based on the results of an unpublished multiple-dosing study that showed a dosage of 500 ng/kg twice weekly to be equally safe and well tolerated as 300 ng/kg twice weekly or 500 ng/kg weekly. In the same 12-week trial, the dosages of 300 ng/kg twice weekly and 500 ng/kg twice weekly seemed to be equally effective during the treatment period; however, one patient treated with the 500-ng/kg dosage had a sustained virologic response (Genetics Institute, data on file). Based on this experience, it was determined that doses ranging from 30 to 500 ng/kg were safe and well tolerated and that the highest dosage might ultimately yield better efficacy.

The study was then unblinded, following which the placebo group received 500 ng/kg IL-12 subcutaneously twice weekly for 48 weeks and the IL-12-treated cohort continued open-label treatment for another 36 weeks. At the end of the 48-week treatment period, patients with an end-of-treatment virologic response (defined as undetectable HCV RNA on 2 occasions) were followed up for another 24 weeks to evaluate efficacy (sustained response) and safety. Patients who failed to clear HCV RNA at the

end of treatment were followed up for 4 weeks to assess safety. All serum samples were analyzed at a single central laboratory. HCV RNA and genotype analysis were determined as described below. All histology specimens were assessed and graded according to the Knodell score by a single pathologist blinded to treatment regimen and outcome. The histologic activity index (HAI) was scored as the sum of inflammatory scores for portal, periportal, and lobular inflammation (range, 0-18). Fibrosis was scored as 0 (no fibrosis), 1 (fibrous portal expansion), 3 (bridging fibrosis), or 4 (cirrhosis).<sup>14</sup> The primary efficacy parameter was the clearance of serum HCV RNA at the end of follow-up, and the secondary efficacy parameters included normalization of ALT level and improvement in liver histology.

**Study Evaluations.** The baseline evaluation included patient history (including demographic information) and complete physical examination. Other tests performed at baseline were serum biochemistry, hematology, thyroid function tests, occult blood in stool, pregnancy tests in women of childbearing potential, chest x-ray, and electrocardiography. Patients were evaluated weekly for adverse events, and the blinded study drug was administered twice weekly on-site by a health care professional for the first 12 weeks. Home administration was allowed thereafter, with IL-12 doses documented in a diary. As part of the study protocol, a liver biopsy was to be obtained within 4 weeks of stopping treatment.

Safety data on all patients were reviewed at 12 and 24 weeks, and adverse events were graded according to the modified World Health Organization scale for acute and subacute toxic effects.<sup>15</sup> If more than 20% of patients experienced grade 3 or 4 adverse events at either point, the trial would be discontinued.

**Measurement of HCV RNA.** Quantitation of serum HCV RNA was performed by a single central laboratory using multicycle reverse-transcription polymerase chain reaction (SUPERQUANT; National Genetics Institute, Culver City, CA) with a lower limit of detection of 100 copies/mL as previously described.<sup>16</sup> HCV genotyping was performed using a line-probe assay (Inno-LiPA; InnoGenetics NV, Zwijnaarde, Belgium).<sup>17</sup>

**Statistical Analysis.** Baseline demographics are descriptively summarized. Differences in continuous variables (expressed as means  $\pm$  SD) were analyzed by ANOVA. Fisher's exact test or  $\chi^2$  test were used for categorical data to compare differences in adverse events between the placebo and treatment groups as well as to assess changes in HAI or Knodell fibrosis scores on follow-up biopsies. All tests were 2-tailed, and significance was determined at  $P < .05$ .

**Table 1. Baseline Patient Demographics**

	IL-12 (n = 113)	Placebo (n = 112)
Age (y)	47.8 $\pm$ 7.9	48.1 $\pm$ 7.1
Sex (M/F)	88/25	71/41
Weight (kg)	86.9 $\pm$ 16.4	84.1 $\pm$ 16.0
Race		
White	85	87
Black	13	13
Hispanic	11	7
Other	4	5
Serum ALT ( $\times$ upper limit of normal)	3.0 $\pm$ 1.7	3.2 $\pm$ 1.7
Serum HCV RNA (copies/mL)	3.55 $\times 10^6 \pm 1.77 \times 10^6$	4.24 $\times 10^6 \pm 4.64 \times 10^6$
Genotype*		
1	98	93
Non-1	15	18
Baseline HAI (range)†	13 (4-16)	13 (4-16)
Bridging fibrosis or cirrhosis (%)	54/85 (63)	41/83 (49)

NOTE. All values are expressed as mean  $\pm$  SD except as otherwise noted. All differences were not significant. Biopsy specimens were obtained in 85 and 83 patients in the IL-12 and placebo arms, respectively.

\*Genotype not available in one patient in the placebo group.

†HAI is the sum of portal, periportal, and lobular inflammation and scored 0-18. Value shown as median score (range).

## Results

**Study Patients.** A total of 225 patients were randomized to receive either IL-12 (n = 113) or placebo (n = 112). There were no differences at baseline between the 2 groups in terms of patient demographics such as age, sex, or race or viral characteristics including genotype and HCV RNA levels (Table 1). Although patients in the IL-12 group had a higher proportion of patients with Knodell stage 3 or 4 fibrosis compared with placebo, these differences were not significant (63% vs. 49%;  $P = .09$ ). The trial was discontinued early after only 9 patients had completed a full 48 weeks of treatment and 160 patients had finished the initial 8 weeks of therapy because of the frequency of adverse effects, the concern regarding severe hematologic adverse events, and the lack of virologic response (2-log decrease in HCV RNA) in most patients.

**Virologic and Biochemical Responses.** Only 9 patients completed 48 weeks of IL-12 therapy and follow-up as defined by the study protocol. Overall, 160 patients received at least 8 weeks of IL-12 therapy before this trial was halted early due to a lack of efficacy and serious adverse events. Nine of these 160 patients (5.6%) had a 2-log or greater (100-fold) decrease in HCV RNA levels compared with baseline.

A further 7 of 160 patients (4.4%) achieved an end-of-treatment viral clearance. Thus, 16 patients achieved ei-

ther end-of-treatment viral clearance or a 2-log decrease in HCV RNA levels (partial response), and most of these patients had HCV genotype 1 infection (10 of 16 [62%]). There seemed to be a higher proportion of patients with genotype non-1 infection who achieved a partial response (6 of 16 [37.5%]) compared with the remaining cohort that completed 8 weeks of treatment but failed to achieve a similar virologic response (nonresponders) (18 of 143 [12.6%]; genotype unknown,  $n = 1$ ). However, these differences did not reach significance ( $P = .07$ ), probably reflecting the small number of genotype non-1-infected patients ( $n = 6$ ) in the partial response group. Furthermore, patients achieving a partial response had lower mean baseline HCV RNA levels ( $\pm$ SD) compared with the nonresponder cohort ( $6.27 \pm 0.43$  vs.  $6.48 \pm 0.36$   $\log_{10}$  copies/mL;  $P = .03$ ). Although the median HAI score was also lower in patients achieving a partial response (11 vs. 13;  $P = .02$ ), there were no differences between the 2 groups for either Knodell fibrosis stage distribution ( $P = .19$ ) or proportions of patients with advanced fibrosis or cirrhosis (5 of 15 vs. 78 of 129;  $P = 0.65$ ). There were no other significant baseline differences between partial responders and nonresponders in terms of mean age ( $\pm$ SD) ( $46.9 \pm 9.2$  vs.  $48.1 \pm 7.4$  years;  $P = .56$ ), sex (male/female, 13/3 vs. 105/39;  $P = .56$ ), and mean ALT ratio ( $\pm$ SD) ( $3.18 \pm 2.02$  vs.  $3.07 \pm 1.65$ ;  $P = 0.79$ ). Two patients who completed treatment achieved sustained viral clearance (sustained viral response of 1.2%). Both patients were genotype 1b. No patient in the placebo arm achieved a 2-log reduction in HCV RNA levels, an end-of-treatment response, or a sustained virologic response.

An end of follow-up biochemical response (normalization of ALT to  $\leq 40$  IU/L) was observed in 16 of 225 patients. This included both patients who achieved sustained viral response and another patient who cleared HCV RNA at the end of treatment but for whom no follow-up HCV RNA results were available. Of the remaining 13 patients who had a biochemical response, HCV RNA levels decreased by more than 2 log copies/mL in one patient but did not change in the other 12 patients.

During the initial 12-week double-blind phase of the trial, there was a general decline in HCV RNA levels in patients treated with IL-12 compared with those receiving placebo, although the differences were only significant at week 8 and were probably not clinically significant given the small change (Fig. 1). Similar declines among the IL-12-treated patients were also observed for hemoglobin and absolute neutrophil counts (Figs. 2 and 3). ALT levels and platelet counts did not change significantly with

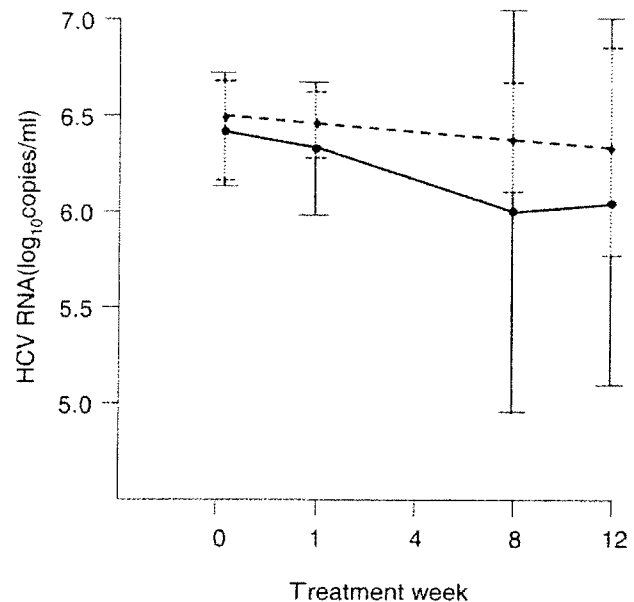


Fig. 1. Graph of  $\log_{10}$  HCV RNA levels during the initial 12-week double-blind phase of the trial. Geometric means and error bars representing standard deviations are shown for the IL-12 (● and solid bar) and placebo (◆ and dashed bar) groups. There was a gradual decline in HCV RNA levels for the IL-12-treated patients compared with the placebo group. However, only small differences of unclear clinical relevance between the 2 groups at week 8 reached statistical significance (6.0 vs. 6.45  $\log_{10}$  copies/mL;  $P = 0.01$ ).

IL-12 treatment compared with placebo during this phase of the trial (Figs. 4 and 5).

**Histologic Evaluation.** Paired liver biopsy specimens were available for evaluation in 54 patients who received IL-12 therapy. The median duration of treatment in these patients was 261 days for the IL-12 group ( $n = 30$ ) and 289 days for the placebo group ( $n = 24$ ). There were no significant differences in the direction of change for HAI (defined as an increase or decrease of  $\geq 2$  points) compared with baseline ( $P = .343$ ). Patients were more likely to have no change in their fibrosis scores following treatment than either an increase or decrease of more than one point on their follow-up biopsy (59% vs. 41%;  $P < .001$ ) (Table 2). Among patients who achieved end-of-treatment viral clearance, 3 of 7 had paired biopsies (of whom 2 had a decrease in HAI of more than 2 points) and one had an increase in HAI of more than 2 points. This latter patient also achieved a sustained viral response but had an increase in the Knodell fibrosis score from 1 to 4 on a follow-up biopsy 12 months after the baseline evaluation. The reasons for this apparent rapid progression of fibrosis are unclear and may be related to a sampling error on the baseline liver biopsy rather than an effect of IL-12.

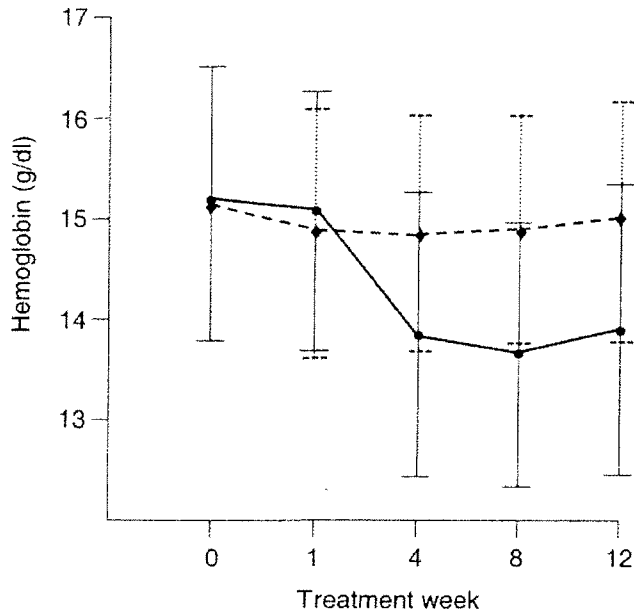


Fig. 2. Hemoglobin levels during the initial 12-week double-blind phase of the trial. Geometric means and error bars representing standard deviations are shown for the IL-12 (● and solid bar) and placebo (◆ and dashed bar) groups. After the first week of therapy, there was a gradual decline in mean hemoglobin levels for the IL-12-treated patients compared with the placebo group. Differences in mean hemoglobin levels were noted between the 2 groups at week 4 (13.8 vs. 14.8 g/dL;  $P < .0001$ ), week 8 (13.6 vs. 14.8 g/dL;  $P < .0001$ ), and week 12 (13.8 vs. 15.0 g/dL;  $P < .0001$ ).

**Adverse Events.** The most common clinical adverse events during treatment included flu-like symptoms such as headache, chills, fever, and asthenia. These occurred in most patients following the first dose of IL-12. Injection-site reactions, stomatitis, and gastrointestinal symptoms were also reported frequently (Table 3). Transient and reversible decreases in absolute neutrophil counts were also observed during treatment with IL-12 and were not accompanied by changes in hemoglobin levels. Most of these events were not serious enough to warrant dose reduction or withdrawal of therapy.

Of concern were the 14 serious adverse events of which 7 were related or possibly related to the study drug. These included immune thrombocytopenic purpura, profound neutropenia, anemia, ascites, melena, and abdominal pain requiring hospitalization in 2 patients. Adverse events resulted in withdrawal of 50 patients (22%) from the study within the first few weeks. Additionally, the lack of efficacy of IL-12 at an interim analysis resulted in the premature termination of this study.

## Discussion

This large, multicenter, randomized, double-blind, placebo-controlled trial evaluated recombinant IL-12 therapy in patients with chronic hepatitis C who had pre-

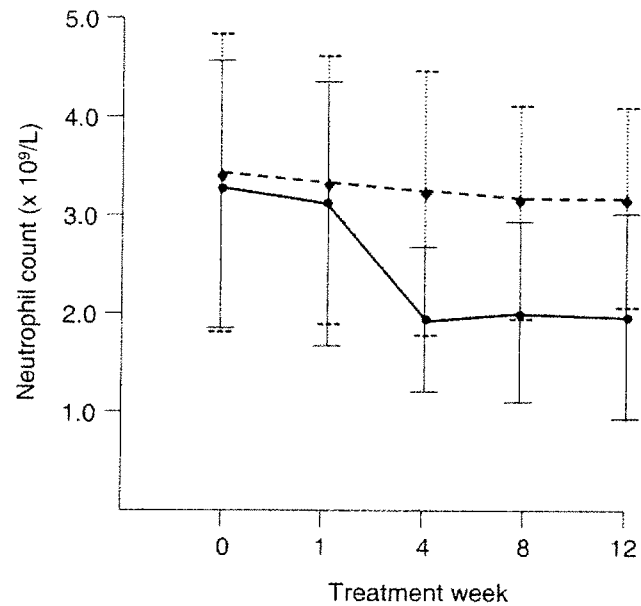


Fig. 3. Neutrophil counts ( $\times 10^9/L$ ) during the initial 12-week phase of the trial. Geometric means and error bars representing standard deviations are shown for the IL-12 (● and solid bar) and placebo (◆ and dashed bar) groups. After the first week of therapy, there was a gradual decline in mean neutrophil counts for the IL-12-treated patients compared with the placebo group. Differences in mean neutrophil counts were noted between the 2 groups at week 4 ( $1.92$  vs.  $3.16 \times 10^9/L$ ;  $P < .0001$ ), week 8 ( $1.94$  vs.  $3.05 \times 10^9/L$ ;  $P < .0001$ ), and week 12 ( $1.93$  vs.  $3.05 \times 10^9/L$ ;  $P < .0001$ ).

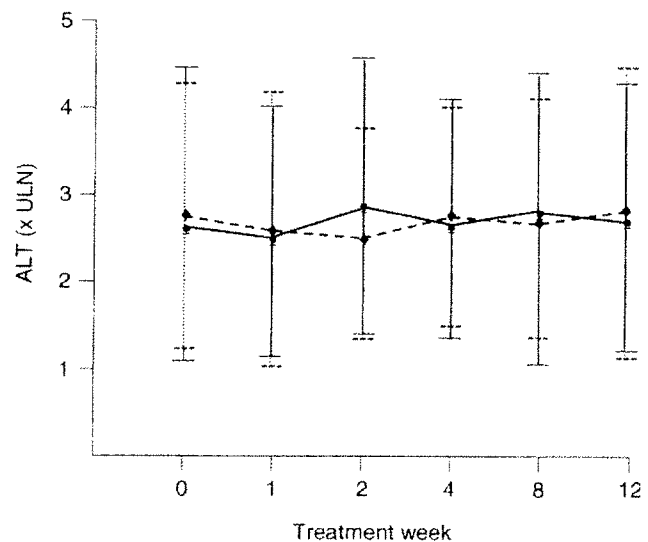


Fig. 4. Variation in ALT as a ratio to the upper limit of normal (ULN) level during the initial 12-week double-blind phase of the trial. Geometric means and error bars representing standard deviations are shown for the IL-12 (● and solid bar) and placebo (◆ and dashed bar) groups. No significant differences were noted between the 2 groups during this initial treatment phase, and the geometric mean for the ALT ratio remained relatively steady with values between 2.4 and 2.8.

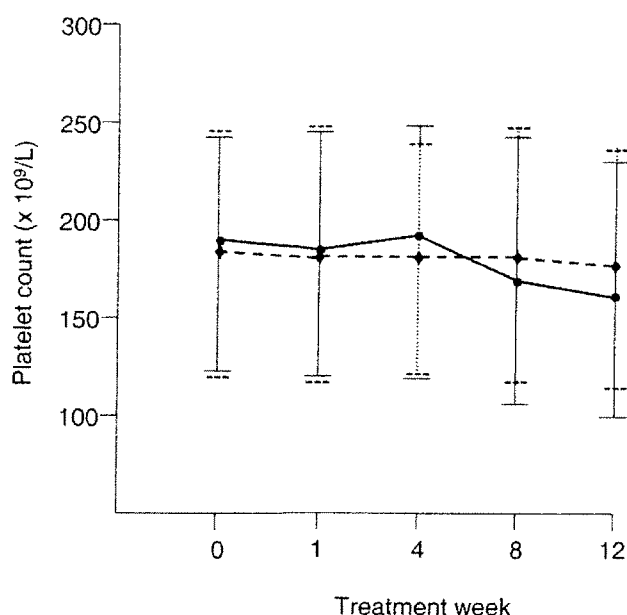


Fig. 5. Mean platelet count ( $\times 10^9/L$ ) during the initial 12 weeks of the trial. Geometric means and error bars representing standard deviations are shown for the IL-12 (● and solid bar) and placebo (◆ and dashed bar) groups. No significant differences in mean platelet count were noted between the 2 groups and remained relatively steady between 160 and 190  $\times 10^9/L$ .

viously failed to achieve sustained viral clearance with IFN- $\alpha$  alone or IFN- $\alpha$  plus ribavirin. The results show an end-of-treatment virologic response in 7 of 160 (4.4%) and sustained virologic response in 2 of 160 (1%) for patients who received at least 8 weeks of IL-12 therapy. However, 7 of 225 (3%) developed severe adverse events probably related to therapy; as a result, this study was terminated early. The low efficacy in terms of virologic or histologic response compared with conventional IFN- $\alpha$  and ribavirin therapy in this prior treatment failure group, combined with the significant toxicity observed in this

**Table 2. Changes in Histology With IL-12 Treatment Among 54 Patients With Paired Biopsy Specimens**

	No. of Patients (%) (n = 4)
HAI*	
Improved $\geq 2$ points	22 (41)
Worsened $\geq 2$ points	19 (35)
No change or $\pm 1$ point	13 (24)
Knodell fibrosis score	
Improved $\geq 1$ point	5 (9)
Worsened $\geq 1$ point	17 (31)
No change	32 (59)†

\*Differences shown not significant for HAI ( $P = .343$ ).

†Patients were more likely to have no change in their fibrosis scores following treatment than either an increase or decrease of  $\geq 1$  point on their follow-up biopsy (59% vs. 41%;  $P < .001$  by  $\chi^2$  test) for Knodell fibrosis score.

**Table 3. Common Adverse Events Observed With IL-12 Compared With Placebo**

	IL-12 (n = 113)	Placebo (n = 112)
Headache	93 (82)	63 (56)
Chills	88 (78)	24 (21)
Fever	90 (80)	22 (20)
Arthralgia	52 (46)	29 (26)
Injection-site reaction	43 (38)	4 (4)
Insomnia	37 (33)	19 (17)
Anorexia	36 (32)	6 (5)
Stomatitis	17 (15)	0 (0)
Constipation	13 (12)	3 (3)
Depression	13 (12)	3 (3)

NOTE. The most common and significant adverse events as reported by patients during the initial 12-week blinded part of the trial compared with placebo. IL-12 vs. placebo: all differences  $P < .001$ . Values in parentheses are percentages.

study, suggests that IL-12 as monotherapy probably has no further role in the treatment of chronic hepatitis C.

The common adverse events of flu-like symptoms and fatigue were also observed in a previous small dose-ranging study<sup>12</sup> but no serious adverse events were reported, although the highest dosage used was 300 ng/kg twice weekly for 12 weeks compared with the 500-ng/kg dosing regimen used in our study. In the unpublished 12-week trial using dosages of 300 ng/kg and 500 ng/kg, no patients experienced grade 4 adverse events; however, one patient receiving 500 ng/kg experienced a grade 4 laboratory toxicity (neutropenia) not observed in the lower-dose group. It seems clear from our study that a longer duration of therapy at the 500-ng/kg dosage resulted in more significant adverse events and laboratory toxicities than anticipated. In retrospect, there was probably too rapid a transition from the initial studies showing only marginal efficacy of this cytokine against HCV to a multicenter trial. It would have been advantageous to evaluate other safety and efficacy studies with intermediate end points (such as a decrease in viral load) before designing this trial. The lack of efficacy and safety issues that led to early termination of this trial are not surprising in view of the pilot study data. In addition, another phase 1/2 trial using a different formulation of IL-12 administered once weekly for 10 weeks showed 2 serious adverse events in the 500-ng/kg group, but both were believed to be unrelated to the study drug.<sup>13</sup> However, no patients achieved viral clearance at any stage in either of these prior studies.

Recombinant IL-12 has antiviral effects mediated through augmentation of cytotoxic T-lymphocyte and natural killer cell activity leading to lysis of virus-infected cells and suppression of viral replication, probably through natural killer cell IFN- $\gamma$  production.<sup>8,9</sup> Unfortunately, the dose required to achieve a 2-log reduction in HCV RNA in any chronically infected patient is associ-

ated with an unacceptable adverse-effect profile, as shown in this study. Th1 cytokine profiles or IL-12 levels were not evaluated in this study, and it is possible that, despite the twice-weekly dosing schedule, the actual levels of IL-12 *in vivo* were insufficient to influence a significant shift toward a Th1 immune response. A lower dose and more frequent subcutaneous administration schedule may have provided a better pharmacokinetic and safety profile; despite this, it seems unlikely that the antiviral efficacy of IL-12 would compare with currently available IFN-based therapy for chronic hepatitis C, even in previously treated patients. The role of IL-12 as adjunctive therapy with IFN- $\alpha$  has not been evaluated.

The patients with chronic hepatitis C recruited to this trial were previous nonresponders. These were patients who failed to clear circulating HCV RNA during at least 12 consecutive weeks of treatment with standard IFN- $\alpha$  alone or in combination with ribavirin. Furthermore, 91 of 225 patients (40%) had advanced fibrosis or cirrhosis at baseline and most were infected with genotype 1; these factors may have precluded a higher response than observed when this trial was terminated. The incidence of significant bone marrow suppression with treatment was also relatively low despite the presence of patients with advanced liver disease.

Other Th1 immunomodulatory therapies currently under study include IL-2, IFN- $\gamma$ , thymosin, and histamine analogues.<sup>18-21</sup> The proposed mechanisms of actions of these compounds are slightly different from one another and from IL-12; therefore, it is unknown whether the findings of this study can be extrapolated to other Th1-inducing cytokines. Separate randomized, controlled trials of these compounds will be required to evaluate their efficacy.

In conclusion, IL-12 given alone for the treatment of chronic hepatitis C is not efficacious and is poorly tolerated. The antiviral efficacy and histologic benefits of the newer pegylated IFNs in combination with ribavirin suggest that immunomodulation through IL-12 should not be developed as future therapy for chronic hepatitis C.

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