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A COMPARISON OF THREE INTERFERON ALFA-2b REGIMENS FOR THE LONG-TERM TREATMENT OF CHRONIC NON-A, NON-B HEPATITIS

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Abstract Background. We studied the effects of long-term treatment with interferon on histologic features of the liver and serum alanine aminotransferase concentrations in patients with chronic non-A, non-B hepatitis.

Methods. Consecutive patients who met the inclusion criteria were enrolled in the study. The diagnosis of chronic non-A, non-B hepatitis was established on the basis of the liver-biopsy findings and an abnormal serum alanine aminotransferase value (more than 1.5 times the normal value) for at least one year. All patients were treated for 6 months with 3 million units of interferon alfa-2b given subcutaneously three times a week and were then randomly assigned to the same treatment for an additional 12 months (group 1), a regimen of 1 million units three times a week for 12 months (group 2), or no further treatment (group 3). Patients in group 3 who had elevated serum alanine aminotransferase concentrations for three consecutive months underwent the initial regimen once again. Follow-up continued for two years after the discontinuation of treatment. Histologic improvement was defined as a decrease of at least one point in the score for necroinflammatory activity (0, no activity; 1, mild; 2, moderate; or 3, severe) between the first liver biopsy and a biopsy performed at 18 months.

INTERFERON alfa is effective in reducing serum alanine aminotransferase concentrations during treatment and, to a lesser extent, during the year after treatment in patients with chronic hepatitis C virus (HCV) infection.¹ Liver-biopsy findings may be more

Results. Of the 329 patients initially treated, 303 were randomized: 103 to group 1, 101 to group 2, and 99 to group 3. Of the 286 patients tested, 252 (88.1 percent) had antibodies to hepatitis C virus. In an intention-to-treat analysis, 46 of the patients in group 1 (44.7 percent) had normal serum alanine aminotransferase values at 18 months, as compared with 27 of the patients in group 2 (26.7 percent, $P=0.008$) and 30 of those in group 3 (30.3 percent, $P=0.04$). Between 19 and 42 months, 23 of the patients in group 1 (22.3 percent) continued to have normal serum alanine aminotransferase values (measured every 6 months), as compared with 10 of the patients in group 2 (9.9 percent, $P=0.02$) and 8 of those in group 3 (8.1 percent, $P=0.005$). Among the 176 patients with repeated liver biopsies at 18 months, more patients in group 1 had improved histologic-activity scores (69.6 percent) than in group 2 (47.6 percent, $P=0.02$) or group 3 (38.6 percent, $P<0.001$).

Conclusions. Among patients with chronic non-A, non-B hepatitis, a regimen of 3 million units of interferon alfa-2b given three times a week for 18 months produced better histologic findings and serum alanine aminotransferase values than regimens involving a lower dose or a shorter duration of treatment. (N Engl J Med 1995;332:1457-62.)

accurate than serum alanine aminotransferase values as a surrogate marker of the response to therapy. Among patients with chronic HCV infection, morbidity and mortality occur only in those with severe chronic active hepatitis or cirrhosis. In patients with chronic viral hepatitis, portal and lobular necroinflammatory lesions may be precursors of cirrhosis.² It is reasonable to assume that a reduction in inflammation and necrosis in patients with cirrhosis may reduce mortality.

There is no clear evidence that serum alanine aminotransferase values can accurately predict the liver-biopsy findings in patients with HCV infection, whether or not they receive treatment with interferon. Nevertheless, evaluation of the efficacy of treatment and identification of possible prognostic factors are often based on serum alanine aminotransferase measurements alone.

We studied the effect of three interferon alfa-2b regimens over an 18-month period on liver-biopsy findings

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and serum alanine aminotransferase concentrations in patients with chronic non-A, non-B hepatitis. After the treatment period, follow-up continued for two years. We also studied the relation between changes in liver-biopsy findings and changes in serum alanine aminotransferase concentrations.

METHODS

Patients

Patients enrolled in the study had a diagnosis of chronic non-A, non-B hepatitis established on the basis of liver-biopsy findings and abnormal serum alanine aminotransferase values (higher than 1.5 times the normal value) for at least one year. Patients were excluded if they met any of the following criteria: age under 18 years, a positive test for serum hepatitis B surface antigen, current drug addiction, a positive test for serum antibodies to the human immunodeficiency virus, a liver biopsy performed more than six months earlier, major iron deposits in the liver, pregnancy or absence of contraceptive use in women of childbearing age, a severe associated disease or decompensated cirrhosis, or failure to provide written informed consent. The study was conducted in 39 centers. Consecutive patients who met the eligibility criteria were enrolled between 1989 and 1991.

Treatment

All patients were treated for six months with interferon alfa-2b (Intron A, Schering, Kenilworth, N.J.) in a dose of 3 million units administered subcutaneously three times a week. After six months, the patients were randomly assigned to one of three groups. The assignments were made with the use of sealed envelopes, without knowledge of any clinical or biologic data. Patients in group 1 received 3 million units of interferon three times a week for an additional 12 months, or a total of 18 months. Patients in group 2 received 1 million units of interferon three times a week for an additional 12 months. Patients in group 3 received no further treatment with interferon, unless their serum alanine aminotransferase concentrations were above the upper limit of normal for 3 consecutive months, in which case they received 3 million units of interferon three times a week through the 18th month after the initial treatment.

Liver-Biopsy Studies

Liver-biopsy specimens obtained at the time of enrollment and at 18 months were assessed independently by two of us, who were not aware of the timing of the biopsy or of any clinical or biochemical data. The specimens were evaluated according to a previously validated scoring system,³ which includes 27 semiquantitatively scored items. The last item assesses necroinflammatory activity (0, no activity; 1, mild; 2, moderate; or 3, severe), taking into account the severity of portal and lobular necroinflammatory lesions. Histologic improvement was defined as a decrease of at least one point in the score for histologic activity between the first and second liver biopsies.

Virologic Data

At the beginning of the study, data on antibodies to HCV were not available, and assays were performed during follow-up. For the molecular studies, either stored frozen serum samples obtained before or after enrollment or fresh samples were used. Polymerase-chain-reaction (PCR) studies were performed with the Amplicor Roche Diagnostic System (Hoffmann-LaRoche, Basel, Switzerland), quantification by branched DNA was performed with Amplex Chiron (Chiron, Emeryville, Calif.), and genotyping was performed with PCR and fluorescent competitive oligonucleotide primers, a technique that has recently been validated.⁴

Statistical Analysis

The main end point chosen to calculate the required sample size was the anticipated serum alanine aminotransferase response between 7 and 18 months after the initiation of treatment. It was calculated that 100 patients per group were needed to detect a differ-

ence of 20 percent in the proportion of patients with responses, at least between groups 1 and 2 (40 and 20 percent, respectively), with an alpha error of 5 percent and a beta error of 10 percent.

Five end points involving serum alanine aminotransferase measurements were used: a complete response to interferon at 6 months (a normal serum alanine aminotransferase concentration at the 5th and 6th months), at 18 months (a normal concentration at the 17th and 18th months), and between the 7th and 18th months (a normal concentration each month); a partial or complete response at 3 months (a serum alanine aminotransferase concentration lower than twice the upper limit of the normal value); and a complete response sustained throughout the 2 years after the end of treatment (a normal serum alanine aminotransferase concentration every 6 months).

Statistical methods (two-tailed) included the chi-square test, Fisher's exact test, Student's t-test, and the Mann-Whitney nonparametric test.⁵ Regression analysis was used to assess the independent effect of treatment on potential prognostic factors. Since there was a trend toward a better serum alanine aminotransferase response in group 1 at six months (when all groups had received the same treatment), separate logistic-regression analyses were performed to control for this difference. All comparisons of serum alanine aminotransferase values were performed twice: according to the intention-to-treat method and according to a per-protocol strategy. In the intention-to-treat analysis, no patients were excluded after randomization, even in the case of noncompliance or missing data. In the per-protocol analysis, patients with missing data were excluded. When two consecutive serum alanine aminotransferase values were missing, the patient was considered not to have had a response. To evaluate the possibility of bias, the patients who underwent two liver biopsies were compared with the patients who underwent only one, with the use of univariate and multivariate techniques (data not shown).

All patients provided written informed consent before randomization. The protocol was approved by the ethics committee of Paris Sud University.

RESULTS

Of the 329 patients enrolled in the study, 20 stopped treatment during the first six months because of adverse events, 3 were lost to follow-up, 2 declined to undergo randomization, and 1 died of hepatocellular carcinoma. At six months, the remaining 303 patients were randomly assigned to one of the three groups; 103 were assigned to group 1, 101 to group 2, and 99 to group 3.

There were no significant differences among the groups at the beginning of the study (Table 1). Tests for serum HCV antibodies were performed with the enzyme-linked immunosorbent assay (first or second generation) in 286 patients; 252 (88.1 percent) had HCV antibodies.

Compliance with Treatment and Protocol

In group 1, 31 patients stopped treatment: 19 because of adverse events or the development of other diseases, 9 because they did not wish to continue with the treatment, and 3 because their physicians did not follow the protocol. In group 2, 22 patients stopped treatment: 15 because of adverse events or the development of other diseases and 7 because they did not wish to continue. In group 3, 46 patients followed the protocol; 12, including 6 with complete and sustained biologic responses, were not retreated with interferon because their serum alanine aminotransferase con-

Table 1. Base-Line Characteristics of 303 Patients with Non-A, Non-B Hepatitis Treated with Interferon Alfa-2b.*

CHARACTERISTIC	GROUP 1 (N = 103)	GROUP 2 (N = 101)	GROUP 3 (N = 99)
Age (yr)	49±1.5	51.2±1.4	50.4±1.4
Male sex (% of patients)	51	55	49
White race (% of patients)	99	97	97
Duration of abnormal alanine aminotransferase (mo)	31±3	42±8	35±5
Time since infection (mo)†	77±6	102±10	80±8
History of blood transfusion (% of patients)	54	45	47
Cirrhosis on initial liver biopsy (% of patients)	28	27	23
Score on Knodell index‡	9.0±3.2	9.6±3.5	8.2±3.5
Serum alanine aminotransferase (×35 U/liter)§	3.7±2.1	3.8±2.5	3.3±2.2
Serum γ -glutamyltransferase (×30 U/liter)§	2.1±3.3	2.1±2.3	2.3±2.7
Genotype 1b (% of patients)¶	43	44	53
Quantification by branched DNA	21±7	33±8	18±5

*Plus-minus values are means \pm SD. See the text for definitions of the three groups.

†The time from the date of infection (through transfusion or intravenous drug addiction), when known, to the date of enrollment.

‡The Knodell index is a histologic scoring system (0 to 22) assessing portal inflammation (0 to 4), periportal bridging necrosis (0 to 10), and fibrosis (0 to 4).

§The value in parentheses is the upper limit of the normal range.

¶Genotypes were assessed retrospectively in 58 patients (14 in group 1, 25 in group 2, and 19 in group 3).

||Quantification by branched DNA was performed retrospectively with stored serum samples obtained before treatment from 51 patients (15 in group 1, 19 in group 2, and 17 in group 3); the results are expressed in multiples of 10^5 equivalent viral copies per milliliter.

centrations were not elevated for three consecutive months. In 4 of the 34 patients who were retreated according to the protocol, retreatment was stopped because of adverse events. The protocol was not followed for 53 of the patients in group 3; in 46 patients who had elevated serum alanine aminotransferase concentrations for three consecutive months, treatment was not restarted, mainly because the patients had had adverse events during the initial treatment and therefore declined further treatment; in 6 patients, the initial treatment was not stopped at six months; and in 1 patient, treatment was restarted despite normal serum alanine aminotransferase concentrations.

The mean number of missing serum alanine aminotransferase values per patient was 0.5 during the first 6 months and 3.3 between the 7th and 18th months, with no differences among the three groups. During the two-year follow-up period after treatment, no serum alanine aminotransferase values were available for 37 patients in group 1, 27 in group 2, and 41 in group 3.

Serum Alanine Aminotransferase Concentrations and Virologic Responses

In group 1, as compared with groups 2 and 3, there was a signifi-

cant increase in the percentage of patients with complete serum alanine aminotransferase responses at 18 months, between 7 and 18 months, and during the 2 years after treatment (Table 2). The results of the per-protocol analyses were similar (data not shown). Viral data were retrospectively investigated for 100 patients. A total of 210 HCV PCR analyses and 135 quantifications of branched DNA were performed in the 100 patients, with 51 quantifications performed before treatment and 84 after treatment. Genotypes were identified in 58 patients. As compared with the patients in groups 2 and 3, those in group 1 were more likely to have negative results on HCV PCR analyses after treatment and to have lower quantities of virus as measured by the branched-DNA technique (Table 2).

Histologic Responses

Of the 103 patients in group 1, 56 underwent liver biopsies at 18 months, as did 63 of the 101 patients in group 2 and 57 of the 99 patients in group 3. The percentage of patients in group 1 with histologic-activity scores that improved by at least one grade was 69.6 percent (39 of 56), as compared with 47.6 percent in group 2 (30 of 63 patients; odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.4; $P=0.02$) and 38.6 percent in group 3 (22 of 57 patients; odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.9; $P<0.001$). A logistic-regression analysis that took into account the serum alanine aminotransferase response at six months showed that the patients in group 1 had stronger histologic responses than the patients in group 2 (odds ratio for an improvement in histologic-activity score by at least one grade, 2.4; 95 percent confidence interval, 1.1 to 5.3; $P=0.03$) or those in group 3 (odds ratio, 3.7; 95 percent confidence interval, 1.7 to 8.0; $P=0.002$).

Data on histologic changes with treatment are shown in Table 3. Patients in group 1 were significantly more likely than those in either group 2 or group 3

Table 2. Normal Serum Alanine Aminotransferase Concentrations (Intention-to-Treat Analysis), Disappearance of Serum Hepatitis C Virus, and Residual Viremia.

GROUP	NORMAL SERUM ALANINE AMINOTRANSFERASE				NO SERUM HEPATITIS C VIRUS AFTER TREATMENT	RESIDUAL VIREMIA (BRANCHED DNA)* AFTER TREATMENT
	AT 6 MO	AT 18 MO	BETWEEN 7 AND 18 MO	AFTER TREATMENT (19-42 MO)		
	no. of patients (%)				no. of patients/total no. (%)	mean \pm SE
1 (n = 103)	51 (49.5)	46 (44.7)†	25 (24.3)‡	23 (22.3)§	17/26 (65.4)¶	18 \pm 13 (n = 26)
2 (n = 101)	41 (40.6)	27 (26.7)	15 (14.9)	10 (9.9)	8/29 (27.6)	30 \pm 9 (n = 29)
3 (n = 99)	38 (38.4)	30 (30.3)	7 (7.1)	8 (8.1)	9/29 (31.0)	32 \pm 10 (n = 29)
Chi-square	2.8	8.2	11.4	10.5	10.5	
P value	0.23	0.02	0.003	0.005	0.005	0.008

*Expressed in multiples of 10^5 equivalent viral copies per milliliter.

†For group 1 versus group 2, $P=0.008$; for group 1 versus group 3, $P=0.04$.

‡For group 1 versus group 3, $P<0.001$.

§For group 1 versus group 2, $P=0.02$; for group 1 versus group 3, $P=0.005$.

¶For group 1 versus group 2, $P=0.005$; for group 1 versus group 3, $P=0.01$.

||For group 1 versus group 2, $P=0.003$; for group 1 versus group 3, $P=0.003$.

Table 3. Changes in Histologic Scores, According to Treatment Group.

EVALUATION OF LESION*	HISTOLOGIC SCORE		
	GROUP 1 (N=56)	GROUP 2 (N=63)	GROUP 3 (N=57)
	<i>mean ±SD</i>		
Portal fibrosis			
Before treatment	2.5±0.1	2.8±0.1	2.5±0.1
After treatment	2.2±0.2	2.7±0.2	2.4±0.2
Difference	-0.3±0.1	-0.1±0.1	-0.1±0.1
Portal inflammation			
Before treatment	1.8±0.1	1.8±0.1	1.6±0.1
After treatment	1.4±0.1	1.6±0.1	1.5±0.1
Difference	-0.4±0.1†	-0.1±0.1	-0.1±0.1
Piecemal necrosis			
Before treatment	1.6±0.1	1.7±0.1	1.3±0.1
After treatment	0.7±0.1	1.1±0.1	0.9±0.1
Difference	-0.8±0.1‡	-0.5±0.1	-0.4±0.1
Lobular necrosis			
Before treatment	0.7±0.1	0.8±0.1	0.6±0.1
After treatment	0.3±0.1	0.5±0.1	0.3±0.1
Difference	-0.5±0.1	-0.3±0.1	-0.4±0.1
Knodell score			
Before treatment	8.8±0.3	9.6±0.4	8.2±0.4
After treatment	5.7±0.3	7.5±0.4	6.7±0.4
Difference	-3.3±0.1§	-2.1±0.1	-1.5±0.1
Global-activity score			
Before treatment	2.61±0.09	2.75±0.10	2.44±0.11
After treatment	1.77±0.09	2.05±0.13	2.05±0.13
Mean reduction (%)	30±3¶	17±4	11±5

*Portal fibrosis was graded as follows: 0, no fibrosis; 1, portal fibrosis without septa; 2, portal fibrosis with rare septa; 3, numerous septa without cirrhosis; or 4, cirrhosis. Portal inflammation and piecemal necrosis were graded as follows: 0, absent; 1, mild; 2, moderate; or 3, severe. Lobular necrosis was graded as follows: 0, absent or mild; 1, moderate; or 2, severe. The Knodell score is an index of histologic activity, as defined by Knodell et al.⁶ The global-activity score is based on the Metavir scoring system, which combines the scores for necrosis and inflammation.³

†For group 1 versus group 2, $P=0.02$; for group 1 versus group 3, $P=0.01$.

‡For group 1 versus group 2, $P=0.02$; for group 1 versus group 3, $P=0.001$.

§For group 1 versus group 2, $P=0.06$; for group 1 versus group 3, $P=0.006$.

¶For group 1 versus group 2, $P=0.03$; for group 1 versus group 3, $P=0.006$.

to have improvement in portal inflammation or piecemal necrosis.

Among the 132 patients without evidence of cirrhosis on the first liver biopsy, the incidence of cirrhosis throughout 18 months of follow-up was 6.8 percent in group 1 (3 of 44), as compared with 13.6 percent in group 2 (6 of 44, $P=0.24$) and 15.9 percent in group 3 (7 of 44, $P=0.18$).

Correlation between Histologic and Serum Alanine Aminotransferase Responses

The percentages of patients with histologic improvement at 18 months, according to the serum alanine aminotransferase responses at 6 and 18 months, are shown in Figure 1. Sixty-one percent of the patients randomly assigned to group 1 had histologic improvement despite abnormal serum alanine aminotransferase concentrations at 6 months or at 18 months.

Cirrhosis, age, and the initial serum γ -glutamyltransferase value were not associated with histologic responses in either univariate or multivariate analyses (data not shown). Genotype 1b was associated with a lower rate of histologic responses. Eight of 26 patients (30.8 percent) with genotype 1b had an improved histologic-activity score, as compared with 18 of 30 patients

(60.0 percent) who did not have genotype 1b ($P=0.03$). Among the patients with genotype 1b, 4 of 6 in group 1, 4 of 10 in group 2, and none of 10 in group 3 had histologic improvement ($P=0.008$ by Fisher's exact test, two-tailed). Genotype 1b was associated with higher mean (\pm SE) levels of viremia both before treatment ($40\pm 8\times 10^5$ equivalent viral copies per milliliter in 20 patients with genotype 1b vs. $19\pm 5\times 10^5$ in 21 patients without genotype 1b, $P=0.03$) and after treatment ($49\pm 12\times 10^5$ equivalent viral copies per milliliter in 24 patients with genotype 1b vs. $37\pm 14\times 10^5$ in 27 patients without genotype 1b, $P=0.04$). Among the 80 patients from whom serum samples were collected after treatment, the mean level of viremia was significantly lower in the group of 40 patients with histologic improvement ($18\pm 9\times 10^5$ equivalent viral copies per milliliter) than in the group of 40 without histologic improvement ($34\pm 8\times 10^5$ equivalent viral copies per milliliter, $P=0.003$).

Adverse Events

Adverse events of grade 3 or 4 in severity, according to the classification of the World Health Organization,⁷ were documented. For clinical events, grade 3 is defined as severe, and grade 4 as very severe. Grade 3 neutropenia is defined as less than 900 leukocytes per cubic millimeter, and grade 3 thrombocytopenia as less than 49,000 platelets per cubic millimeter. Adverse events of grade 3 or 4 occurred in 35 percent, 30 percent, and 31 percent of the patients in groups 1, 2, and 3, respectively, during the initial 18 months. From 7 to 18 months, the incidence of adverse events was 11, 6, and 7 percent in groups 1, 2, and 3, respectively. The differences among the groups were not significant. The most frequent adverse events were asthenia (in 50 percent of the patients), neutropenia (in 20 percent), myalgia (in 20 percent), headache (in 16 percent), an influenza-like syndrome (in 13 percent), thrombocytopenia (in 10 percent), and depression (in 9 percent). Some patients had more than one adverse event.

DISCUSSION

The patients were followed for an additional 24 months after the discontinuation of treatment with interferon alfa-2b. Those treated for 18 months with 3 million units three times a week continued to have serum alanine aminotransferase and virologic responses. Histologic responses at 18 months were assessed in only 176 of the 303 randomized patients. Because the clinical and biologic findings did not differ according to whether the patients had one or two biopsies, bias due to the small number of patients assessed was unlikely. Liver-biopsy specimens were assessed in a blinded fashion, with a scoring system that had previously been validated.³ The histologic-activity score, which was the main end point, has been shown to be a better scoring system than the Knodell activity index, in terms of intraobserver and interobserver variation.⁸ The score we used did not include an assessment of

liver fibrosis, which differs from necroinflammatory activity in terms of severity and responsiveness to treatment.⁶

None of the patients in group 1 had severe chronic active hepatitis at the second liver biopsy. The greater improvement in piecemeal necrosis and total inflammation in group 1 and the lower incidence of cirrhosis during follow-up suggest that the interferon regimen used in this group can sometimes prevent cirrhosis. It is also noteworthy that some patients with cirrhosis initially also had substantial histologic improvement. Although the diagnosis of cirrhosis is highly concordant among pathologists,³ sampling variability can affect its recognition. A future trial might test the hypothesis that continuous treatment with interferon can significantly reduce the incidence of cirrhosis in patients with chronic non-A, non-B hepatitis.

Serum alanine aminotransferase responses were significantly associated with histologic improvement, but we do not believe this association was strong enough to justify its use in clinical practice. Serum alanine aminotransferase measurements, even when repeated, were inaccurate in predicting the presence or absence of histologic improvement. We believe a repeated liver biopsy is required to assess the efficacy of treatment with interferon. In our study, it would have been a mistake to stop treatment in patients without a serum alanine aminotransferase response at six months. Indeed, a total of 61 percent of the patients without responses at 6 months (32 of 52) had improved histologic findings at 18 months, and the results were similar for patients without responses at 3 months (data not shown). These findings do not support the recommendations for treatment with interferon in the United States and in France, which suggest that interferon may be discontinued if there is no response after 16 weeks.^{9,10} Similarly, we do not believe the absence of a serum alanine aminotransferase response between 7 and 18 months is a reliable predictor that continued treatment will not be beneficial.

Several previously identified factors were significantly associated with the serum alanine aminotransferase response, including age, the presence of cirrhosis, and the initial serum γ -glutamyltransferase value. None of these factors, however, were associated with histologic improvement in univariate or multivariate analyses. These differences were not related to a potential bias in the selection of patients who underwent two biopsies, since the discrepancy persisted even when the analysis of factors related to the serum alanine aminotransferase responses was restricted to patients with two biopsies. Therefore, we do not believe that the selection of patients for treatment with interferon should be based on these factors.

Genotype and viremia were assessed retrospectively, and the findings should therefore be interpreted with caution. Since genotypes were, in part, determined retrospectively in samples obtained after treatment, data on genotypes were available for fewer pa-

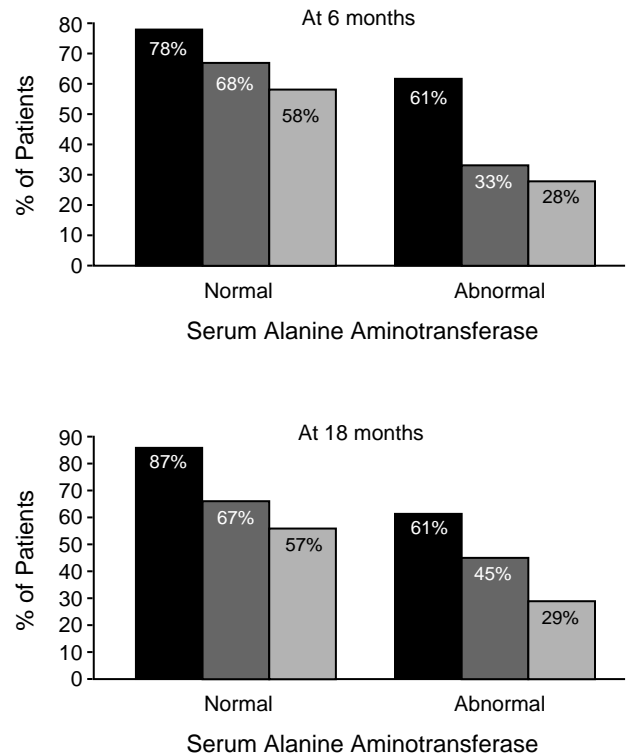


Figure 1. Histologic Improvement at 18 Months in the Three Treatment Groups, According to the Serum Alanine Aminotransferase Response at 6 Months (Upper Panel) and 18 Months (Lower Panel).

Among the patients with normal serum alanine aminotransferase concentrations at six months, histologic improvement was observed in 78 percent of the patients in group 1 (40 of 51), 68 percent of those in group 2 (28 of 41), and 58 percent of those in group 3 (22 of 38). Among the patients with elevated serum alanine aminotransferase concentrations at six months, histologic improvement was observed in 61 percent of the patients in group 1 (35 of 57), 33 percent of those in group 2, (20 of 60), and 28 percent of those in group 3 (17 of 61). Among the patients with normal serum alanine aminotransferase concentrations at 18 months, histologic improvement was observed in 87 percent of the patients in group 1 (40 of 46), 67 percent of those in group 2 (18 of 27), and 57 percent of those in group 3 (17 of 30). Among the patients with elevated serum alanine aminotransferase concentrations at 18 months, histologic improvement was observed in 61 percent of those in group 1 (35 of 57), 45 percent of those in group 2 (33 of 74), and 29 percent of those in group 3 (20 of 69).

tients in group 1 than in the other groups, because the PCR results were more often negative in the patients in group 1. Before and after treatment, genotype 1b was associated with a higher level of viremia than were other genotypes, but it was not possible to estimate whether these two factors were independently correlated with the serum alanine aminotransferase or histologic response. For example, patients with genotype 1b were on average 10 years older than those without genotype 1b ($P=0.006$), and 62 percent of the patients with genotype 1b had cirrhosis, as compared with 30 percent of the patients without this genotype ($P=0.02$). Nevertheless, among the patients

with genotype 1b and two liver biopsies, histologic improvement was greater in group 1 than in the other groups.

We found that patients with histologic improvement at 18 months had about 50 percent less viremia during the 2 years of follow-up after treatment than the patients without improvement at 18 months. The greater efficacy of long-term treatment with interferon, as compared with a shorter duration of treatment or a lower dose of the drug, may be explained by the reduction or eradication of HCV viremia.

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APPENDIX

The Multicenter Study Group included the following investigators: *Lyons*: J. Desbaumes, C. Trepo, and P. Paliard; *Paris Pitié Salpêtrière*: P. Opolon, D. Valla, and F. Lunel; *Paris Saint Antoine*: R. Poupon, T. Andreani, J.D. Grange, Y. Calmus, and E. Froguel; *Paris Saint Louis*: X. Abensour and J.C. Rambaud; *Paris Laennec*: C. Brechot, S. Pol, and P. Berthelot; *Paris Bichat*: G. Cadiot; *Bordeaux*: P. Bernard, P. Couzigou, and A. Quinton; *Toulouse*: J.L. Payen and J.P. Pascal; *Clamart*: T. Poynard, P. Mathurin, and J.C. Chaput; *Marseilles*: A. Gauthier, M. Antoni, J. Sahel, and F. Klotz; *Nice*: J. Delmont, J.G. Fuzibet, P. Dujardin, A. Tran, P. Rampal, and C. Grimaldi; *Toulon*: X. Moreau and L. Aubert; *Besançon*: J.P. Miguet and A. Franza; *Tours*: Y. Bacq and E.H. Metman; *Bobigny*: D. Roulot; *Grenoble*: J.P. Zarski; *Strasbourg*: D. Vetter and M. Doffoel; *Montpellier*: M. Veyrac; *Clichy*: P. Marcellin, J.P. Benhamou, and M. Pouteau; *Bondy*:

M. Beaugrand; *Angers*: P. Cales; *Montauban*: D. Grasset; *Saint Etienne*: H. Coppre; *Nancy*: M.A. Bigard; *Versailles*: J. Andrieu and J. Doll; *Limoges*: B. Pillegand; *Corbeil*: D. Constantini; *Dijon*: P. Hillon; *Cannes*: C. Gueyffier; and *Compiègne*: J.C. Barbare. Pathologists: P. Bedossa (Bicêtre) and M. Chevallier (Lyons); Schering-Plough: J. Cougnard and C. Lemonnier; molecular biologists: M. Sajus, M. Olivi, J.M. Costa, and M. Vidaud (CNRS URA 1484 Paris, Hôpital Américain de Paris).

REFERENCES

1. Tine F, Magrin S, Craxi A, Pagliaro L. Interferon for non-A, non-B chronic hepatitis: a meta-analysis of randomised clinical trials. *J Hepatol* 1991;13:192-9.
2. Cooksley WG, Bradbear RA, Robinson W, et al. The prognosis of chronic active hepatitis without cirrhosis in relation to bridging necrosis. *Hepatology* 1986;6:345-8.
3. The French Metavir Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994;20:15-20.
4. Sajus M, Olivi M, Vidaud M, et al. Analysis of genotypes by a fluorescent competitive oligonucleotide priming PCR (COP PCR): AASLD Chicago 1994. *Hepatology* 1994;20:244a. abstract.
5. Dixon WG, ed. BMDP statistical software manual. Vol. 1, part 2. Los Angeles: BMDP Statistical Software, 1991.
6. Knodell RG, Ishak KG, Black WC, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-5.
7. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
8. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991;13:372-4.
9. Physician's desk reference. 49th ed. Montvale, N.J.: Medical Economics, 1995:2266.
10. Vidal 1995. 71st ed. Paris: Editions Vidal, 1995:757.

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CORRECTION

A Comparison of Three Interferon Alfa-2b Regimens for the Long-Term Treatment of Chronic Non-A, Non-B Hepatitis

A Comparison of Three Interferon Alfa-2b Regimens for the Long-Term Treatment of Chronic Non-A, Non-B Hepatitis . On page 1461, the numbers in the legend for Figure 1 were calculated incorrectly. The corrected legend appears below.

Among the patients with normal serum alanine aminotransferase concentrations at six months, histologic improvement was observed in 78.6 percent of the patients in group 1 (22 of 28), 68.0 percent of those in group 2 (17 of 25), and 55.0 percent of those in group 3 (11 of 20). Among the patients with elevated serum alanine aminotransferase concentrations at six months, histologic improvement was observed in 60.7 percent of the patients in group 1 (17 of 28), 34.2 percent of those in group 2 (13 of 38), and 29.7 percent of those in group 3 (11 of 37). Among the patients with normal serum alanine aminotransferase concentrations at 18 months, histologic improvement was observed in 83.9 percent of the patients in group 1 (26 of 31), 72.2 percent of those in group 2 (13 of 18), and 57.9 percent of those in group 3 (11 of 19). Among the patients with elevated serum alanine aminotransferase concentrations at 18 months, histologic improvement was observed in 52.0 percent of those in group 1 (13 of 25), 37.8 percent of those in group 2 (17 of 45), and 28.9 percent of those in group 3 (11 of 38).