Randomized Trial Comparing Three Different Regimens of Alpha-2a-Interferon in Chronic Hepatitis C

LILIANA CHEMELLO,[1] PAOLA BONETTI,[1] LUISA CAVALLETTO,[1] FABIOLA TALATO,[1] VALTER DONADON,[2] PIETRO CASARIN,[3] FABIO BELUSSI,[4] MARIO FREZZA,[5] FRANCO NOVENTA,[1] PATRIZIA PONTISSO,[1] LUISA BENVEGNÙ,[1] CARLA CASARIN,[1] ALFREDO ALBERTI,[1] AND THE TRIVENETO VIRAL HEPATITIS GROUP[6]

Alpha-interferon (IFN-α) is an effective treatment for chronic hepatitis C, but only 20% to 30% of patients are apparently cured with the currently recommended schedule of 3 MU given three times a week for 6 months. To evaluate the efficacy of more aggressive treatment regimens, we have conducted a randomized trial in 174 patients with chronic hepatitis C using three different schedules: (1) 12-month treatment starting with 6 MU/ three times a week and decreasing the dose on the basis of serum alanine transaminase (ALT) activities (group A: 59 cases); (2) fixed dose of 3 MU three times a week for 12 months (Group B: 61 cases), (3) fixed dose of 6 MU three times a week for 6 months (Group C: 54 cases). Patients were evaluated during therapy for biochemical and virological response and followed for at least 12 months after therapy to assess long-term efficacy and liver histological outcome. The genotype of infecting HCV was also analyzed in all patients, and predictors of response were determined by multivariate analysis. Serum ALT became normal during therapy in 76% of patients (95% confidence interval [CI]: 63 to 86), 65% (CI: 52 to 77), and 74% (CI: 60 to 85) in groups A, B, and C, respectively (P = NS). The corresponding figures for sustained response 12 months after therapy were 49% (CI: 36 to 62), 31% (CI: 20 to 44), and 28% (CI: 16 to 42) (A vs. B, P = .06; A vs. C, P = 0.03). Eighty-six percent of patients with sustained response cleared HCV-RNA from serum, and 72% improved histologically. Patients infected with HCV genotypes 2a and 3 had higher sustained response rates than those with 1b, independent of treatment schedule. In patients infected with genotype 1b, the rate of sustained response was related to dose and duration of therapy being 28% with schedule A, 16% with schedule B, and 9% with schedule C. Multivariate analysis indicated that younger age (P = .016), shorter disease duration (P = .003), and infection with HCV genotypes 2a (P = .0017) and 3 (P = .0083) were independent predictors of sustained response. These results indicate that sustained response to IFN-α in chronic hepatitis C is affected by dose and duration of therapy, particularly in patients infected with HCV genotype 1b. (HEPATOLOGY 1995;22:700-706.)

Chronic hepatitis C is a very common disease that is often asymptomatic and mild but may slowly progress to cirrhosis[1] and eventually to hepatocellular carcinoma. Alfa interferons (IFN-α) are the only substances that have been shown to be effective in the treatment of the disease and have indeed been licensed in several countries for therapy of chronic hepatitis C. Randomized trials have documented that a minimum dose of 3 MU of IFN-α, given three times a week for at least 6 months, can be used.[2-4] With this regimen, approximately half of the treated patients respond, with serum alanine transaminase (ALT) values becoming normal and loss of hepatitis C virus (HCV) RNA from serum during therapy, but only 20% to 25% maintain this response after cessation of treatment. Although it is doubtful that a transient response is likely to be clinically significant considering the natural history of hepatitis C, patients in whom HCV infection is eradicated certainly benefit from therapy. The long-term sustained response rate has been disappointingly low, resulting in considerable debate about whether the results of therapy justify its costs and side effects.

More recent studies[5-7] have explored whether treatment regimens using higher doses of IFN-α for longer periods may improve the long-term efficacy of IFN-α in chronic hepatitis C. Results, however, have been conflicting and inconclusive, often not being obtained in randomized controlled trials. Moreover, the rate of sustained response has usually been evaluated after short observation periods (6 months after stopping therapy).

Abbreviations: ALT, alanine transaminase; HCV, hepatitis C virus; IFN-α, interferon-alfa.

From the [1]Clinica Medica 2, University of Padova; [2]3st. Medical Division, Pordenone Hospital; [3]Division of Medicine, Sacile Hospital; [4]Division of Infectious Disease, Venice Hospital; and [5]Gastroenterology, University of Trieste, Italy. [6]The following institutions and persons participated to The TriVeneto Viral Hepatitis Group: Pordenone Hospital: Carlo Donada, MD; Sacile (VE) Hospital: Antonio Cellini, MD; Venezia-Mestre (VE) Hospital: Francesca Cavinato, MD, and Maurizio D'Aquino, MD; S. Vito al T. (PN) Hospital: Tiziano Croatto, MD; Trieste University Hospital: Gabriele Pozzato, MD, Marilena Terpin, MD, and Flavia Urban, MD; Udine Hospital: G. Da Broi, MD, Claudio Macor, MD, and Piero Brosolo, MD; Bolzano Hospital: G. Pristerà, MD; Padova Hospital: Paolo Cadrobbi, MD, and Carlo Crivellaro, MD; Cittadella (PD) Hospital: S. Martinelli, MD; Mirano (VE) Hospital: G. Donà, MD

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Address reprint requests to: Alfredo Alberti, MD, Clinica Medica 2, via Giustiniani, 2, 35100 Padova, Italy.

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In 1989, we started a randomized trial in which three different schedules of recombinant alpha-2a-IFN were compared to simultaneously evaluate the importance of total dose of IFN-α and of duration of treatment. All patients included in the trial have been followed for at least 12 months after cessation of treatment to assess the rate of sustained biochemical and virologic response. Several pretreatment variables were also evaluated by univariate and multivariate analysis including the genotype of infecting HCV.

PATIENTS AND METHODS

Patients

From September 1989 to November 1990, one hundred seventy-four patients were enrolled in the study.

Inclusion and Exclusion Criteria. Inclusion criteria were age between 18 and 70 years; elevated serum levels of ALT at least twice the upper limit of normal for 6 months before entry; compensated liver disease with chronic hepatitis on biopsy; diagnosis of non-A, non-B hepatitis by exclusion criteria; capability of attending treatment and follow-up regularly; and life expectancy of at least 2 years. Patients were excluded from the study for the following reasons: previous immunosuppressive, steroid, or antiviral therapy; pregnancy or lactating status; any serious illness that might prevent completion of the study; current alcoholism or drug abuse; serum positivity for hepatitis B surface antigen, anti-human immunodeficiency virus or autoantibodies; serum creatinine above 1.7 mg/dL; low platelet (below 100×10^3 per liter) or white cell count (below 3×10^3 per liter) or granulocyte count (below 1.5×10^3 per liter). Patients with advanced or decompensed cirrhosis (ascites, portal hypertension, B and C Child-Pugh classes) were excluded. All eligible patients were randomly assigned to one of the three treatment groups using a computer-generated list. The study was approved by the local ethics committees. Patients were treated with recombinant-alpha-2a-IFN given intramuscularly three times weekly according to the following schedules: (1) *Schedule A*: Fifty-nine patients received an initial dose of 6 MU given for 4 months. If serum ALT levels became normal, this was followed by a maintenance dose of 3 MU for a further 8 months. Patients in whom hepatitis relapsed when the dose of IFN was decreased were reassigned to the 6 MU dose. Patients not showing ALT normalization after 6 months at 6 MU were treated with 9 MU for an additional month, and therapy was then discontinued if there was no response (total IFN-α dose ranged from 570 to 756 MU; mean dose, 607 MU). (2) *Schedule B*: Sixty-one patients received a fixed dose of 3 MU for 12 months (total IFN-α dose: 468 MU). (3) *Schedule C*: Fifty-four patients received a fixed dose of 6 MU for 6 months (total IFN-α dose: 468 MU). All patients were seen on days 15 and 30 after therapy was begun and then at monthly intervals up to the end of treatment. After cessation of IFN therapy, patients were seen every 3 months to complete a 12-month follow-up period. On each occasion patients were evaluated clinically for signs of liver disease and side effects of IFN.

Serum bilirubin, albumin, aspartate transaminase, ALT levels, complete blood count, and serum creatinine concentrations were measured. A 5-mL aliquot of serum was obtained and stored at -20°C for evaluation of viral markers.

Criteria of Evaluation. The criteria for response to treatment were established in advance and were based on the ALT profile. The evaluation was completed retrospectively by adding to the ALT data the virologic assessment of response based on serum HCV-RNA determination and the histologic assessment of response based on the comparison between pretreatment and posttreatment liver biopsy specimens. The definition of primary response was normalization of ALT during therapy confirmed on at least two consecutive monthly determinations, independent of whether response was maintained up to the end of therapy. A relapse was defined as a return to abnormal serum ALT values after primary response. A lack of response was defined as persistence of abnormal serum ALT or its transient normalization for fewer than two consecutive determinations. Sustained response was defined as persistently normal serum ALT levels up to the end of the follow-up period of therapy (12 months).

To evaluate the virological response, serum was tested for HCV-RNA at the end of treatment and at the end of follow-up. The histological response was evaluated comparing pairs of liver biopsy specimens taken before randomization and between 6 and 12 months after treatment. These biopsy specimens were evaluated by a pathologist who was blinded with respect to treatment schedule and to chronological order of the biopsies in each pair. Histologic status was defined as unchanged, improved, or worsened according to the following criteria: (1) Patients progressing from chronic persistent hepatitis to chronic active hepatitis were defined as having worsened, and those changing from chronic active hepatitis to chronic persistent hepatitis were considered improved; (2) In patients with cirrhosis at pretreatment evaluation, improvement was defined as regression from active to inactive disease.

Methods

Liver and hematologic tests were performed using standard laboratory methods (SMAC Technicon System and Coulter System, NJ). Hepatitis B surface antigen was determined by a commercial radioimmunoassay (Abbott Laboratories, North Chicago, IL). Anti-HCV was tested by first-generation enzyme-linked immunosorbent assay (Ortho Diagnostic Systems, Raritan, NJ), by second-generation enzyme-linked immunosorbent assay (Ortho), and by recombinant immunoblot assay-2 (Chiron Corporation, Emeryville, CA). Anti-human immunodeficiency virus was determined by enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, IL). Organ- and non-organ-specific antibodies were studied by indirect immunofluorescence.

Serum HCV-RNA. Serum HCV-RNA was studied by the polymerase chain reaction using two sets of primers specific for the 5′ untranslated region of HCV genome and nested amplification as previously described in detail.[8] To avoid contamination, all reagents were treated with ultraviolet light, and positive display pipettes (Pipetman, GIBCO BRL) were used. Results were considered valid only if they were obtained in at least two separate experiments.

Characterization of the HCV genotype. The genotype of the infecting HCV was evaluated in all 174 patients on pretreatment serum samples using a dot-blot hybridization assay with genotype-specific oligonucleotide probes, as recently described.[8] The probes used were prepared to recognize HCV genotypes 1a, 1b, 2a, and 3, according to Simmonds et al's classification,[9] whereas direct sequency of the 5′ untranslated region was performed in cases that could not be classified by the screening dot-blot hybridization procedure.

Statistical Analysis. ANOVA and χ^2 for contingency tables were used to compare continuous and categorical variables in the three treatment groups. Kaplan-Meier curves evaluated primary response and relapse rate in the three groups and

TABLE 1. Comparison of Clinical, Virological, and Histological Pretreatment Features of the Patients Assigned to the Three Treatment Schedules

Group	A	B	C	P (*)
No. of cases	59	61	54	NS
Age (yrs, as mean ± SD)	42 ± 15	47 ± 15	44 ± 14	NS
(range)	(21-62)	(22-65)	(21-64)	
Male/Female	44/12	38/23	40/14	NS
Body weight				
(kg, as mean ± SD)	70 ± 11	71 ± 12	72 ± 11	NS
(range)	(48-97)	(44-100)	(50-102)	
Disease duration				
(months, as mean ± SD)	62 ± 39	67 ± 54	75 ± 53	NS
(range)	(10-144)	(9-160)	(8-210)	
ALT				
(IU/L, as mean ± SD)	245 ± 139	234 ± 179	217 ± 188	NS
(range)	(90-560)	(85-552)	(87-497)	
Bilirubin				
(mmol/L, as mean ± SD)	6.6 ± 8.3	5.5 ± 5.2	6.5 ± 8.6	NS
(range)	(0.4-38.8)	(0.3-18.8)	(0.2-34.2)	
Anti-HCV positive (%)				
(ELISA II gen.)	52 (88)	55 (90)	49 (91)	NS
Serum HCV-RNA (%)				NS
Negative	15 (25)	14 (23)	9 (17)	
Positive	44 (75)	47 (77)	45 (83)	
HCV (†) genotype (%)				NS
1a	5 (11)	1 (2)	0 (—)	
1b	18 (41)	25 (53)	21 (47)	
2a	13 (30)	14 (30)	12 (27)	
2b	1 (2)	1 (2)	5 (11)	
3	7 (16)	6 (13)	6 (13)	
4	0 (—)	0 (—)	1 (2)	
Histology (%)				NS
CPH/CLH	21 (35)	16 (26)	11 (20)	
CAH	29 (49)	33 (54)	33 (61)	
CAH-CIRR	9 (16)	12 (20)	10 (19)	

Abbreviations: CPH, chronic persistent hepatitis; CLH, chronic lobular hepatitis; CAH, chronic active hepatitis; CIRR, cirrhosis.

* ANOVA test.

† Referring only to HCV-RNA positive cases.

were compared by Mantel-Cox test. Stepwise logistic regression, by both forward and backward methods, was used to identify independent predictors of sustained response after having excluded hidden interactions among variables.

RESULTS

Table 1 shows that there were no significant differences in main baseline pretreatment demographic, serum biochemical, and serological features in the three groups of patients. Of the 174 patients included, 10 withdrew from therapy (4 in group A, 4 in group B, and 2 in group C) because of adverse effects. Eleven additional patients (4 in group A, 5 in group B, and 2 in group C) were lost before completing the follow-up period. All of these patients withdrawn from treatment or from follow-up were classified as nonresponders (intent-to-treat analysis) independently of ALT behavior.

In group A, the treatment schedule was determined by the ALT profile: 48 patients received 6 MU three times a week for 4 to 6 months and then 3 MU to complete the 12-month treatment period; 4 patients were retreated with 6 MU after the initial reduction from 6 MU to 3 MU because of reactivation of hepatitis; and in 7 patients ALT levels did not become normal after 6 months of 6 MU and they were therefore given 9 MU three times a week of IFN-α. None of these cases normalized ALT after 1 month at 9 MU and were therefore withdrawn from treatment and classified as nonresponders.

Figure 1 shows the Kaplan-Meier curves for primary response and of relapse rates occurring over time in groups A, B, and C. All primary responses were seen during treatment, most during the first 4 months of therapy. Relapses after primary response were rarely seen during therapy in group A, being more frequent in groups B and C (Table 2).

Most relapses after therapy withdrawal occurred during the first 3 months in all three groups (overall 43 of the 49 relapses after cessation of IFN-α occurred in this period). Comparison of these curves by Mantel-Cox test showed a highly significant difference between groups A and B ($P < .001$) and also between groups A and C ($P < .001$), but no difference between groups B and C (P = NS).

Table 2 summarizes the overall results of the trial. The percentage of nonresponders ranged from 24% to 34%, without significant differences among the three groups. The percentage of primary response with complete ALT normalization during therapy ranged from 65% to 76%, again without significant difference. The percentage of patients with normal ALT at the end of therapy was 72% in group A, 55% in group B, and 64% in group C. Among patients with primary response, those showing reactivation either during or after therapy (Table 2) were 36% in group A and 62% in group C, the difference being statistically significant ($P = .02$). As a consequence, a sustained biochemical response was observed in 29 (49%) patients from group A, in 19 (31%) from group B, and in 15 (28%) from group C. The difference was statistically significant between group A and group C ($P = .03$) and nearly significant ($P = .06$) between groups A and B. In some patients classified as sustained responders, transient reactivation of ALT was observed after primary response. This occurred in six cases from group A (in all six during treatment), in five from group B (four during and one after treatment), and in two from group C (one during and one after treatment). The transient ALT peak reached 1.2 to 5.1× the upper limit of normal for less than 60 days in all cases. All 13 patients had persistently normal serum ALT activities during the last 6 months of follow-up. All patients with normal ALT at the end of therapy or at the end of follow-up were tested at both of these points for serum HCV-RNA by the polymerase chain reaction to define rates of virologic response (Table 3). At the end of the treatment period, 6 of 43 cases in group A (14%), 13 of 34 in group B (38%), and 6 of 35 in group C (17%) were HCV-RNA positive by the polymerase chain reaction while showing normal ALT (A vs. B: $P = .02$). During the 12-

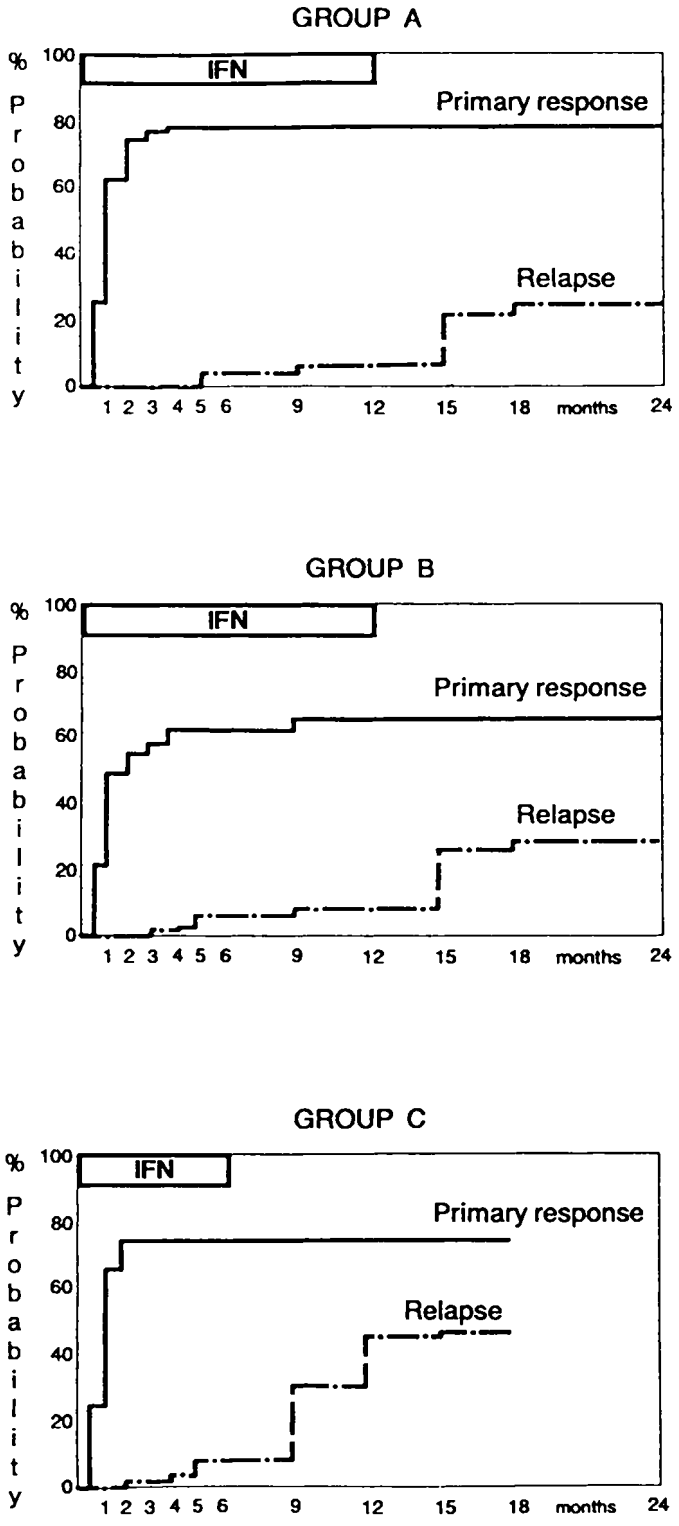

FIG. 1. Probability of achieving a primary response and of relapsing as seen in patients of groups A, B, and C. According to Kaplan-Meier estimates, the rates of patients maintaining ALT normalization were significantly different ($P < .001$ by Mantel-Cox test).

TABLE 2. Biochemical Response in Relation to Treatment Regimens

Group	A	B	C
Primary response during therapy	45 (76%)	40 (65%)	40 (74%)
Reactivation	16 (36%)*	21 (52%)	25 (62%)*
during therapy	2	6	5
after therapy	14	15	20
Sustained response	29 (49%)†	19 (31%)†	15 (28%)†
No response	14 (24%)	21 (34%)	14 (26%)

* Group A vs. C, $P = .02$.
† Group A vs. B, $P = .06$ and group A vs. C, $P = .03$ (χ^2 test).

month period after IFN-α withdrawal, reactivation of hepatitis was observed in 64% of these HCV-RNA positive cases compared with 38% of HCV-RNA negative cases ($P = .03$). Twelve months after therapy, among patients classified as sustained responders at the biochemical level, serum HCV-RNA was negative in 25 of 29 (86%) in group A, in 15 of 19 (79%) in group B, and in 14 of 15 (93%) in group C. Thus the rate of sustained biochemical and virological response was 42% in group A (25 of 59 cases), 25% in group B (15 of 61), and 26% in group C (14 of 54).

Using pretreatment serum samples, 70 patients (42.2%) were found to be infected with HCV genotype 1 (6 with 1a and 64 with 1b), whereas 46 (26.4%) patients were infected with genotype 2 (39 with 2a and 7 with 2b), 19 (11%) with HCV genotype 3, and 1 (0.6%) with HCV genotype 4. The remaining 38 (22%) cases could not be genotyped because of a negative HCV-RNA result. Rates of sustained response seen in patients infected with the different types of HCV are shown in Table 4. The numbers of patients infected with HCV genotypes 1b, 2a, and 3 were large enough to allow comparison. Patients infected with HCV genotypes 2a and 3 showed higher rates of sustained response compared with those infected with genotype 1b independently of the treatment schedule used. The only difference among treatment groups was related to patients infected with HCV genotype 1b, in whom the rate of sustained response was dose and duration dependent, being remarkably higher with the more aggressive treatment schedule A (28%) compared with schedules B (16%) and C (9%).

TABLE 3. Behavior of Serum HCV-RNA in Patients With Normal ALT at the End of the Treatment Period and at the End of the Follow-up Period

	Treatment Group (No. of cases)	HCV-RNA Negative (%)
At the end of treatment	Group A (43)	37 (86)
	Group B (34)	21 (62)
	Group C (35)	29 (83)
At the end of follow-up	Group A (29)	25 (86)
	Group B (19)	15 (79)
	Group C (15)	14 (93)

TABLE 4. Sustained Long-term Responders (LTR) to Different Schedules of Alpha-IFN Therapy in Relation to the Genotype of Infecting HCV

HCV Genotypes	Schedule A		Schedule B		Schedule C	
	No.	LTR (%)	No.	LTR (%)	No.	LTR (%)
1a	5	—	1	—	0	—
1b	18	5 (28)	25	4 (16)	21	2 (9)
2a	13	6 (46)	14	5 (36)	12	5 (42)
2b	1	1 (100)	1	1 (100)	5	2 (40)
3	7	7 (100)	6	4 (67)	6	4 (67)
4	0	—	0	—	1	—

The histological comparison between pretreatment and posttreatment biopsies is shown in Fig. 2. Liver biopsy specimens were obtained from 131 patients (75% of treated cases) 6 to 12 months after cessation of IFN-α therapy (group A: 45 cases; mean months $\pm$ SD: 9.4 $\pm$ 2.3; group B: 46 cases; 9.3 $\pm$ 2.4 months; and group C: 40 cases, 8.9 $\pm$ 1.5 months). Improvement of histology was more frequent in group A (55%), and worsening was more common in groups B (20%) and C (20%). Patients classified as sustained responders at the biochemical level had a significantly higher rate of histological improvement (P = .01), with no case of worsening, compared with patients with transient or no response independent of the treatment schedule. Histologic improvement reached 81% in sustained responders who cleared HCV-RNA from serum and in 48% of them posttreatment biopsy showed normal liver histology or only minimal unspecific changes. Patients classified as nonresponders had the highest rate of worsening of liver histology after therapy. Sustained response was observed in 33% of anti-HCV negative and in 36% of anti-HCV positive patients, in 66% of

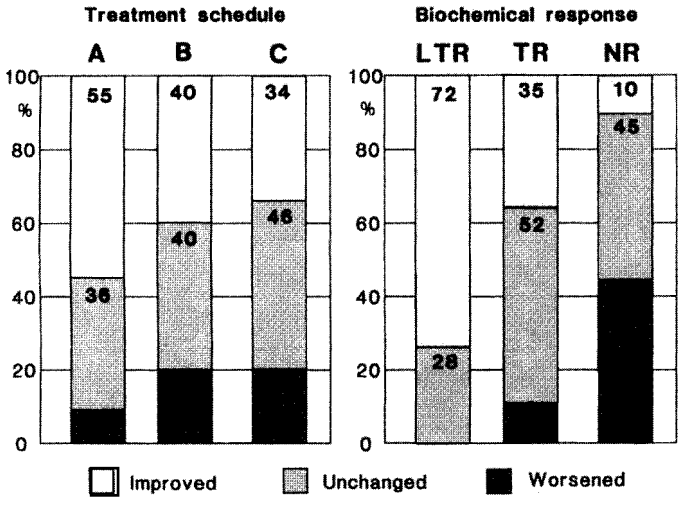

FIG. 2. Comparison of pretreatment and posttreatment liver biopsy specimens in relation to treatment schedules (groups A, B, and C) and to biochemical response. LTR, sustained long-term responders; TR, transient responders; NR, nonresponders.

TABLE 5. Multivariate Analysis of Pretreatment Variables Versus Sustained Response by Stepwise Logistic Regression

Pretreatment Variables	Coefficient	Standard Error	Log Odds	P Value
Age	0.032	0.014	1.03	.016
Disease duration	0.015	0.005	1.01	.003
Histology				
CPH	—	—	—	NS
CAH	—	—	—	NS
CIRR	—	—	—	NS
ALT	—	—	—	NS
HCV genotype				
1b	—	—	—	NS
2a	1.69	0.54	0.18	.0017
3	1.89	0.69	0.15	.0083

HCV-RNA negative, and in 20% of HCV-RNA positive cases, in 40% of those without cirrhosis, and in 19% of those with cirrhosis. Univariate analysis indicated that younger age (P = .0027), shorter disease duration (P = .0021), normal serum gamma-glutamyltransferase levels (P = .0001), infection with genotypes 2a and 3 (P = .0001), and absence of cirrhosis (P = .05) were factors associated with sustained response, whereas gender, body weight, and basal ALT levels were not related. Pretreatment variables were also analyzed in relation to their statistical association with sustained response in a multivariate stepwise logistic regression analysis. These variables included age, sex, body weight, duration of disease, baseline ALT, histologic diagnosis, and the genotype of infecting HCV. As shown in Table 5, younger age, shorter duration of hepatitis, and genotypes 2a and 3 were identified as variables independently associated with a sustained response to IFN-α. Conversely, baseline ALT levels and pretreatment histology were not found to affect the probability of achieving a sustained response to IFN-α therapy. The same variables found to be significant in this analysis of biochemical response also applied to achievement of biochemical (normal ALT levels) plus virological (HCV-RNA negative) sustained response. Side effects during therapy are described in Table 6. Frequency of some of these side effects was influenced by the weekly dose whereas others were apparently more linked to duration of therapy. Dropout rate during therapy was 7% in group A, 7% in group B, and 4% in group C (P = NS).

DISCUSSION

The results of this randomized controlled trial indicate that a sustained response to recombinant alpha-2a-IFN (lasting 12 months after cessation of therapy) was significantly more likely in patients with chronic hepatitis C treated with 6 MU three times a week initially, followed by dose modification according to ALT behavior, for a total period of 12 months. Almost half of our patients treated in this way had a sustained normalization of ALT, and many of them had HCV-

TABLE 6. Side Effects During Interferon Therapy in Relation to Treatment Schedules

	% Cases of		
	Group A	Group B	Group C
Flulike syndrome	61	33	63
Fatigue	17	28	44
Depression	7	17	22
Dizziness	1	3	2
Hair loss	2	21	24
Weight loss (>5% kg)	10	16	27
Reduction in white blood cells count (<3,000/mm^3)	0	16	10
Reduction in platelets count (<100,000/mm^3)	4	7	3
Peripheral neuropathy	1	0	0
Autoimmune hepatitis	0	1	0
Epileptic crisis	0	1	0

RNA cleared from serum with a consistent improvement in liver histology. They were therefore apparently cured of chronic hepatitis C, because reactivation is rarely expected to occur in patients who maintained normal ALT and negative viremia for 12 months after cessation of therapy.[10] This result appeared to be the consequence of the combined effect of the 6 MU dose, which increased the rate of primary response compared with the 3 MU dose, although not reaching statistical significance, and of therapy prolongation to 12 months, which was associated with a lower rate of posttreatment reactivation compared with the 6-month schedule. Conversely, our results clearly indicate that there is no reason for increasing the dose of IFN-α in patients not showing a biochemical response after 6 months of treatment with 6 MU. These patients are nonresponsive to IFN-α and should be withdrawn from treatment. Interestingly, with the more aggressive schedule A, the percentage of patients showing ALT normalization but persistence of viremia at the end of therapy was lower than in the other two treatment arms. This may have affected the different rate of posttherapy reactivation. Indeed, our patients with normal ALT but positive HCV-RNA at the end of treatment were more prone to relapse, confirming previous description of discrepancy between biochemical and virological response,[11] and suggesting that serum ALT alone may not be appropriate as an end point to assess therapy efficacy.

The excellent results obtained in our patients with the more aggressive schedule, reaching almost 50% sustained cure, may not be transferable to other patient populations because the response to IFN-α is influenced by the age of the patient and by the duration of disease, as shown in our study by multivariate analysis, and possibly also by presence or absence of cirrhosis.[12] In this respect, our patients were relatively young individuals with a recent diagnosis of hepatitis C and a low rate of cirrhosis. The distribution of different HCV genotypes among our patients may also have been important, because the HCV genotype has been shown to influence the response to IFN-α. In agreement with previous reports from Japan,[13] and with our recent data obtained by using a serotyping method,[14] we have confirmed that patients infected with HCV genotypes 2a or 3 are much more likely to develop a sustained response to IFN-α compared with those infected with HCV genotype 1b, independent of the treatment used. However, in many parts of the world, including the United States, genotypes 1a and 1b are much more common, and the percentage of cases with chronic persistent hepatitis is lower and that with cirrhosis is higher, so that results as favorable as those seen in our study are unlikely to be obtained. It should be emphasized, however, that the more aggressive schedule A was particularly useful in our patients with HCV genotype 1b because it significantly improved the response rate in this subgroup only, whereas patients with HCV genotypes 2a and 3 could be successfully treated with less aggressive regimens. Thus, the characterization of the infecting HCV genotype may be used not only to predict the response to IFN-α, but also to decide the schedule because higher dose and longer course seem important for genotype 1b and not so much for genotypes 2 and 3. This assumption needs to be validated on a prospective basis. The predictive value of genotyping needs also to be compared with that provided by quantitative assessment of the pretreatment virus load, another parameter that has been described to correlate with response to IFN-α.[15,16] Finally, it should be clear that our results were obtained with recombinant-alpha-2a-IFN and may not apply to other forms of interferon until dose equivalence has been confirmed or disproven.

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