

Peginterferon Alfa-2a (40 Kilodaltons) and Ribavirin in Patients With Chronic Hepatitis C and Normal Aminotransferase Levels

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Background & Aims: Patients with chronic hepatitis C and persistently normal alanine aminotransferase (ALT) levels have been routinely excluded from large randomized treatment trials; consequently, the efficacy and safety of antiviral therapy in this population are unknown. **Methods:** Patients with at least 3 normal ALT values over an 18-month period were randomized (3:3:1) to treatment with peginterferon alfa-2a 180 µg/wk plus ribavirin 800 mg/day for 24 weeks (212 patients), the same combination for 48 weeks (210 patients), or no treatment (69 patients) in a multinational study. All patients were monitored for 72 weeks. The primary measure of efficacy was sustained virologic response (SVR), defined as undetectable serum hepatitis C virus (HCV) RNA by qualitative polymerase chain reaction at the end of 24 weeks of untreated follow-up. **Results:** No patient cleared HCV RNA in the untreated control group. SVR rates of 30% and 52% were obtained in the 24- and 48-week treatment groups, respectively. In patients infected with HCV genotype 1, SVR rates of 13% and 40% were obtained with 24 and 48 weeks of treatment, respectively ($P < .0001$). In patients infected with genotypes 2 or 3, SVR rates were 72% and 78% with 24 and 48 weeks of treatment, respectively ($P = .452$). Treatment-related flares in ALT activity were not observed. **Conclusions:** The efficacy and safety of peginterferon alfa-2a and ribavirin combination therapy in patients with chronic hepatitis C and persistently normal ALT levels are similar to that in patients with elevated ALT levels. The indication for treatment of hepatitis C can be evaluated independently from baseline ALT activity.

Combination therapy with pegylated interferon (peginterferon) and ribavirin produces sustained virologic response (SVR) rates of 54%–63% in patients with chronic hepatitis C and elevated alanine aminotransferase (ALT) levels^{1–3} and is the standard of care in this population.⁴ Approximately 30% of pa-

tients with chronic hepatitis C have ALT activity that is persistently within the normal range.⁵ Several studies have reported marked liver lesions, including cirrhosis, in patients with persistently normal ALT levels and chronic hepatitis C^{6–8}; however, there is no reliable method to identify patients at risk of progressing to severe liver disease. This subgroup has been routinely excluded from pivotal treatment trials; consequently, knowledge of the efficacy of interferon-based therapies in this population is limited. US and European experts have recommended against treating these individuals until data from large multicenter trials become available.^{4,9} This is the first randomized, controlled, multicenter study to evaluate the efficacy and safety of peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C and persistently normal serum ALT levels.

Patients and Methods

Patient Selection

Treatment-naive patients aged 18 years or older with a positive antibody to hepatitis C virus (HCV) antibody test, detectable HCV RNA in serum (Cobas Amplicor HCV Monitor Test, version 2.0; Roche Molecular Systems, Branchburg, NJ; limit of quantitation, 1000 IU/mL), biopsy findings consistent with a diagnosis of chronic hepatitis C, and persistently normal ALT levels were eligible for the study. Persistently normal serum ALT levels were defined as ALT activity equal to or below the upper limit of normal

Abbreviations used in this paper: CI, confidence interval; peginterferon, pegylated interferon; RR, relative risk; SVR, sustained virologic response; ULN, upper limit of normal.

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(ULN) documented on at least 3 occasions, a minimum of 4 weeks apart, with at least one value obtained during the 42-day screening period and at least one value obtained 6–18 months before screening.

To accommodate regional differences in clinical practice, ALT measurements were performed in local laboratories. This allowed for recruitment of patients in accordance with local definitions of normal ALT ranges and ensured that the results of the trial reflect real clinical practice. Local ALT values were transformed to “study values” by multiplying the local value by the ratio of the ULN for the study (30 IU/L) to the ULN for the local laboratory. The transformed study values are reported in this paper.

Liver biopsy specimens obtained within 36 months before study onset were evaluated using the Ishak histologic activity index score.¹⁰ Individuals with no histologic evidence of liver disease were excluded, as were patients with one or more elevated ALT values (ie, greater than the ULN) within the previous 18 months. Patients with transition to cirrhosis or cirrhosis on liver biopsy, a history of bleeding from esophageal varices, or other conditions consistent with decompensated liver disease were excluded to avoid the possibility of including individuals whose ALT levels had returned to the normal range as a consequence of advanced liver disease. Other exclusion criteria included the following: neutropenia (absolute neutrophil count <1500 cells/mm³), thrombocytopenia (<90,000 platelets/mm³), anemia (hemoglobin concentration <12 g/dL in women and <13 g/dL in men) or a medical condition that would be significantly worsened by anemia, serologic evidence of infection with human immunodeficiency virus or hepatitis A or B virus, and serum creatinine level >1.5 times the ULN. Organ transplant recipients, individuals with severe cardiac disease, individuals with a history of severe psychiatric disease (especially depression), individuals with evidence of drug abuse (including excessive alcohol consumption) within the preceding year, and individuals with other serious systemic disease were ineligible for the trial. Pregnant or lactating women and male partners of pregnant women were also excluded. All fertile men and women who participated in the trial were required to use 2 forms of effective contraception during treatment and for 6 months after the end of treatment.

Study Design

This randomized, open-label, international, controlled clinical trial was conducted in 70 centers in Australia, Europe, New Zealand, North America, and

South America. Patients were randomized to treatment with subcutaneous peginterferon alfa-2a (40 kilodaltons) 180 µg once weekly (Pegasys; Roche, Basel, Switzerland) plus ribavirin 400 mg twice daily (Copegus; Roche) for 24 weeks (group A) or 48 weeks (group B) or to no treatment (group C) in a 3:3:1 ratio to maximize the number of patients receiving treatment. Randomization was centralized and stratified by geographic region and HCV genotype (1 vs non-1). Patient identification numbers were allocated sequentially according to the order of enrollment. The randomization procedure was prepared and managed by ICTI (Lambertville, NJ). Participants were followed up for a total of 72 weeks, representing 48 weeks of follow-up after 24 weeks of therapy (group A), 24 weeks of follow-up after 48 weeks of therapy (group B), or 72 weeks of untreated follow-up (group C).

Stepwise modifications of the dosage of peginterferon alfa-2a to 135, 90, and 45 µg/wk and of ribavirin to 600 mg/day were permitted in patients experiencing clinically significant adverse events. The dosage of ribavirin was reduced in patients who experienced a decrease in hemoglobin concentration to <10 g/dL. In patients with stable cardiovascular disease, the dosage of ribavirin was reduced to 600 mg/day if the hemoglobin concentration decreased by >2 g/dL during any 4-week period. Treatment with ribavirin was discontinued if hemoglobin concentrations decreased to <8.5 g/dL or to <12 g/dL in patients with stable cardiovascular disease despite 4 weeks of treatment with a reduced dosage of the drug. Patients were allowed to receive peginterferon alfa-2a monotherapy in the event that ribavirin was discontinued; ribavirin monotherapy was not allowed.

Patients were required to keep drug diaries. Compliance was assessed by reconciliation of diary entries with returned medication vials and tablet counts.

Assessment of Efficacy

All patients in the treatment groups who received ≥ 1 dose of study drug and all untreated control patients with at least one postbaseline assessment were included in the efficacy analysis. Serum HCV RNA concentration was determined by qualitative polymerase chain reaction assay (Cobas Amplicor HCV Monitor Test, version 2.0; limit of detection, 50 IU/mL) at weeks 4, 12, and 24 during treatment in groups A and B, at weeks 36 and 48 during treatment in group B, and after 12 and 24 weeks of untreated follow-up in groups A and B. HCV RNA concentration was determined at weeks 4, 12, 24, 36, 48, 60, and 72 in patients in the untreated control group (group C). In patients with a positive qualitative polymerase chain reaction test, HCV RNA was quantified

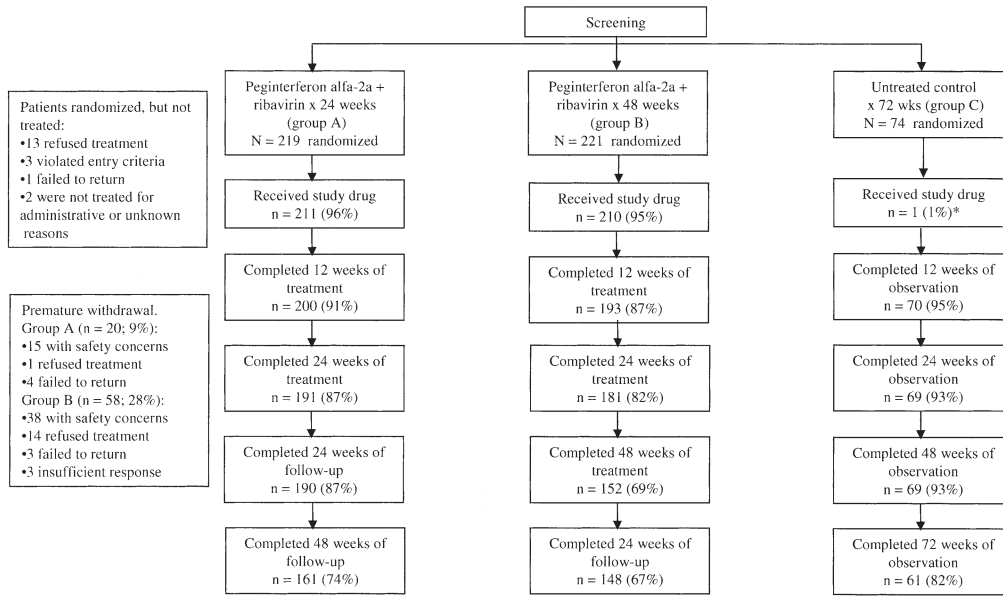


Figure 1. Flow of patients through the trial. *One patient was randomized to the control group but due to a transcription error was enrolled in group A and received 24 weeks of treatment. Therefore, this patient was included in group A for the analysis of results.

(Cobas Amplicor HCV Monitor Test, version 2.0; limit of detection, 600 IU/mL).

The primary efficacy end point was SVR, defined as undetectable serum HCV RNA by qualitative polymerase chain reaction at the end of the 24-week untreated follow-up period in groups A and B. Patients without follow-up data were considered not to have achieved an SVR.

HCV genotyping by sequence analysis of the 5' non-coding region and HCV RNA qualitative and quantitative analyses were performed by the Nichols Institute (San Juan Capistrano, California).

Statistical Analysis

The study was designed to have 80% power to detect an increase in the SVR rate from 5% in the untreated control group to between 22% and 25% in either of the treated groups at a 2-sided significance level of .05. Pairwise comparisons among the 3 treatment groups were made using the Cochran–Mantel–Haenszel test stratified by geographic region and pretreatment HCV genotype.

Preplanned exploratory analyses were performed to examine the effects of various baseline prognostic factors on SVR rates in treated patients. For the purposes of this analysis, SVR rates were based on a single HCV RNA determination during follow-up. Logistic regression and analysis of covariance were used to analyze categorical and continuous variables, respectively. Prognostic variables included age, sex, ethnicity, body weight, body surface area, baseline viral load, and treatment duration. The analysis was performed separately for patients infected with HCV genotype 1 and non-1 genotypes, be-

cause HCV genotype exerts a significant and independent influence on SVR rates.

Study Conduct

The study was designed by the sponsor in collaboration with expert hepatologists. Institutional review boards at all participating centers approved the protocol and all amendments. All patients provided written informed consent. Data were collected by the PEGASYS International Study Group. The study was conducted according to the guidelines of the Declaration of Helsinki, under the provisions of good clinical practices, as defined in the US Code of Federal Regulations on the Protection of Human Subjects for the United States, and/or according to the local laws and regulations of the country in which the research was conducted.

Results

Patient Demographics

Patient enrollment started in August 2000, and the study ended in April 2003. The disposition of patients throughout the trial is shown in Figure 1. A total of 440 patients were randomized to treatment, and 421 received ≥ 1 dose of study medication. Seventy-four patients were randomized to the control group, one of whom was treated by mistake with medication for 24 weeks; this patient was included in group A for the efficacy and safety analysis.

Baseline characteristics of the patients were similar across the 3 groups (Table 1). Ten patients had ≥ 1 qualifying ALT value above the ULN. Because these

Table 1. Characteristics of Patients at Baseline

	Peginterferon alfa-2a + ribavirin for 24 wk (n = 212)	Peginterferon alfa-2a + ribavirin for 48 wk (n = 210)	Untreated control (n = 69)
No. male/female (% male)	90/122 (42)	82/128 (39)	26/43 (38)
Age (y) ^a	43.8 ± 10.0	43.9 ± 9.7	41.0 ± 10.2
Weight (kg) ^a	73.9 ± 16.4	73.7 ± 16.8	71.1 ± 15.1
Body surface area (m ²) ^a	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2
Ethnicity, no. (%)			
White	183 (86)	180 (86)	57 (83)
Black	17 (8)	20 (10)	3 (4)
Asian	5 (2)	4 (2)	3 (4)
Other	7 (3)	6 (3)	6 (9)
Mode of infection, no. (%)			
Injection drug use	64 (30)	63 (30)	24 (35)
Transfusion	43 (20)	57 (27)	14 (20)
Other	36 (17)	22 (10)	9 (13)
Unknown	69 (33)	68 (32)	22 (32)
Maximum ALT value (IU/L) ^{a,b}	23.7 ± 6.7	24.5 ± 6.4	23.9 ± 4.9
Maximum ALT quotient, no. (%) ^c			
0–1	209 (99)	204 (97)	68 (99)
>1–1.5	1 (<1)	3 (1)	1 (1)
>1.5–3	2 (<1)	3 (1)	0
Histologic diagnosis (Ishak score)			
Necroinflammation (% of patients)			
<5	156 (74)	157 (75)	55 (80)
5–10	53 (25)	50 (24)	13 (19)
>10	1 (<1)	1 (<1)	0
Missing values	2 (<1)	2 (<1)	1 (1)
Mean necroinflammation score	3.7 ± 1.87	3.5 ± 1.80	3.3 ± 1.56
Fibrosis (% of patients)			
0–1	140 (66)	145 (69)	53 (77)
2	45 (21)	43 (20)	10 (14)
3–4	25 (12)	19 (9)	5 (7)
>4	0	1 (<1)	0
Missing values	2 (<1)	2 (<1)	1 (1)
Mean fibrosis score	1.2 ± 1.02	1.2 ± 1.0	1.0 ± 0.85
HCV RNA × 10 ³ IU/mL ^a	1222 ± 1452	1055 ± 1287	1303 ± 1302
HCV RNA × 10 ³ IU/mL, median (range)	525 (10–10,600)	521 (10–10,700)	600 (14–4980)
HCV genotype, no. (%)			
Type 1	144 (68)	141 (67)	47 (68)
1a	77 (36)	88 (42)	26 (38)
1b	65 (31)	53 (25)	21 (30)
Other	2 (<1)	0	0
Type non-1	68 (32)	69 (33)	22 (32)
2	38 (18)	41 (20)	13 (19)
3	20 (9)	18 (9)	6 (9)
4	8 (4)	9 (4)	2 (3)
5	1 (<1)	0	0
6	1 (<1)	1 (<1)	1 (1)

NOTE. Some percentages do not add up to 100% because of rounding.

^aMean ± SD.

^bMaximum of the 3 measurements that qualified a patient for the trial.

^cMaximum of the 3 measurements that qualified a patient for the trial divided by the ULN range.

violations of study protocol were not identified before the start of therapy, treatment was continued for ethical reasons. Histologically, 18% of the patients had a fibrosis score of 2 and 9.5% had a fibrosis score of 3 or 4. The total mean fibrosis score was 1.4. One patient with cirrhosis was enrolled in group B and received treatment. Liver biopsy results were not

available for 5 patients (2 each in groups A and B and one in group C).

Efficacy

An SVR was achieved by 30% and 52% of the patients treated for 24 and 48 weeks, respectively, (relative risk [RR], 1.7; 95% confidence interval [CI], 1.4–

Table 2. Efficacy Results: Patients With SVR

	Peginterferon alfa-2a + ribavirin for 24 wk (n = 212)	Peginterferon alfa-2a + ribavirin for 48 wk (n = 210)	Risk difference, % (95% CI)	RR, 48 vs 24 wk (95% CI)
All patients (%)	63/212 (30; 23.6–35.9) ^a	109/210 (52; 45.1–58.7) ^a	22 (13–31)	1.7 (1.4–2.2); <i>P</i> < .001
SVR as a function of HCV genotype and baseline viral load ^b				
Genotype 1 (%)	19/144 (13%; 7.7–18.7) ^a	57/141 (40%; 32.3–48.5) ^a	27 (17–37)	3.1 (1.9–4.9); <i>P</i> < .001
Low viral load	14/87 (16)	42/89 (47)		
High viral load	5/55 (9)	14/51 (27)		
Non-1 genotypes (%)	44/68 (65)	52/69 (75)		
Low viral load	25/36 (69)	30/38 (79)		
High viral load	19/32 (59)	22/31 (71)		
Genotypes 2 or 3 (%)	42/58 (72; 60.9–83.9) ^a	46/59 (78; 67.4–88.5) ^a	6 (–10 to 21)	1.1 (0.9–1.3); <i>P</i> = .452
Low viral load	24/30 (80)	25/31 (81)		
High viral load	18/28 (64)	21/28 (75)		
Genotype 4 (%)	1/8 (13)	5/9 (56)		
Low viral load	1/6 (17)	4/6 (67)		
High viral load	0/2 (0)	1/3 (33)		

NOTE. Baseline values were missing for 3 patients infected with HCV genotype 1.

^aRanges are 95% CI.

^bLow, $\leq 800,000$ IU/mL; high, $> 800,000$ IU/mL.

2.2; *P* < .001) (Table 2). No patient in the untreated control group cleared HCV.

SVR rates were significantly higher in patients infected with HCV genotype 1 who were treated for 48 weeks (40%) compared with those treated for 24 weeks (13%) (RR, 3.1; 95% CI, 1.9–4.9; *P* < .001). In contrast, the difference in SVR rates between the 2 treatment groups was not statistically significant in patients infected with genotypes 2 and 3 (72% and 78% with 24 and 48 weeks of treatment, respectively; RR, 1.1; 95% CI, .9–1.3; *P* = .452). SVR rates in patients infected with genotype 4 were similar to those infected with HCV genotype 1 (13% in patients treated for 24 weeks and 56% in those treated for 48 weeks).

Viral load influenced SVR rates in patients infected with HCV genotypes 1 or 4 (Table 2). In contrast, viral load did not influence SVR rates in patients infected with HCV genotypes 2 or 3 who were treated for either 24 or 48 weeks.

Prognostic Factors for SVR

In patients infected with HCV genotype 1, treatment duration (24 vs 48 weeks: odds ratio, 4.39; 95% CI, 2.42–7.98) and baseline viral load ($> 8 \times 10^5$ vs $\leq 8 \times 10^5$ IU/mL: odds ratio, 2.21; 95% CI, 1.20–4.09) significantly and independently affected SVR rates. No other factors exerted a statistically significant influence on SVR rates. In patients with a baseline HCV RNA concentration $\leq 8 \times 10^5$ IU/mL, the unadjusted proba-

bility of achieving an SVR was 77% higher than in patients with a viral load $> 8 \times 10^5$ IU/mL (unadjusted RR, 1.77; 95% CI, 1.12–2.82). In contrast, neither treatment duration nor baseline viral load had a significant effect on SVR rates in patients infected with non-1 genotypes; age was the only independent variable that was significantly associated with SVR rates in this subgroup (40 years or younger vs older than 40 years: odds ratio, 2.31; 95% CI, 1.02–5.24). Patients aged 40 years or younger had a 26% higher probability of achieving an SVR compared with patients who were older than 40 years (RR, 1.26; 95% CI, 1.02–1.55).

Safety

The overall incidence of adverse events, serious adverse events, and laboratory abnormalities leading to premature withdrawal or dosage modification is presented in Table 3. Adverse events reported in patients in groups A and B were typical of those previously associated with peginterferon alfa-2a and ribavirin treatment. Adverse events were generally mild in severity, and no new adverse events were identified. The most common events in treated patients were headache, fatigue, and myalgia. A considerable proportion of untreated patients (77%) reported adverse events during the study, with fatigue and asthenia being the most frequent. Patients treated for 24 weeks had a lower incidence of dosage reductions and premature withdrawal from therapy due to adverse events or laboratory abnormalities than those treated for 48 weeks (Table 3). Severe depression was

Table 3. Adverse Events and Dosage Modifications

Adverse events (%)	Peginterferon alfa-2a + ribavirin for 24 wk (n = 212)	Peginterferon alfa-2a + ribavirin for 48 wk (n = 210)	Untreated control (n = 69)
Any adverse event	209 (99)	207 (99)	53 (77)
Severe adverse events	56 (26)	70 (33)	10 (14)
Life-threatening adverse events	3 (1)	8 (4)	2 (3)
Treatment-related adverse events ^a	204 (96)	206 (98)	NA
Serious adverse events	18 (8)	34 (16)	4 (6)
Treatment-related serious adverse events ^a	6 (3)	20 (10)	NA
Deaths	0	0	1
Premature withdrawal for adverse events or laboratory abnormalities	15 (7)	38 (18)	NA
Dose modification for adverse events			
Peginterferon alfa-2a	23 (11)	40 (19)	NA
Ribavirin	42 (20)	62 (30)	NA
Dose modifications for laboratory abnormalities			
Peginterferon alfa-2a	33 (16)	47 (22)	NA
Ribavirin	19 (9)	45 (21)	NA
Incidence of specific adverse events ^b			
Headache	93 (44)	117 (56)	5 (7)
Fatigue	109 (51)	107 (51)	12 (17)
Myalgia	81 (38)	93 (44)	5 (7)
Pyrexia	64 (30)	90 (43)	2 (3)
Insomnia	74 (35)	76 (36)	5 (7)
Nausea	68 (32)	84 (40)	1 (1)
Arthralgia	68 (32)	62 (30)	3 (4)
Depression	55 (26)	57 (27)	4 (6)
Irritability	58 (27)	55 (26)	1 (1)
Rigors	50 (24)	53 (25)	1 (1)
Alopecia	43 (20)	59 (28)	0
Asthenia	47 (22)	48 (23)	7 (10)
Diarrhea	40 (19)	55 (26)	3 (4)
Pruritus	34 (16)	42 (20)	1 (1)
Incidence of specific laboratory abnormalities			
Hemoglobin <10.0 to ≥8.5 g/dL	10 (5)	24 (11)	0
Hemoglobin <8.5 g/dL	3 (1)	1 (<1)	0
Neutrophils <0.5 × 10 ⁹ /L	10 (5)	10 (5)	0
Platelets <50 × 10 ⁹ /L	3 (1)	4 (2)	0
Hypothyroidism ^c	0	5 (2)	0
Hyperthyroidism ^c	1 (<1)	3 (1)	0
Incidence of ALT elevations			
>30 to <60 IU/L	84 (40)	79 (38)	31 (45)
60 to <150 IU/L	29 (14)	23 (11)	4 (6)
≥150 IU/L	4 (2)	2 (1)	1 (1)

NOTE. The safety population comprised all patients in groups A and B who received at least one dose of medication and had at least one postbaseline safety assessment and all patients in the untreated control group who had at least one postbaseline safety assessment.

NA, not applicable.

^aEvents judged by an investigator to be possibly or probably related to treatment.

^bAdverse events for which the incidence was >20% in at least one study group.

^cNumber of patients who required permanent dosage reductions or discontinued therapy. Thyroid dysfunction was manifested only by abnormal serum hormone levels.

reported in 5 (2%) and 6 (3%) patients in the 24-week and 48-week treatment groups; one (<1%) and 7 (3%) patients withdrew prematurely for depression-related events, respectively. The incidence of depression in the untreated control group was 6%.

Transient elevations in ALT activity were detected in treated and control patients during the study (Table 3). The majority of moderate elevations coincided with virologic relapses in treated patients. Median ALT activity

remained stable in untreated control patients but decreased up to 10 IU/L in treated patients and remained low in sustained responders (Figure 2).

Discussion

In the present study, an SVR was achieved by 30% and 52% of patients with chronic hepatitis C and persistently normal ALT levels treated for 24 and 48

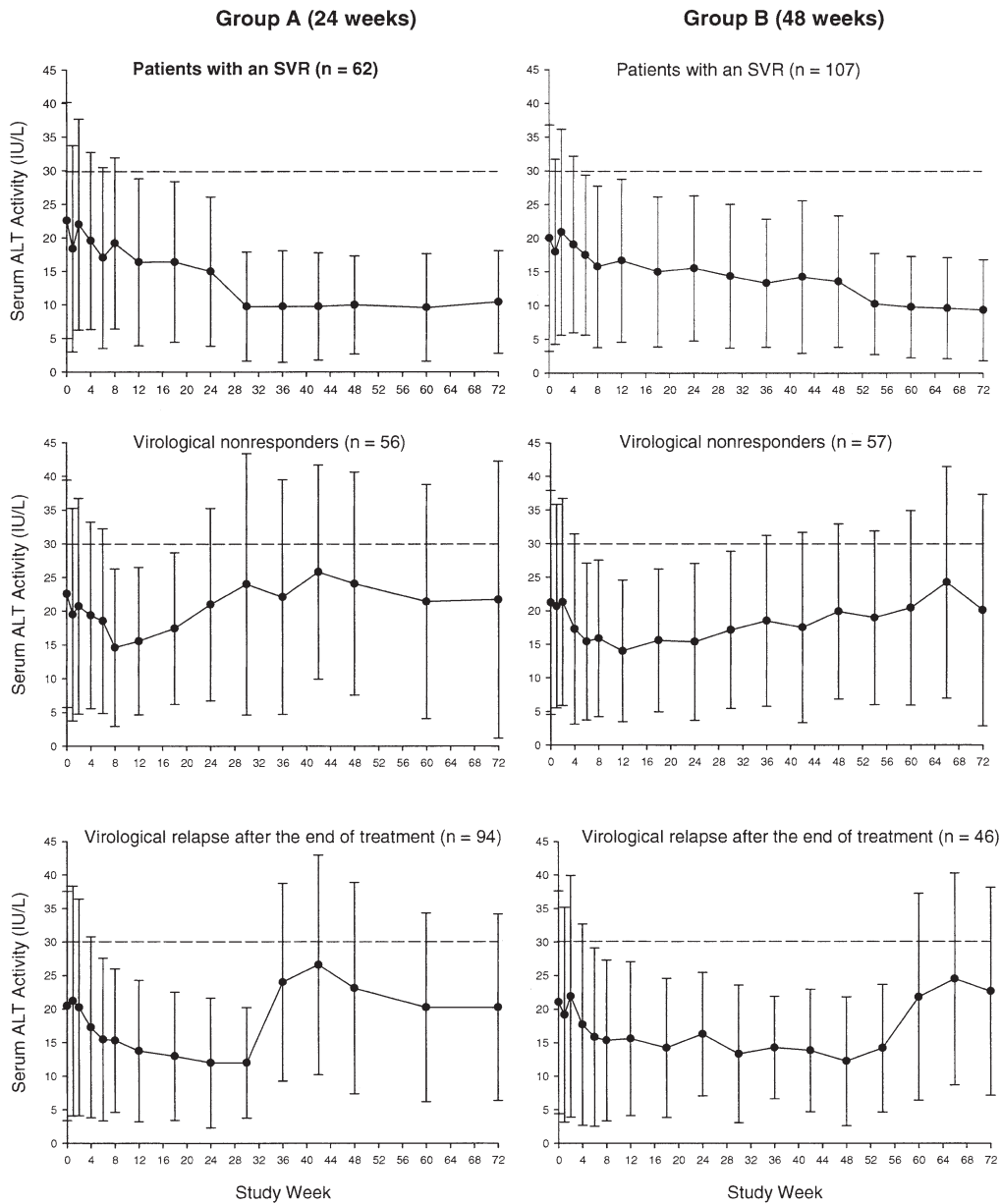


Figure 2. Median ALT levels (\pm interquartile range) in patients treated for 24 weeks or 48 weeks according to virologic response at the end of follow-up. All patients included in the safety population. The ULN is indicated by *dashed lines*. Note that 10 of 491 patients (2%) violated the inclusion criteria with ≥ 1 qualifying ALT value above the ULN.

weeks, respectively. No patient in the untreated control group cleared the virus. The combination of peginterferon plus ribavirin has consistently provided significantly higher SVR rates than conventional interferon plus ribavirin in patients with elevated ALT levels.¹⁻³ In the 48-week treatment group, the overall response rate (52%) was higher than that previously obtained with conventional interferon and ribavirin in small trials involving a limited number of patients with normal ALT activity.^{11,12} Therefore, peginterferon and ribavirin appears to be the optimal therapy for patients with chronic hepatitis C and normal ALT activity.

The SVR rate was strongly influenced by HCV genotype and treatment duration. In patients infected with HCV genotype 1, a higher SVR rate was achieved in the

48-week treatment group (40% vs 13% in patients treated for 24 weeks). In contrast, patients with HCV genotypes 2 or 3 had similar response rates irrespective of the treatment duration (72% and 78%). These results are consistent with those observed in a multicenter study in patients with elevated ALT activity.² In that study, 45% of noncirrhotic patients infected with HCV genotype 1 achieved an SVR after 48 weeks of treatment with peginterferon alfa-2a 180 μ g/wk and ribavirin 800 mg/day, and 87% of patients infected with HCV genotype 2 or 3 achieved an SVR after 24 weeks of treatment with the same regimen. SVR rates are significantly higher in patients infected with HCV genotype 1 who receive a higher weight-based dosage of ribavirin (1000 or 1200 mg/day) compared with those who receive a lower fixed

dosage of 800 mg/day.² Thus, a higher weight-based dosage of ribavirin would be expected to result in higher SVR rates in patients infected with HCV genotype 1 and persistently normal ALT values.

The safety profile was similar to that in patients with elevated ALT levels receiving peginterferon alfa-2a plus ribavirin. The most common adverse events (fatigue, headache, insomnia, and depression) were reported in 5%–10% of patients in the untreated control group, implying that some adverse events that are frequently attributed to interferon therapy may be clinical manifestations of chronic hepatitis C.

The definition of normal serum ALT levels is arbitrary and must be revised as our understanding of the factors that influence ALT levels improves. This fact is illustrated by the results of a recent study of 6835 prospective blood donors in Italy.¹³ After excluding patients with undiagnosed HCV infection and those with behavioral risks for blood-borne disease, the ULN for serum ALT levels was redefined from 30 IU/L to 19 IU/L in women and from 40 IU/L to 30 IU/L in men. The analysis also showed a strong correlation between ALT levels and body mass index that persisted after adjustment for potential confounding variables. Thus, even obese individuals should be excluded when establishing normal ranges for serum ALT values.¹³

In the present study, decreases in median ALT values coincided with the start of therapy and were maintained throughout treatment and follow-up in patients who achieved an SVR. Median ALT values returned to pretreatment levels after a brief decline in virologic nonresponders and after completion of treatment in patients who experienced a virologic relapse. Similar observations have been reported by others,¹¹ suggesting that, in this patient population, the “normal” ALT values before treatment may actually be higher than individuals’ true normal level and that viral clearance and the subsequent reduction in hepatic inflammation cause a decrease towards healthy ALT levels.

Remarkably, 52% of the patients in the untreated control group experienced elevations of ALT activity above the ULN during the study. This incidence is higher than previously reported^{6,14,15} and supports the concept that, in many patients, the persistence of the ALT activity within normal levels is a function of monitoring frequency.⁸ Furthermore, increases in ALT levels are unpredictable and may reflect the risk of progression of liver disease.¹⁶ This suggests that ALT activity may be an unreliable guide for treatment decisions and, when considered with the absence of viral clearance in the untreated control patients in our study, argues against a conservative, watchful-waiting strategy. Indeed, treat-

ment of patients with chronic hepatitis C should rely on the probability of viral eradication, symptoms, histology, anticipated progression of disease, and the risk of transmission (eg, health care workers) rather than on a single biochemical parameter. Thus, patients should not be routinely excluded from therapy because they have “normal” ALT levels.

In conclusion, the combination of peginterferon alfa-2a and ribavirin produces SVR rates in patients with normal ALT activity that are comparable to those achieved in patients with elevated ALT activity. No severe flares of ALT activity were associated with treatment, and the benefit-risk ratio was positive. SVR rates according to genotype in patients with normal ALT activity were similar to those obtained in patients with elevated ALT levels, suggesting that the treatment algorithm for patients with elevated ALT activity can be extended to patients with persistently normal ALT activity.

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