Peginterferon Alfa-2a for Hepatitis C After Liver Transplantation: Two Randomized, Controlled Trials

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There is currently no effective treatment for recurrent hepatitis C after orthotopic liver transplantation (OLT). We therefore performed two randomized, controlled trials—a prophylaxis trial and a treatment trial—to evaluate the safety and efficacy of peginterferon alfa-2a in patients who had undergone OLT. The prophylaxis trial enrolled 54 patients within 3 weeks after OLT, and the treatment trial enrolled 67 patients 6 to 60 months after OLT. In each trial, patients were randomized to treatment with once weekly injections of 180 μg peginterferon alfa-2a or no antiviral treatment for 48 weeks and were followed up for 24 weeks thereafter. Peginterferon alfa-2a treated patients had significantly lower hepatitis C virus RNA levels and more favorable changes in hepatic histological features compared with untreated controls. However, only 2 treated patients in the prophylaxis trial (8%) and 3 in the treatment trial (12%) achieved a sustained virological response. In the prophylaxis trial, 8 patients (31%) in the peginterferon alfa-2a group and 9 (32%) in the untreated group were withdrawn prematurely; whereas in the treatment trial, 10 patients (30%) in the peginterferon alfa-2a group and 6 (19%) in the untreated group were withdrawn prematurely. The incidence of acute rejection was similar in the treated and untreated groups in both the prophylaxis (12% vs. 21%; $P = .5$) and treatment (12% vs. 0%; $P = .1$) trials. In conclusion, peginterferon alfa-2a treatment for 48 weeks is safe and tolerable and offers some efficacy in the post-OLT setting. Randomized controlled studies are needed to establish the efficacy of pegylated interferon and ribavirin in patients who have undergone OLT. (HEPATOLOGY 2005; 41:289-298.)

Hepatitis C virus (HCV) infection is the leading cause of cirrhosis and liver failure leading to orthotopic liver transplantation (OLT) in the United States.[1] Recurrent infection with HCV after OLT, however, is almost universal and is a significant cause of allograft dysfunction and allograft failure.[2-4]

Preemptive interferon therapy (prophylaxis) in the early post-transplantation period may reduce the incidence and/or severity of recurrent HCV infection. In one study, 86 patients were randomized within 2 weeks after OLT to 3 million units of interferon alfa-2b or no treatment for 1 year.[5] Although interferon therapy did not significantly affect HCV RNA levels, it significantly reduced the incidence of recurrent hepatitis. In another controlled study, 24 patients were randomized within 2 weeks after OLT to interferon therapy or no treatment for 6 months.[6] Although interferon treatment did not reduce the incidence or severity of recurrent hepatitis C, it significantly delayed the time to recurrence. Some preliminary reports suggested that preemptive therapy with interferon or a combination of interferon plus ribavirin may lead to less severe HCV recurrence after OLT.[7-9] However, there have been no controlled studies evaluating the safety and efficacy of prophylactic pegylated interferon in liver transplant recipients with HCV.

There is also significant interest in treating established recurrent hepatitis C with interferon-related therapies.

Abbreviations: HCV, hepatitis C virus; OLT, orthotopic liver transplantation; SVR, sustained virological response; HAI, hepatic activity index; AE, adverse event.

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Received August 4, 2004; accepted November 21, 2004

Supported by a grant from Roche Laboratories Inc., Nutley, NJ.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20560

Conflict of interest: Nothing to report.

Standard interferon monotherapy is associated with a lower sustained virological response (SVR) in the transplantation population. For example, in a recent study in which 52 liver transplant recipients were randomized to interferon plus ribavirin or no antiviral treatment for 12 months, there was no difference in liver histological features between the groups at the end of treatment, but the group treated with interferon and ribavirin had a significantly higher SVR rate than the untreated group (21% vs. 0%; $P = .036$).[10] However, 43% of patients receiving interferon and ribavirin were withdrawn from the study, mostly because of ribavirin-related side effects, including anemia. Recent preliminary reports also have suggested a role for pegylated interferon in the treatment of recurrent hepatitis C,[10-14] but these studies were small and were not randomized.

To improve our ability to manage hepatitis C in the post-OLT setting, we conducted two prospective, randomized, open-label, multicenter, phase IIIb trials of pegylated interferon alfa-2a (peginterferon alfa-2a) in liver transplant recipients. Peginterferon alfa-2a is a highly effective treatment for chronic hepatitis C in the nontransplant setting, particularly in combination with ribavirin.[15,16] The objective of our first trial was to evaluate the safety, efficacy, and tolerability of peginterferon alfa-2a when given preemptively within 3 weeks of OLT to prevent recurrence of hepatitis C (prophylaxis trial). The objective of our second trial was to evaluate the safety, efficacy, and tolerability of peginterferon alfa-2a as a treatment for recurrent hepatitis C in patients 6 to 60 months after liver transplantation (treatment trial).

Patients and Methods

Study Design. In the prophylaxis trial, eligible participants in whom OLT had been performed 3 weeks previously were randomized to receive weekly subcutaneous injections of 180 μg peginterferon alfa-2a or no antiviral therapy for 48 weeks. In the treatment trial, eligible recipients in whom OLT had been performed 6 to 60 months previously were randomized to receive weekly subcutaneous injections of 180 μg peginterferon alfa-2a or no antiviral therapy for 48 weeks. The 6- to 60-month eligibility interval was chosen to maintain consistency in the practice patterns of immunosuppression and other post-transplantation care. In both trials, liver biopsies were performed before randomization (baseline) and 48 and 72 weeks after randomization. The institutional review boards of the participating centers approved the protocol, and all patients provided written informed consent.

Eligibility Criteria. For both trials, eligible participants were male and female adult ($\geq$18 years of age), HCV-infected, post-OLT recipients. All patients had ongoing HCV infection with a positive serum anti-HCV antibody and serum HCV RNA of 1,000 IU/mL or more, as measured by the Roche Amplicor HCV 2.0 assay (Roche Diagnostics, Indianapolis, IN) (lower limit of detection, 50 IU/mL). All participants had documented elevation of serum alanine aminotransferase ($\geq$1.5 upper limit of normal) before OLT (prophylaxis trial) or before enrollment (treatment trial). For both trials, eligible participants must not have received prior interferon therapy. In the prophylaxis trial, where the baseline liver biopsy samples were obtained within 3 weeks after OLT, patients were required to have no histological evidence of acute cellular rejection based on Banff International Consensus Schema.[17] In the treatment trial, patients were required to have histological evidence of hepatitis without evidence of rejection on a liver biopsy sample obtained within 8 weeks before randomization. For both trials, the use of hematopoietic growth factors or mycophenolate mofetil was not allowed.

Patients were excluded from the study if they had a neutrophil count of less than 1,500/μL, a platelet count of less than 75,000/μL, a hemoglobin count of less than 10 g/dL, serum creatinine level of more than 2.0 mg/dL, histological evidence of cirrhosis or cholestatic fibrosing hepatitis, history of uncontrolled seizure disorder, alcohol or drug abuse within 1 year of entry, or severe psychiatric illness. Patients were also excluded if they had a history of significant immune disorder, chronic pulmonary disease, cardiac disease, or poorly controlled thyroid disease.

Assessment of Efficacy. The primary efficacy endpoint was SVR, defined as undetectable ($<$50 IU/mL) HCV RNA at the end of the 24-week treatment-free follow-up period (week 72). Secondary endpoints included the proportion of patients with virological response, defined as undetectable HCV RNA ($<$50 IU/mL), the proportion with a 2 $\log_{10}$ drop in HCV RNA, the proportion with biochemical response (*i.e.*, with normalized alanine aminotransferase), and mean changes in hepatic activity index (HAI) and fibrosis score from baseline. All liver biopsy specimens were assessed for HAI and fibrosis score by a single central pathologist who was blinded to therapy and to the time at which the biopsy was taken, using the criteria of Ishak et al.[18]

Assessment of Safety. Safety was assessed by clinical laboratory testing and by evaluation of adverse events (AEs) at weeks 1, 2, 4, 6, and 8, and every 4 weeks thereafter throughout the 48-week treatment and 24-week follow-up periods. The dose of peginterferon alfa-2a was reduced by 45 μg decrements for clinical or laboratory AEs.

Statistical Methods. All efficacy parameters were analyzed on an intention-to-treat basis, and the analyses in-

cluded all randomized patients who had at least one postbaseline observation. The primary and secondary efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel general association test adjusted for genotype and viral load stratum. Safety analyses included all randomized patients who had at least one postbaseline safety assessment. The number and percentage of patients with AE were tabulated by treatment group. A chi-square test or Fisher's exact test was used to test the difference in the proportion of patients with rejection between treatment groups.

The covariate effects of selected demographic (age [<50 years vs. ≥50 years], sex, race, and weight [≤85 kg vs. >85 kg]) and baseline clinical (viral load stratum, baseline viral load, genotype, alanine aminotransferase [≤60 U/L vs. >60 U/L], and HAI score [≤10 vs. >10]) characteristics on SVR were explored using logistic regression analyses. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC). A P value less than 0.05 was considered statistically significant.

Results

Fifty-four patients participated in the prophylaxis trial, with 26 randomized to peginterferon alfa-2a and 28 to no treatment. Fifteen patients in each group completed the study (Fig. 1A). Selected demographic and clinical characteristics were well matched in the two groups (Table 1). In the treatment trial, 34 of the 67 patients were randomized to peginterferon alfa-2a and 33 to no antiviral therapy. Twenty patients in the peginterferon alfa-2a group and 26 in the control group completed the 72-week study (Fig. 1B). Selected demographic and clinical characteristics in the two groups also were well matched (Table 1).

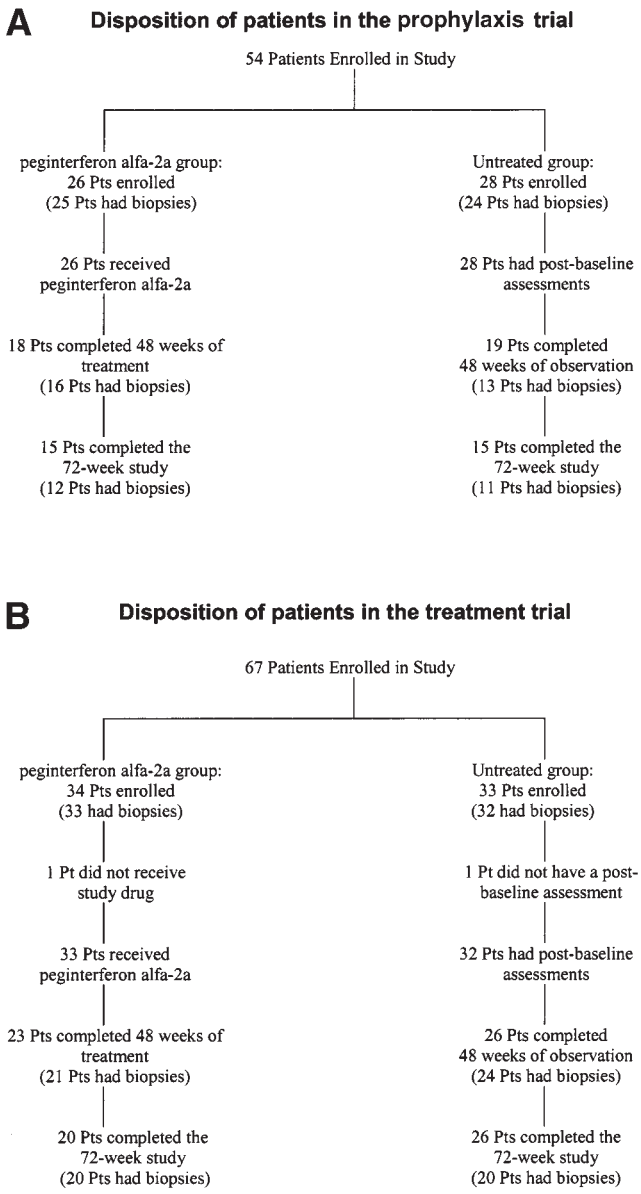

Fig. 1. (A) Disposition of patients (Pts) in the prophylaxis trial (n = 54). (B) Disposition of patients in the treatment trial (n = 67).

Virological and Biochemical Responses

Prophylaxis Trial. Baseline serum HCV RNA levels did not differ significantly between the two groups (Table 1). The pattern of virological response over time is shown in Table 2. Compared with the untreated group, patients receiving peginterferon alfa-2a had higher virological response, which was of statistical significance or marginal significance at various intervals (Table 2). SVR was achieved by 2 patients (8%) in the peginterferon alfa-2a group, but by no patient in the untreated group ($P = .14$). One of the patients who achieved SVR was infected with HCV genotype 1, and the other was infected with HCV genotype 2. Patients in the peginterferon alfa-2a group had a significantly lower viral load than patients in the untreated group (P values from .001 to .01) at each scheduled postbaseline assessment, except week 72 ($P = .4$; Table 2 and Fig. 2A). Patients receiving peginterferon alfa-2a had a significantly greater drop in HCV RNA at weeks 4 and 24 than the untreated patients ($P = .003$ and .02, respectively). Biochemical response did not differ significantly between the peginterferon alfa-2a and untreated groups at week 48 (19% vs. 25%, respectively; $P = .6$) or week 72 (15% vs. 21%, respectively; $P = .6$).

Treatment Trial. Baseline serum HCV RNA levels did not differ significantly between the two groups (Table 1). The pattern of virological response over time in both groups is shown in Table 2. Compared with the untreated patients, patients treated with peginterferon alfa-2a had a significantly higher virological response rate, both during treatment and at the end of follow-up. SVR was achieved

Table 1. Baseline Demographic and Clinical Characteristics of Patients Enrolled in Both Trials

	Prophylaxis Trial (n = 54)			Treatment Trial (n = 65)		
	Treated (n = 26)	Untreated (n = 28)	*P* Value	Treated (n = 33)	Untreated (n = 32)	*P* Value
Age (yr)	51 ± 1.3	54 ± 1.7	.5	53 ± 1.4	51 ± 1.2	.2
Males (%)	92	68	.04	76	81	.7
African Americans (%)	12	4	.4	0	3	.8
Weight (kg)	81 ± 4.4	80 ± 3.6	.9	89 ± 3.5	92 ± 4.3	.2
Height (cm)	173 ± 1.8	168 ± 2.2	.1	176 ± 1.9	176 ± 1.8	.9
BMI (kg/m^2)	26.6 ± 1.4	28.4 ± 1.4	.3	28.1 ± 0.8	29.8 ± 1.2	.6
Time since OLT (d)	16 ± 5.9	19 ± 7.7	.1	759 ± 591	683 ± 481	.7
Serum creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.1	.3	1.4 ± 0.1	1.3 ± 0.1	.5
Estimated GFR (mL/min)*	95 ± 32	99 ± 30	.4	90 ± 15.5	79 ± 11	.9
Hemoglobin (g/dL)	10.5 ± 0.4	10.7 ± 0.4	.9	14 ± 0.3	14.8 ± 0.3	.05
White cell count	8.8 ± 0.8	8.0 ± 0.7	.5	5.8 ± 0.4	6.1 ± 0.4	.8
Absolute neutrophil count	6.9 ± 0.6	6.3 ± 0.6	.6	3.6 ± 0.2	4.1 ± 0.3	.4
Platelet count	197.9 ± 17.2	173.4 ± 21.3	.2	162.2 ± 10.5	150.7 ± 10.7	.4
HCV RNA ($\times 10^6$ IU/mL)	2.0 ± 3.8	3.0 ± 7.2	.5	3.4 ± 2.7	3.0 ± 2	.9
HCV genotype 1 (%)	73	75	.5	79	75	.8
Baseline ALT (U/L)	95 ± 32	99 ± 30	.4	90 ± 15.5	79 ± 10.9	.9
Baseline HAI score	1.0 ± 0.2	1.0 ± 0.2	.8	5.5 ± 0.5	4.8 ± 0.5	.3
Baseline fibrosis	0.2 ± 0.1	0 ± 0.04	.2	0.9 ± 0.1	0.9 ± 0.2	.4
Primary immunosuppression†						
Tacrolimus (%)	100	89	.09	70	59	.4
Mean daily dose ± SD	5.8 ± 3	5.4 ± 3		5.6 ± 3.9	3.0 ± 1.6	
Cyclosporine (%)	12	25	.2	36	41	.7
Mean daily dose ± SD	395 ± 144	278 ± 91		188 ± 38	203 ± 77	
Prednisone (%)	88	93	.9	12	18	.7
Mean daily dose ± SD	9.8 ± 3.7	8.7 ± 2.8		16.2 ± 13	4.0 ± 1.3	

NOTE. Data presented as mean ± SE unless specified otherwise.

Abbreviations: GFR, glomerular filtration rate; ALT, alanine aminotransferase.

* Calculated using Cockrodt-Gault equation.

† Primary immunosuppression was interchanged in seven patients in the prophylaxis trial and six patients in the treatment trial.

Table 2. Patterns of Virological Response Over Time

	Prophylaxis Trial (n = 54)			Treatment Trial (n = 65)		
	Treated (n = 26)	Untreated (n = 28)	*P* Value	Treated (n = 33)	Untreated (n = 32)	*P* Value
Virological response, n (%)*						
Week 4	3 (12)	0	.07	4 (12)	0	.02
Week 12	4 (15)	0	.03	10 (30)	0	<.001
Week 24	5 (19)	0	.01	10 (30)	0	<.001
Week 48	4 (15)	0	.03	9 (27)	0	<.001
Week 72	2 (8)	0	.14	4 (12)	0	.03
2 $\log_{10}$ drop in HCV RNA, n (%)						
Week 4	7 (27)	0	.003	12 (36)	0	<.001
Week 12	5 (19)	0	.012	15 (45)	0	<.001
Week 24	7 (27)	0	.002	17 (52)	0	<.001
Week 48	6 (23)	1 (4)	.03	15 (45)	0	<.001
Week 72	2 (8)	0	.14	4 (12)	0	<.03
HCV RNA titers ($\times 10^6$ IU/mL; mean ± SE)						
Week 0	2.0 ± 0.7	3.0 ± 1.4	.5	3.4 ± 0.4	3.0 ± 0.3	.9
Week 4	1.8 ± 0.7	5.2 ± 1.3	.001	1.0 ± 0.2	2.6 ± 0.5	<.001
Week 12	2.2 ± 0.7	6.2 ± 1.8	.01	0.6 ± 0.2	2.0 ± 0.3	<.0001
Week 24	1.3 ± 0.3	5.4 ± 1.8	.003	0.7 ± 0.2	2.2 ± 0.4	<.001
Week 48	1.5 ± 0.4	4.0 ± 0.8	.01	1.0 ± 0.6	1.8 ± 0.3	<.001
Week 72	2.6 ± 0.5	2.4 ± 0.6	.4	2.1 ± 0.4	2.0 ± 0.4	.9

* <50 copies/mL of HCV-RNA.

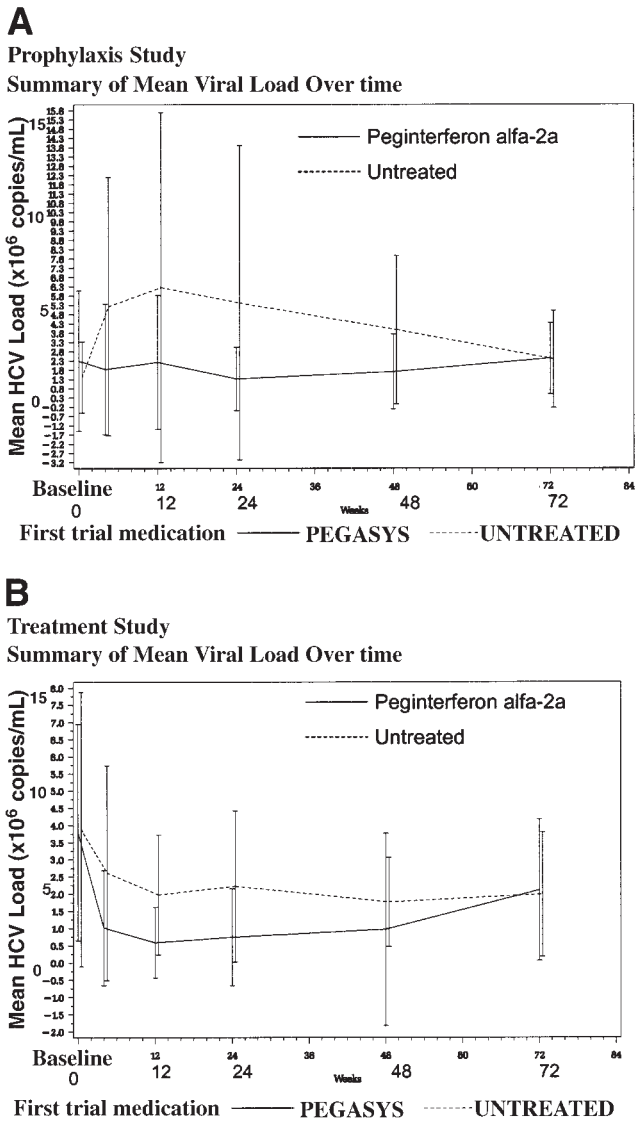

Fig. 2. (A) Mean viral loads during the prophylaxis trial. (B) Mean viral loads during the treatment trial. HCV, hepatitis C virus.

by 4 patients (12%) in the peginterferon alfa-2a group, but by none of the patients in the untreated group ($P = .03$). Of the patients who achieved SVR, 1 was infected with genotype 1, 2 were infected with genotype 2, and 1 was infected with genotype 3. Patients in the peginterferon alfa-2a group had a significantly lower viral load than patients in the untreated group at each scheduled postbaseline assessment ($P < .001$ each), except week 72 ($P = .9$; Fig. 2B). In addition, patients in the peginterferon alfa-2a group had a significantly greater decrease from baseline in HCV RNA titers than patients in the untreated group at weeks 4, 12, 24, and 48 ($P < .001$ each) and at week 72 ($P < .03$). Biochemical response did not differ significantly between the peginterferon alfa-2a and untreated groups at week 72 (33% vs. 22%, respectively; $P = .3$), but patients in the untreated group had a higher biochemical response at week 48 (28% vs. 9%; $P = .048$).

Histological Outcomes

Prophylaxis Trial. Baseline liver biopsies were obtained from 25 patients in the peginterferon alfa-2a group and 24 in the untreated group; week 48 biopsies were obtained from 16 patients in the peginterferon alfa-2a group and 13 in the untreated group; and week 72 biopsies were obtained from 12 patients in the peginterferon alfa-2a group and 11 in the untreated group (Fig. 1A). The changes in liver histological features between baseline and paired week 48 and week 72 biopsies are shown in Table 3 and Fig. 3A. The HAI activity scores at baseline and at week 72 were 0.8 ± 0.4 and 3.5 ± 0.9, respectively, in the peginterferon alfa-2a group and 1.2 ± 0.4 and 5.2 ± 1.0, respectively, in the untreated group. The increase in HAI score over the 72-week period seemed to be lower in the peginterferon alfa-2a group than in the untreated group, but this difference was not statistically significant (2.7 ± 0.8 vs. 4.0 ± 1.0, respectively; $P = .3$). Fibrosis scores at baseline and at week 72 were 0.2 ± 0.1 and 0.6 ± 0.2, respectively, in the peginterferon alfa-2a group and 0.1 ± 0.1 and 1.1 ± 0.3, respectively, in the untreated group. The increase in fibrosis score over the 72-week study period seemed to be lower in the peginterferon alfa-2a group than in the untreated group, but again, this difference was not statistically significant (0.4 ± 0.2 vs. 1.0 ± 0.3, respectively; $P = .3$). Between baseline and week 48, HAI inflammatory scores improved

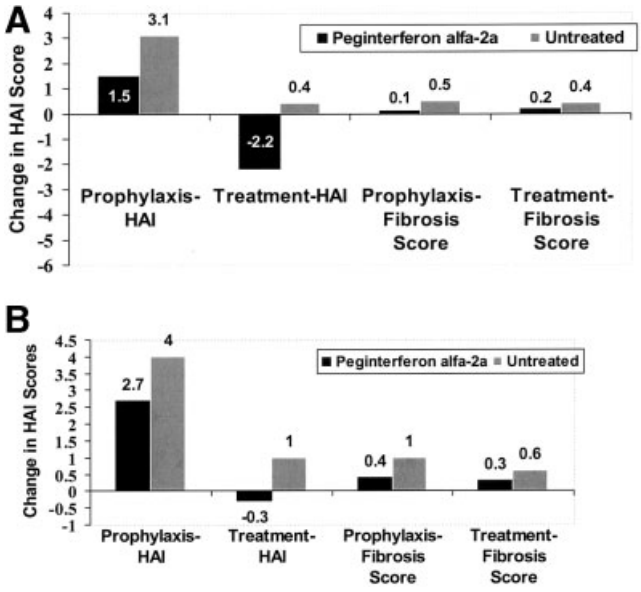

Fig. 3. (A) Mean change from baseline to 48 weeks in hepatic activity index (HAI) and fibrosis scores in both trials. (B) Mean change from baseline to 72 weeks in HAI and fibrosis scores in both trials.

Table 3. Changes in Liver Histology Features Over Time

Comparison	Prophylaxis Trial			Treatment Trial		
	Treated	Untreated	P Value	Treated	Untreated	P Value
Baseline and week 48						
No. patients	16	13		21	24	
HAI baseline	0.9 ± 0.3	1.1 ± 0.3		5.2 ± 0.6	4.6 ± 0.5	
HAI week 48	2.4 ± 0.5	4.2 ± 1.0		3.0 ± 0.5	5.0 ± 0.5	
Change in HAI	1.5 ± 0.6	3.1 ± 1.0	.3	−2.2 ± 0.6	0.4 ± 0.6	.004
Fibrosis score baseline	0.1 ± 0.1	0.1 ± 0.1		0.7 ± 0.2	0.7 ± 0.1	
Fibrosis score week 48	0.3 ± 0.2	0.6 ± 0.2		0.9 ± 0.2	1.0 ± 0.2	
Change in fibrosis score	0.1 ± 0.2	0.5 ± 0.2	.047	0.2 ± 0.2	0.4 ± 0.2	.6
Baseline and week 72						
No. patients	12	11		20	20	
HAI baseline	0.8 ± 0.4	1.2 ± 0.4		5.3 ± 0.6	4.2 ± 0.5	
HAI week 72	3.5 ± 0.9	5.2 ± 0.8		5.0 ± 0.6	5.2 ± 0.7	
Change in HAI	2.7 ± 0.8	4.0 ± 1.0	.3	−0.3 ± 0.8	1.0 ± 0.9	.2
Fibrosis score baseline	0.2 ± 0.1	0.1 ± 0.1		0.8 ± 0.2	0.7 ± 0.2	
Fibrosis score week 72	0.6 ± 0.2	1.1 ± 0.3		1.1 ± 0.2	1.3 ± 0.2	
Change in fibrosis score	0.4 ± 0.2	1.0 ± 0.3	.3	0.3 ± 0.2	0.6 ± 0.2	.2

in 20%, stabilized in 13%, and worsened in 67% of patients in the peginterferon alfa-2a group, whereas fibrosis score improved in 7%, stabilized in 80%, and worsened in 13%. In comparison, for untreated patients there was no improvement in fibrosis, stabilization occurred in only 38% of untreated patients, and worsening occurred in 62% of untreated patients.

Treatment Trial. Baseline liver biopsies were obtained from all participants, week 48 biopsies were obtained from 21 patients in the peginterferon alfa-2a group and from 24 patients in the untreated group, and week 72 biopsies were available from 20 patients in each group (Fig 1B). The changes in liver histological features between baseline and week 48 and week 72 biopsies are shown in Table 3 and Fig. 3B. The HAI scores at baseline and at week 72 were 5.3 ± 0.6 and 5 ± 0.6, respectively, in the peginterferon alfa-2a group and 4.2 ± 0.5 and 5.2 ± 0.7, respectively, in the untreated group. The change in HAI score over the 72-week period seemed to be lower in the peginterferon alfa-2a group than in the untreated group, but this difference was not statistically significant (−0.3 ± 0.8 vs. 1.0 ± 0.9, respectively; $P = .2$). Fibrosis scores at baseline and at week 72 were 0.8 ± 0.2 and 1.1 ± 0.2, respectively, in the peginterferon alfa-2a group and 0.7 ± 0.2 and 1.3 ± 0.2, respectively, in the untreated group. The increase in fibrosis score over the 72-week study period seemed to be lower in the peginterferon alfa-2a group than in the untreated group, but this difference was not statistically significant (0.3 ± 0.2 vs. 0.6 ± 0.2, respectively; $P = .2$). Between baseline and week 48, HAI score improved in 76%, stabilized in 10%, and worsened in 14% of the patients in the peginterferon alfa-2a group, whereas fibrosis score improved in 10%, stabilized in 63%, and worsened in 24% in these patients. Changes in inflammation for the untreated group were 29% improved, 33% stabilized, and 38% worsened; whereas fibrosis changes did not differ from those in the untreated group at 8%, 63%, and 29%, respectively.

Predictors of Virological Response

In a stepwise logistic regression analysis consisting of age, sex, race, weight, alanine aminotransferase level, baseline HCV RNA, genotype, week 12 virological response, and pretreatment HAI or fibrosis score, in both trials only genotype was independently associated with SVR (*i.e.*, patients with HCV genotype 1 were less likely to achieve SVR than those with HCV genotype non-1). In the prophylaxis trial, the association between genotype non-1 and viral response at various time points was: week 12 (OR, 13.5; 95% CI, 1.1-166; $P = .04$), week 24 (OR, 24; 95% CI, 1.9-295; $P = .01$), and week 48 (OR, 19; 95% CI, 1.1-342; $P = .045$). (Week 72 could not be fit into the model because of the small number of patients with SVR.) In the treatment trial, the association between genotype non-1 and viral response at various time points was: week 12 (OR, 22; 95% CI, 1.6-309; $P = .02$), week 24 (OR, 14; 95% CI, 1.4-144; $P = .02$), week 48 (OR, 33; 95% CI, 3.1-353; $P = .004$), and week 72 (OR, 32.5; 95% CI, 1.8-600; $P = .02$).

Safety Evaluation

Prophylaxis Trial. The number of AEs, serious AEs, rejection episodes, and deaths in the peginterferon alfa-2a and untreated groups were similar. The nature and frequency of common AEs in both groups are shown in

Table 4. Five patients were judged to have life-threatening AEs during the trial, 2 in the peginterferon alfa-2a group (severe hypoglycemia and severe rejection) and 3 in the untreated group (respiratory failure, severe anemia, and allograft failure). Three patients died during the study: 1 in the peginterferon alfa-2a group as a result of post-transplantation lymphoproliferative disorder with Corynebacterium bacteremia and 2 in the untreated group as a result of sepsis and allograft dysfunction in one patient and as a result of respiratory failure resulting from bronchiolitis obliterans in another patient. All of these life-threatening AEs and deaths were judged by the site investigator to be unrelated to participation in this trial. Three patients in the peginterferon alfa-2a group (12%) and 6 in the untreated group (21%) had acute cellular rejection during the trial ($P = .5$; Table 4). Three patients in the peginterferon alfa-2a group and 4 in the untreated group received a full course of antirejection treatment (high-dose steroids for 3 consecutive days or more or antithymocyte or lymphocyte globulin or OKT3 for 1 day or more).

The proportion of patients who were withdrawn from the trial during the 48-week treatment period was similar: 8 patients (31%) in the peginterferon alfa-2a group and 9 (32%) in the untreated group (Fig. 1A and Table 5). Eleven patients (42%) in the peginterferon alfa-2a group required a dose reduction because of AEs or laboratory abnormalities, with the most common causes of dose adjustment being thrombocytopenia and/or neutropenia (9 patients).

Table 4. Frequency (%) of Common Adverse Events During the Trials

	Prophylaxis Trial (n = 54)		Treatment Trial (n = 65)	
	Treated (n = 26)	Untreated (n = 28)	Treated (n = 33)	Untreated (n = 32)
Headache	50	43	52	19
Pyrexia	50	36	48	13
Abdominal pain	38	57	15	16
Diarrhea	42	50	33	28
Fatigue	38	54	61	25
Tremor	35	29	21	3
Edema	35	25	21	28
Nausea	15	36	36	28
Hypertension	23	21	24	22
Myalgia	23	4	24	6
Anemia	8	18	15	3
Depression	19	11	27	6
Constipation	12	25	9	3
Renal failure	8	18	9	0
Hypoglycemia	15	14	3	3
Arthralgia	15	18	21	22
Rejection	12	21	12	0
Total serious AEs	9	10	13	11

Table 5. Reasons for Premature Withdrawal Before Week 48

	Prophylaxis Trial (n = 54)		Treatment Trial (n = 65)	
	Treated (n = 26)	Untreated (n = 28)	Treated (n = 33)	Untreated (n = 32)
Total	8	9	10	6
Patient withdrew consent	2	0	0	2
Progression of hepatitis C	2	6	2	3
Thrombocytopenia	1	0	0	0
Protocol violation	1	2	0	0
Liver abscess	1	0	0	0
Death	0	1	1	0
Rejection	1	0	1	0
Others	0	0	6*	1†

* Others included anemia (n = 1), weakness (n = 1), seizure (n = 1), and cholangitis resulting from bile duct pathological characteristics (n = 1).

† Others included elevated transaminases (n = 1).

At baseline, mean (± SD) hemoglobin concentrations were low but comparable in the two groups: 10.5 ± 0.4 g/dL in the peginterferon alfa-2a group and 10.7 ± 0.4 g/dL in the untreated group. Mean hemoglobin concentration in both groups increased steadily throughout the trial, with the untreated group reaching values within the normal range earlier (24 weeks) than the peginterferon alfa-2a group (week 72). Mean (±SD) neutrophil counts for patients in both groups were normal at baseline but decreased similarly during the trial period. Absolute neutrophil counts of less than 1.0×10^9/L were observed in 23% of patients in the peginterferon alfa-2a group and in 18% of the untreated patients ($P = .3$). Mean (±SD) baseline platelet counts in both groups (198,000/μL ± 17,200/μL in the treated and 173,000/μL ± 21,300/μL in the untreated group) were within the normal range (150,000 to 450,000/μL) and showed a reversible decline during treatment. The magnitude of the decline, however, was greater in the peginterferon alfa-2a group. The maximum mean decrease was 111,400/μL ± 80,000/μL in the peginterferon alfa-2a treated group and 29,000/μL ± 101,000/μL in the untreated group, both at week 24.

Treatment Trial

The nature and frequency of common AEs in the peginterferon alfa-2a and untreated groups are shown in Table 4. Three patients, all in the peginterferon alfa-2a group, were judged to have life-threatening AEs during the trial (one case each of multiorgan failure, allograft failure, and head and neck cancer with lung metastases). Two patients in the peginterferon alfa-2a group died during the trial period (as a result of hepatic and renal failure associated with severe tacrolimus toxicity in one patient and as a result of head and neck cancer with lung metastases in another patient). None of these life-threatening

AEs or deaths was judged by the site investigator to be related to the study drug. Four patients in the peginterferon alfa-2a group (12%), but none in the untreated group, had biopsy-proven or presumed episodes of acute rejection during the trial ($P = .11$). No patient in either group, however, required a full course of antirejection treatment. Ten patients (30%) in the peginterferon alfa-2a group were withdrawn from the trial during the 48-week treatment period, compared with 6 (19%) in the untreated group (Fig. 1B and Table 5). Twenty patients in the treatment group required a dose adjustment because of AEs or laboratory abnormalities, with the most common causes of dose adjustment being thrombocytopenia and/or neutropenia (18 patients).

Mean hemoglobin concentration decreased between weeks 1 and 48 in both groups, but returned to near baseline values after treatment was completed. The decrease was greater in the peginterferon alfa-2a group (from 14.0 ± 0.3 g/dL to 11.9 ± 1.45 g/dL) than in the untreated group (from 14.8 ± 0.3 g/dL to 14.1 ± 1.57 g/dL). In the treated group, the mean neutrophil count decreased from baseline (3,600/μL ± 200/μL) to near the lower limit of the normal range (1,980/μL ± 1200/μL; maximum mean decrease, 1,900/μL), but decreased only slightly in the untreated group. Absolute neutrophil counts of less than 1.0×10^9/L were observed in 36% of patients in the peginterferon alfa-2a group and in none of the untreated patients. Mean platelet count decreased in the treated group between weeks 1 and 24 (from 162,000 ± 10,500/μL to 91,000 ± 39,000/μL; maximum mean decrease, 75,700 ± 55,400/μL), but returned to near baseline values by week 72. Mean platelet counts were essentially unchanged for patients in the untreated group.

Discussion

The two trials presented here show the results of prospective, randomized, controlled trials that evaluated the safety and efficacy of pegylated interferon after liver transplantation. Our trials make several important observations. First, they show that peginterferon alfa-2a therapy is safe and reasonably well tolerated in the post-OLT setting when administered prophylactically soon after OLT or later in the post-OLT period to treat recurrent hepatitis C. Second, although SVR was achieved by only a small number of patients, a sizable proportion of patients had significant viral suppression while receiving treatment (up to 27% in the prophylaxis trial and up to 52% in the treatment trial). Third, our results suggest that while on therapy, peginterferon alfa-2a may affect liver histological features favorably in HCV-infected OLT recipients. Last, these results highlight the risks of liver transplantation recipients for the development of serious AEs unrelated to antiviral therapy and show that a sizable proportion of patients are unable to complete the protocol for reasons unrelated to antiviral therapy.

Although many transplantation centers routinely use pegylated interferon to manage recurrent hepatitis C after OLT,[19] published reports systematically assessing the safety and efficacy of pegylated interferon in the post-OLT setting are limited.[11-14] In one study, 9 liver transplantation recipients with renal failure and recurrent hepatitis C were treated with peginterferon alfa-2b (1.0 μg/kg weekly), but 8 of these patients were intolerant to treatment and required discontinuation within the first 3 months.[11] In a retrospective study, 16 patients, 11 of whom were nonresponders to interferon plus ribavirin therapy, were treated with peginterferon alfa-2b (target dose, 1.5 μg/kg weekly) and ribavirin (target dose, 800-1200 mg/d).[12] Although on-treatment virological response was observed in 6 patients (37.5%), none achieved SVR. In a nonrandomized prospective study, peginterferon alfa-2b and ribavirin were titrated with increasing doses in 19 patients with recurrent hepatitis C for a median duration of 128 weeks after OLT, with therapy continued for 1 year after hepatitis C replication was undetectable by reverse-transcriptase polymerase chain reaction.[13] Of these 19 patients, 12 (63%) completed the protocol, 7 (37%) had an end-of-treatment response, and 5 (26%) achieved SVR, with the latter showing significant improvement in necroinflammatory scores. A pilot study assessed the safety and efficacy of peginterferon alfa-2b and ribavirin in 20 patients with recurrent hepatitis C for a median duration of 28 months after OLT.[14] Most patients were naïve to prior interferon therapy, and the doses were progressively increased from 0.5 to 1.0 μg/kg weekly for peginterferon alfa-2b and from 400 mg/d to 1,000-1,200 mg/d for ribavirin. Four patients (20%) were withdrawn because of AEs, whereas 6 (37.5%) of the 16 patients who completed the study required a reduction in peginterferon alfa-2b dose to 0.5 μg/kg weekly, and 13 (81%) required a reduction in ribavirin dose. On an intention-to-treat basis, end-of-treatment response was achieved by 55% of the patients and SVR by 45%. Importantly, there were significant improvements in mean METAVIR scores (activity, 1.8 vs. 0.3; fibrosis, 2.2 vs. 1.6; $P < .05$ for each).

The histological changes we observed during treatment deserve further discussion. Although SVR was infrequent, patients receiving peginterferon alfa-2a exhibited a trend toward reduced exacerbation of liver histological features at week 48, which became less apparent by week 72. For example, in the prophylaxis trial, patients who received peginterferon alfa-2a had a significantly lower increase in

fibrosis score than the untreated patients at week 48, but this benefit was not evident at week 72. Similarly, in the treatment trial, patients who received peginterferon alfa-2a had a significantly lower increase in HAI score than the untreated patients at week 48, but this benefit disappeared by week 72. In addition, several patients in each trial showed improvement in hepatic histological features in the absence of virological or biochemical response (data not shown). These data suggest that the beneficial histological effects are treatment dependent and that these patients, who are not likely to clear the virus, may require long-term or maintenance antiviral therapy to sustain or improve histological benefits.

Two recently published studies suggest that interferon-based treatment of recurrent hepatitis C may increase the risk of allograft rejection.[20,21] For example, 8 (35%) of 23 liver transplantation recipients with significant recurrent hepatitis C treated predominantly with pegylated interferon monotherapy for a minimum of 24 weeks showed evidence of acute or chronic rejection on post-treatment biopsy; although most of these patients had no previous history of rejection, two experienced graft loss from chronic rejection.[20] Similarly, in 5 (11%) of 44 liver transplantation recipients receiving interferon-based therapy for recurrent hepatitis C, acute rejection developed during therapy, and two patients experienced graft loss because of severe rejection.[21] Although these results raise concerns about the safety of interferon-related therapies in the post-OLT setting, they should be interpreted cautiously, especially in view of their study design. Studies that systematically examined the risk of allograft rejection from combination therapy are not adequate, but in one randomized controlled study, the risk of acute or chronic rejection was not higher in those who received 48 weeks of interferon alfa-2b plus ribavirin compared with untreated controls.[10] Our two prospective, controlled trials did not show that patients treated with peginterferon alfa-2a experienced a higher incidence of rejection, as assessed by clinical criteria or by sequential liver biopsies.

Our trials used stringent eligibility criteria, making the participants likely to represent only a small proportion of those patients who undergo liver transplantation for hepatitis C-related liver disease. Although these eligibility criteria allowed us to study the efficacy of peginterferon alfa-2a in a relatively homogenous group of patients, they diminish the generalizability of our results. For example, our study excluded patients who had received interferon therapy before liver transplantation. This is problematic because at present, many transplant patients have had prior interferon-based treatments.

Interestingly, we did not observe consistent relationships between biochemical and virological responses at weeks 48 and 72, in that several patients had virological responses, but not biochemical responses, at these intervals. This is not surprising, inasmuch as liver transplant recipients frequently exhibit elevations in liver enzymes for reasons other than HCV, including rejection, drug toxicity, or steatosis. This finding suggests, however, that sustained biochemical response is not an optimal efficacy endpoint for antiviral therapy in liver transplant recipients.

Because our two trials were not designed to be compared against each other, we are unable to comment on which strategy (*i.e.*, prophylaxis or treatment of established recurrent hepatitis C) is better for managing HCV in liver transplant recipients. This can be addressed only by a trial in which liver transplant recipients are randomized to receive prophylactic or therapeutic antiviral therapy. For the present, the timing of antiviral therapy will largely depend on the clinical judgment of physicians and the willingness of their patients to undergo treatment.

Although our results reveal disappointing antiviral efficacy for peginterferon alfa-2a monotherapy in the post-OLT setting, they provide a basis for exploring combination therapy, even within 3 weeks after OLT. One controlled study[10] and several uncontrolled studies[22-26] have reported that treatment with conventional interferon plus ribavirin led to higher virological response rates than those achieved by pegylated interferon alone. Based on these results, it is tempting to assume that pegylated interferon plus ribavirin will be more effective than pegylated interferon alone in the post-OLT setting. However, liver transplant recipients may require significant dose reductions of ribavirin because of the higher prevalence in these patients of renal insufficiency,[27] and thus may not derive significant incremental benefit from combination therapy. Randomized controlled studies, with and without hematopoietic growth factors, are urgently needed to establish the efficacy and safety of the combination of pegylated interferon and ribavirin in liver transplant recipients with hepatitis C.

Acknowledgment. We thank Rajinder Sidhu for her contributions to the conduct of this study, Drs. Richard J. Alexander and Jennifer Steeber for medical writing and editing assistance, and Dr. Janet S. Lee for her critical review of the manuscript. Two patients who participated in the treatment trial at the UCLA site were included in another paper published by Dr. Sammy Saab.[21] This was done without the prior knowledge of other members of the Pegasys transplant team or the sponsor. The recognition of this error was promptly shared with the editor.

APPENDIX

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