A Randomized, Double-Blind Trial Comparing Pegylated Interferon Alfa-2b to Interferon Alfa-2b as Initial Treatment for Chronic Hepatitis C

KAREN L. LINDSAY,[1] CHRISTIAN TREPO,[2] TOBIAS HEINTGES,[3] MITCHELL L. SHIFFMAN,[4] STUART C. GORDON,[5] JOHN C. HOEFS,[6] EUGENE R. SCHIFF,[7] ZACHARY D. GOODMAN,[8] MARK LAUGHLIN,[9] RUJI YAO,[9] AND JANICE K. ALBRECHT[9] FOR THE HEPATITIS INTERVENTIONAL THERAPY GROUP[10]

This international, randomized, active-controlled, parallel-group, double-blind dose-finding study compared peginterferon alfa-2b (PegIntron™) to interferon alfa-2b for the initial treatment of compensated chronic hepatitis C. We randomly assigned 1,219 subjects to receive either the standard three-times-weekly (TIW) interferon alfa-2b dose (3 MIU) or the once-weekly (QW) peginterferon alfa-2b (0.5, 1.0, or 1.5 μg/kg). Subjects were treated for 48 weeks and then followed for an additional 24 weeks. All 3 peginterferon alfa-2b doses significantly ($P \leq .042$) improved virologic response rates (loss of detectable serum HCV RNA) after treatment and after follow-up, as compared with interferon alfa-2b. Unlike the end-of-treatment virologic response, the sustained virologic response rate was not dose-related above 1.0 μg/kg peginterferon alfa-2b because of a higher relapse rate among patients treated with 1.5 μg/kg peginterferon alfa-2b, particularly among patients infected with genotype 1. All 3 peginterferon alfa-2b doses decreased liver inflammation to a greater extent than did interferon alfa-2b, particularly in subjects with sustained responses. No new adverse events were reported, and the majority of adverse events and changes in laboratory values were mild or moderate. In conclusion, peginterferon alfa-2b maintained (0.5 μg/kg) or surpassed (1.0, 1.5 μg/kg) the clinical efficacy of interferon alfa-2b while preserving its safety profile. The higher rate of virologic response during treatment with 1.5 μg/kg peginterferon alfa-2b in patients infected with genotype 1 and high viral levels warrants further evaluation. (HEPATOLOGY 2001;34:395-403.)

The current international standard of care treatment for chronic hepatitis C, interferon alfa-2b in combination with ribavirin, has proven highly effective, achieving sustained viral eradication in approximately 40% of patients.[1,2] Interferon alfa-2b is administered as a fixed dose 3 times per week, but this schedule is burdensome to patients and may be associated with virologic breakthrough infections.[3,4]

To maintain constant pressure on the virus and reduce the frequency of drug administration, a pegylated formulation of interferon alfa-2b has been developed. The advantages of protein pegylation are well established, having been described for many clinically applicable proteins.[5-8] Covalently attached polyethylene glycol (peg) delays protein clearance and reduces immunogenicity.[8] The resulting longer plasma half-life increases exposure to the drug and therefore may improve efficacy and allow for less frequent dosing. Less frequent dosing, in turn, may improve patient compliance and quality of life.

Peginterferon alfa-2b (PegIntron™), a protein-conjugate containing a single straight-chain peg with a molecular weight of 12,000 daltons and interferon alfa-2b in a 1:1 ratio, maintains its antiviral activity but has an approximately 10-fold longer plasma half-life than interferon alfa-2b in humans (29-34 hours vs. 3.6 hours) (Laughlin, M., unpublished data, 1995). This delayed-clearance formulation allows for once-weekly (QW) dosing, as opposed to the standard three-times-weekly (TIW) dosing of interferon alfa-2b.[9,10] Preliminary clinical data suggest that peginterferon alfa-2b is active against HCV and has a safety and tolerance profile similar to that of interferon alfa-2b.[9] To overcome any potential problems based on distribution of the drug, dosing is based on weight.

The primary objective of this international, randomized, active-controlled, parallel group, double-blind study was the evaluation of the safety and efficacy of peginterferon alfa-2b (0.5 μg/kg, 1.0 μg/kg, or 1.5 μg/kg QW) compared with interferon alfa-2b (3 MIU TIW) in adult patients with clinically compensated chronic hepatitis C who had not been treated previously with interferon. Interferon alfa-2b was chosen as the comparator because, at study initiation, it was the standard of care for chronic hepatitis C, because the combination

Abbreviations: peginterferon alfa-2b, pegylated interferon alfa-2b; TIW, three times weekly; MIU, million international units; QW, once weekly; HCV RNA, hepatitis C viral RNA; HCV, hepatitis C virus; peg, polyethylene glycol; ALT, alanine transaminase; HIV, human immunodeficiency virus; SC, subcutaneously; ULN, upper limit of normal; HAI, Histology Activity Index; WHO, World Health Organization; ETVR, end of treatment virologic response.

From the [1]University of Southern California, Los Angeles, CA; [2]Hotel Dieu and Inserm v271, Lyon, France; [3]Heinrich-Heine-University, Dusseldorf, Germany; [4]Medical College of Virginia, Richmond, VA; [5]William Beaumont Hospital, Royal Oak, MI; [6]University of California-Irvine, Irvine, CA; [7]University of Miami School of Medicine, Miami, FL; [8]Armed Forces Institute of Pathology, Washington, DC; [9]Schering Plough Research Institute, Kenilworth, NJ; [10]Members and affiliations of the Hepatitis Interventional Therapy Group are listed in the Appendix.

Received February 2, 2001; accepted May 21, 2001.

Supported in part by research contracts from Schering Plough Research Institute, Kenilworth, NJ and a Clinical Research Center grant from University of Southern California (M01RR00043).

Address reprint requests to: Karen L. Lindsay, M.D., Department of Medicine, Keck School of Medicine, University of Southern California, Ambulatory Health Center, 1355 San Pablo Street, Room 128, Los Angeles, CA 90033. E-mail: klindsay@hsc.usc.edu; fax: 323-442-5567.

0270-9139/01/3402-0023$35.00/0
doi:10.1053/jhep.2001.26371

of interferon alfa-2b and ribavirin, the current standard of care, had not yet been approved.

PATIENTS AND METHODS

Selection of Patients. Adult patients with chronic hepatitis C and compensated liver disease who had not previously been treated with interferon were eligible to enter this study if: (1) HCV RNA was detectable in the serum, based on a quantitative polymerase chain reaction assay; (2) results from a liver biopsy within 1 year before enrollment were consistent with a diagnosis of chronic hepatitis; and (3) serum alanine transaminase (ALT) values were abnormally elevated at entry and at least once during the 6 months before screening.

Patients with any other cause for liver disease (hepatitis B infection, hemochromatosis, alpha-1 anti-trypsin deficiency, Wilson disease, autoimmune hepatitis, or alcohol-, drug- or obesity-induced liver disease) were excluded, as were patients with HIV infection, hemophilia, hemoglobinopathies, active substance abuse, and any known preexisting medical condition that could interfere with the patient's participation. The following laboratory test values were required for entry into the study: hemoglobin $\geq$ 12 gm/dL for females and $\geq$ 13 gm/dL for males, WBC $\geq$ 4,000/mm^3, neutrophil count $\geq$ 1,800/mm^3, platelets $\geq$ 130,000/mm^3, alpha fetoprotein value within the normal limits, or $\leq$ 50 ng/mL and ultrasound negative for evidence of hepatocellular carcinoma within 3 months before screening. Females were excluded from participation if they were breastfeeding, and a negative serum pregnancy test was required at entry. Both male and female subjects were required to practice adequate contraception during treatment.

Study Design and Organization. The study was reviewed and approved by an institutional review board (USA) or independent ethics committee (Europe and Australia) at each of the 53 study sites, and written informed consent was obtained from each subject. Enrollment began in August 1997, and the study ended in August 1999. Of the 1,224 subjects initially randomized to treatment groups, 1,219 received at least 1 dose of study medication and thus were included in the analysis; 5 were not treated for reasons unrelated to the study. Of the 1,219 treated subjects, 943 (77%) completed the 72-week study; discontinuation rates were comparable across all treatment groups.

Subjects were randomly assigned to 1 of 4 treatment groups. Three groups were treated with peginterferon alfa-2b (0.5, 1.0, or 1.5 μg/kg subcutaneously (SC) once-weekly (QW), and 1 group was treated with interferon alfa-2b (3 MIU SC 3 times weekly [TIW]). Peginterferon alfa-2b doses were chosen based on 2 previous dose-ranging studies.[9,10] The current study was double-blinded for all peginterferon alfa-2b doses, and dosing of peginterferon alfa-2b was determined by the weight of the subject. Interferon alfa-2b (INTRON® A, Schering Corp., Kenilworth, NJ) and peginterferon alfa-2b (PegIntron™, Schering Corp.), distributed as lyophilized powders, were reconstituted with sterile water and administered subcutaneously. Subjects were treated for 48 weeks (weeks 1-48) and then followed for an additional 24 weeks (weeks 49-72).

At study entry, a medical history and hepatitis disease history were obtained for each subject. Each subject underwent a complete physical examination, chest x-ray, and electrocardiogram, and, if not performed within the past 1 year, a baseline liver biopsy. Years since exposure to HCV was estimated based on the date of the first transfusion, injection drug exposure, or needlestick exposure. Laboratory evaluations included hematologic parameters, fasting blood chemistry panel, serum pregnancy test (females), and serum HCV RNA levels. Throughout the study, subjects were monitored for vital signs, weight, adverse events, study medication compliance, hematologic parameters, blood chemistry values, and serum HCV RNA levels. A liver biopsy was done 24 weeks after end of treatment.

Assessment of Efficacy. Efficacy assessments were obtained in all patients who were randomized and received at least 1 dose of study drug (N = 1,219). The primary endpoint was a sustained virologic response 24 weeks after completion of therapy (study week 72). Secondary endpoints included normalization of ALT and improvement in liver histology. Virologic response was defined as the loss of detectable serum HCV RNA ($<$100 copies/mL serum) at any time during the study. Virologic response was measured by a sensitive, quantitative reverse transcriptase-polymerase chain reaction assay with a lower limit of detection of 100 copies/mL (National Genetics Institute, Culver City, CA). The assay was performed by a central laboratory on samples collected at weeks 4, 12, 24, 36, and 48 of treatment and at 4, 12, and 24 weeks after completion of treatment (study weeks 52, 60, and 72). A sustained virologic response (SVR) was defined as undetectable serum levels of HCV RNA 24 weeks after treatment (study week 72). A relapse in virologic response was defined as undetectable serum levels of HCV RNA at the end of treatment and detectable HCV RNA levels at 24 weeks of follow-up (study week 72). All other patterns of HCV RNA results were classified as virologic nonresponse.

The relapse rate was calculated as the percentage of patients with an end-of-treatment response in whom HCV RNA was detectable at week 72.

Biochemical response, assessed in combination with the virologic response, was defined as the normalization of ALT values, expressed in relationship to the upper limit of normal (ULN). ALT levels were measured at treatment weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48 and follow-up weeks 4, 12, and 24 (study weeks 52, 60, and 72).

Histologic response to treatment was measured by scoring paired liver biopsies according to the Knodell Histology Activity Index (HAI), a semiquantitative scoring system composed of four categories.[11] Categories I, II, and III (portal, periportal, and lobular inflammation) were combined to stage the severity of the necroinflammatory process. Category IV of the Knodell HAI system was used to stage the degree of injury relative to the development of fibrosis or cirrhosis. All liver biopsies were scored by a single pathologist (Z.G.) blinded to patient number, treatment group, and biopsy timing relative to treatment and response.

Changes in the Knodell HAI score were calculated by subtracting the pretreatment score from the posttreatment score; negative scores indicated improvement relative to pretreatment. Subjects with missing pretreatment or posttreatment biopsy analyses were not included in calculations of mean change by treatment group. An "improved" inflammatory score was defined as a decrease of $\geq$2 units. An "improved" fibrosis score was defined as a decrease of $\geq$1 unit relative to pretreatment.

Safety Evaluation. Safety was monitored by clinical and laboratory evaluations. Data collected on adverse events included the severity, frequency, and length of each event, as well as the impact on study treatment and outcome. One certified, central laboratory performed all hematology, blood chemistry, and urinalysis evaluations. Treatment-emergent adverse events were graded as mild, moderate, severe, or life-threatening according to the modified World Health Organization (WHO) guidelines.[12] For any life-threatening adverse event, study medications were discontinued permanently, and the subject was monitored during the 24-week follow-up or every 2 weeks thereafter until the event resolved or the patient's condition stabilized. All grade 3 adverse events except flu-like symptoms were controlled by dose reduction; dose was increased if the adverse event improved to grade 1 or no longer occurred.

Statistical Analyses. Efficacy measurements included all patients who were randomized and received at least 1 dose of study drug (N = 1,219). All statistical tests were two-sided with a .05 level of significance. A peginterferon alfa-2b dose was considered to be efficacious if its sustained virologic response rate was significantly (at a .025 level of significance; χ^2 test) greater than the response rate to interferon alfa-2b. The association of sustained response rates with baseline characteristics and with HCV RNA levels was evaluated using logistic regression analysis.

RESULTS

Patient Characteristics. Baseline demographics and disease characteristics were comparable across all treatment groups,

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	Peginterferon Alfa-2b 0.5 μg/kg QW (n = 315)	Peginterferon Alfa-2b 1.0 μg/kg QW (n = 297)	Peginterferon Alfa-2b 1.5 μg/kg QW (n = 304)	Interferon Alfa-2b 3 MIU TIW (n = 303)
Mean age in years (range)	43.1 (23-72)	43.7 (19-73)	42.9 (23-71)	42.6 (18-72)
Gender: female/male	130 (41%)/185 (59%)	109 (37%)/188 (63%)	114 (38%)/190 (63%)	96 (32%)/207 (68%)
Race: Caucasian	283 (90%)	270 (91%)	286 (94%)	270 (89%)
Mean body weight in kg (range)	80.8 (41-149)	79.2 (44-147)	80.2 (44-142)	81.3 (45-152)
HCV genotype*				
1	212 (67%)	199 (67%)	223 (73%)	217 (72%)
2	35 (11%)	30 (10%)	32 (11%)	28 (9%)
3	53 (17%)	53 (18%)	41 (14%)	53 (18%)
Other	15 (5%)	15 (5%)	8 (2%)	5 (1%)
HCV RNA (copies/mL serum)				
Mean (geometric)	3,405,221	3,276,071	3,041,146	3,682,720
>2 million	231 (73%)	225 (76%)	220 (72%)	227 (75%)
ALT (×ULN)†				
Median (range)	2.3 (0.6-15.9)	2.2 (1.0-11.4)	2.3 (0.5-9.7)	2.3 (0.7-10.9)
AST (×ULN)				
Median (range)	1.6 (0.5-12.1)	1.5 (0.6-8.9)	1.6 (0.6-7.6)	1.6 (0.5-8.4)
Source of HCV exposure				
Transfusion	70 (22%)	77 (26%)	52 (17%)	62 (20%)
Parenteral	152 (48%)	125 (42%)	162 (53%)	149 (49%)
Sporadic/other	93 (30%)	95 (32%)	90 (30%)	92 (30%)
Mean years since exposure‡	18.5	20.4	19.2	18.6
Mean Knodell score				
I + II + III (inflammation)	6.8	6.9	6.7	7.1
IV (fibrosis)	1.4	1.4	1.3	1.4
Knodell IV score (fibrosis)				
3 (bridging fibrosis)	51 (16%)	40 (14%)	35 (12%)	38 (13%)
4 (cirrhosis)	9 (3%)	9 (3%)	12 (4%)	13 (4%)

*Subtypes were classified under their respective genotype. Any mixed genotype that included type 1 was classified as 1, except for any mixed genotype that included type 4, which was classified as type 4 (listed as "other" in this table).

†Five subjects had normal ALT levels at baseline; all had at least one abnormal ALT level before baseline.

‡Includes subjects for whom the number of years since exposure could be estimated.

as shown in Table 1 and confirmed by the Kruskal-Wallis test. All 1,219 subjects had clinically compensated but active liver disease based on evaluations of liver biopsies and ALT levels. The mean age of subjects was 43 years and mean weight was 80.4 kg. Consistent with previous study populations and with patient populations in Europe and North America,[2,13-15] the majority of subjects had baseline serum HCV RNA levels of >2 million copies/mL serum (74%) and were infected with the HCV genotype 1 (70%). However, a higher proportion of subjects with the HCV genotype 1 were randomized to the 1.5-μg/kg peginterferon alfa-2b dose group (73%) than to the 1.0-μg/kg and 0.5-μg/kg peginterferon alfa-2b dose groups (67% for both groups, $P = .09$).

Virologic Response. As summarized in Table 2 and Fig. 1, the end-of-treatment virologic response (ETVR) for peginterferon alfa-2b was dose related. Increase in dose of peginter-

TABLE 2. Virologic and Combined Virologic/Biochemical Responses to Treatment

	Number (%) of Subjects*				P Value†		
	A Peginterferon Alfa-2b 0.5 μg/kg QW (N = 315)	B Peginterferon Alfa-2b 1.0 μg/kg QW (N = 297)	C Peginterferon Alfa-2b 1.5 μg/kg QW (N = 304)	D Interferon Alfa-2b 3 MIU TIW (N = 303)	C vs D	B vs D	A vs D
Virologic Response‡							
End of treatment (week 48)	105 (33)	121 (41)	149 (49)	73 (24)	<0.001	<0.001	0.011
End of follow-up§ (week 72)	57 (18)	73 (25)	71 (23)	37 (12)	<0.001	<0.001	0.042
Combined Virologic Response and Biochemical Response‖							
End of treatment (week 48)	79 (25)	92 (31)	100 (33)	61 (20)	<0.001	0.002	0.142
End of follow-up¶ (week 72)	52 (17)	70 (24)	69 (23)	37 (12)	<0.001	<0.001	0.128

*All subjects with positive HCV RNA or missing data at 24 weeks of treatment were counted as nonresponders.

†χ^2 test.

‡Virologic response was defined as <100 copies of HCV RNA/mL serum.

§95% Confidence intervals for the difference in response rate: C vs. D (−0.172, −0.051), B vs. D (−0.185, −0.062), A vs. D (−0.115, −0.002).

‖Biochemical response was defined as normalization of ALT values.

¶97.5% Confidence intervals for the difference in response rate: C vs. D (−0.174, 0.036), B vs. D (−0.183, −0.044), A vs. D (−0.106, 0.020).

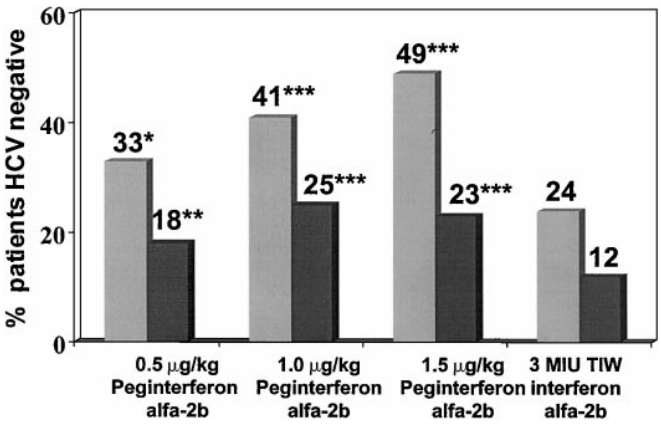

FIG. 1. Virologic response at end of treatment and end of follow up. Percentage of subjects with virologic responses (loss of detectable serum HCV RNA) at the end of treatment (▒) and at the end of follow up (■). *$P = .01$ for the comparison with interferon alfa-2b; **$P = .04$ for the comparison with interferon alfa-2b; ***$P \leq .001$ for the comparison with interferon alfa-2b.

feron alfa-2b (0.5, 1.0, 1.5 μg/kg) was associated with an increase in the virologic response rate (33%, 41%, 49%, respectively). All 3 peginterferon alfa-2b dose groups had significantly higher proportions ($P < .01$) of patients with ETVR compared with the interferon alfa-2b group (24%). The virologic response rates were approximately twofold higher with 1.5 μg/kg peginterferon alfa-2b than with interferon alfa-2b at treatment week 48 (49% vs. 24%; $P < .001$). The higher ETVR rate in patients treated with 1.5 μg/kg peginterferon alfa-2b compared with those treated with 1.0 μg/kg peginterferon alfa-2b (49% compared with 41%, $P = .049$) is largely the result of a significantly higher response rate in HCV genotype 1 infected patients (87/223, 39% compared with 50/199, 25%, respectively, $P = .002$).

As with ETVR, the 3 doses of peginterferon alfa-2b had significantly higher SVR than interferon alfa-2b. The rate of SVR was approximately twofold higher with 1.0 μg/kg peginterferon alfa-2b (25% vs. 12%; $P < .001$) and 1.5 μg/kg peginterferon alfa-2b (23% vs. 12%; $P < .001$), as compared with interferon alfa-2b. However, unlike the virologic response at the end of treatment, there was not a dose response between the 1.0 μg/kg and 1.5-μg/kg peginterferon alfa-2b dose groups for SVR, 25% and 23%, respectively. This was related to a significantly higher relapse rate in the HCV genotype 1 patients treated with 1.5 μg/kg compared with those treated with 1.0 μg/kg peginterferon alfa-2b, 57/87 (66%) and 23/50 (46%), respectively ($P = .025$), whereas the relapse rate among patients infected with genotypes 2 or 3 was similar, 20/56 (36%) and 24/63 (38%), respectively.

Combined Virologic and Biochemical Response. When the virologic response was considered together with the biochemical response to treatment (combined response), the proportion of subjects with undetectable serum HCV RNA and normal ALT values was significantly higher for the 1.0-μg/kg (31%; $P = .002$) and 1.5-μg/kg (33%; $P < .001$) peginterferon alfa-2b dose groups than for the interferon alfa-2b group (20%) at the end of treatment (Table 2). The sustained combined response rate at week 72 was twofold higher in subjects treated with 1.0 μg/kg (24%; $P < .001$) or 1.5 μg/kg (23%; $P < .001$) of peginterferon alfa-2b than in subjects treated with interferon alfa-2b (12%). Although the combined virologic and biochemical response rate to the 0.5 μg/kg peginterferon alfa-2b dose was numerically higher than the response rate to interferon alfa-2b at 48 and 72 weeks, these differences were not statistically significant.

Nearly all subjects who exhibited a sustained loss of HCV RNA had normal ALT values at week 72 (228/238). However, sustained normal ALT values were a poor predictor of sustained HCV RNA loss. Among subjects with normal ALT values after 24 weeks of follow-up, sustained virologic responses occurred in 67% of those treated with interferon alfa-2b, 68% of those given 0.5 μg/kg peginterferon alfa-2b, 80% of those who received 1.0 μg/kg peginterferon alfa-2b, and 82% of those treated with 1.5 μg/kg peginterferon alfa-2b.

Histologic Response. Pretreatment and posttreatment liver biopsies were analyzed in 61% (744/1219) of the subjects. The percentages of subjects with histologic improvement and the mean degrees of improvement are shown in Table 3. Overall, sustained improvement in hepatic inflammation (Knodell HAI categories I, II, III) was observed in all treatment groups. Mean changes in Knodell scores (−1.2 to −1.8) and the proportion of subjects with improved scores (47-50%) were similar across all 3 peginterferon alfa-2b dosing groups and the interferon alfa-2b group.

When treatment groups were stratified according to virologic response (sustained response, relapse after an end-of-treatment response, and no response), improvement in hepatic inflammation scores, defined as at least a two-point decrease in the inflammatory score, was highly associated with sustained virologic response. The proportion of subjects in all treatment groups who showed an improvement in hepatic inflammation was approximately twofold higher among subjects who had a sustained response (77%-90%) than among those who relapsed after an end-of-treatment response (33%-46%) or did not respond at all (33%-41%). In addition, larger decreases in the group mean change from baseline scores were reported among subjects with a sustained response (−4.0 to −5.4) than among those with a relapse following response (−0.2 to −0.9) or no response (−0.3 to −0.7).

Hepatic fibrosis scores improved in 13% to 20% of subjects (Table 3). Similar to the observations with respect to hepatic inflammation scores, the proportion of subjects who showed improvement in hepatic fibrosis score (Knodell HAI category IV) was higher among subjects who had a sustained response (21%-37%) than among those who either relapsed or did not respond (4%-17%).

Factors Associated With Virologic Response. Logistic regression analysis of baseline disease characteristics and demographic variables identified only 2 covariates associated ($P < .001$) with sustained virologic response: an HCV genotype other than 1 and baseline HCV RNA viral levels of ≤2 million copies/mL serum.

Subgroup analysis of end-of-treatment and sustained virologic response by HCV genotype and baseline virus levels (Table 4) revealed that subjects with HCV genotype 2 or 3 and ≤2 million HCV RNA copies/mL serum had the highest sustained response rates in all treatment groups (36%-68%). Among them, the 1.5-μg/kg peginterferon alfa-2b dose group attained the highest sustained response rate (68%), nearly twofold higher than that seen in the interferon alfa-2b group (36%). The end-of-treatment response rate in patients with

TABLE 3. Rates of Histologic Response

Variable	Peginterferon Alfa-2b 0.5 μg/kg QW	Peginterferon Alfa-2b 1.0 μg/kg QW	Peginterferon Alfa-2b 1.5 μg/kg QW	Interferon Alfa-2b 3 MIU TIW
Hepatic inflammation (Knodell scores I + II + II)				
All subjects*	(N = 198)	(N = 178)	(N = 177)	(N = 191)
Percentage with improvement†	49	50	48	47
Mean change	−1.5	−1.8	−1.5	−1.2
Sustained responders	(N = 41)	(N = 48)	(N = 52)	(N = 29)
Percentage with improvement	83	88	77	90
Mean change	−5.0	−5.4	−4.0	−4.7
Relapsers	(N = 35)	(N = 37)	(N = 48)	(N = 24)
Percentage with improvement	46	43	33	33
Mean change	−0.6	−0.9	−0.2	−0.2
Nonresponders	(N = 122)	(N = 93)	(N = 77)	(N = 138)
Percentage with improvement	39	33	38	41
Mean change	−0.6	−0.3	−0.7	−0.7
Hepatic fibrosis (Knodell score IV)				
All subjects	(N = 198)	(N = 178)	(N = 177)	(N = 191)
Percentage with improvement‡	20	19	15	13
Mean change	−0.1	0	0.1	0.1
Sustained responders	(N = 41)	(N = 48)	(N = 52)	(N = 29)
Percentage with improvement	37	31	21	21
Mean change	−0.4	−0.4	−0.1	−0.2
Relapsers	(N = 35)	(N = 37)	(N = 48)	(N = 24)
Percentage with improvement	17	16	6	4
Mean change	0	0	0.2	0.2
Nonresponders	(N = 122)	(N = 93)	(N = 77)	(N = 138)
Percentage with improvement	15	14	16	12
Mean change	0	0.1	0.1	0.2

*All subjects with paired biopsies.

†"Improvement" was defined as a decrease of ≥2 units in posttreatment Knodell HAI score for inflammation (I + II + III), as compared with pretreatment score.

‡"Improvement" was defined as a decrease of ≥1 unit in posttreatment Knodell HAI score for fibrosis (IV), as compared with pretreatment score.

genotype 2/3 infection was similar, however, regardless of the baseline level of HCV RNA.

Among genotype 2/3 infected patients, end-of-treatment virological response to treatment with 1.0 or 1.5 μg/kg peginterferon alfa-2b was nearly identical, 76% and 77%, in all 4 subgroups regardless of viral level. Virologic relapse (Table 5) occurred less frequently in patients with lower baseline levels of HCV RNA, however, in that 19% and 12% of patients with lower levels of HCV RNA relapse after treatment was discontinued, but 45% and 46% of those with higher levels of HCV RNA developed virologic relapse.

The most common viral profile, HCV genotype 1 and >2 million RNA copies/mL serum was present in 652/1219 (53%) subjects. In this subgroup, end-treatment virologic response rates occurred in 20%, 20%, and 35% of subjects in the peginterferon alfa-2b 0.5-, 1.0-, and 1.5-μg/kg treatment groups. End-of-treatment response in the group treated with peginterferon 1.5-μg/kg was nearly fourfold higher than that in the group treated with interferon alfa-2b (35% compared with 9%). On discontinuation of treatment after 48 weeks, 63% to 80% of patients developed virologic relapse, however, resulting in a sustained virological response rates of 5% to 8% in the peginterferon-treated groups and 2% in the group treated with interferon alfa-2b. In contrast to genotype 2/3 infected patients, end-of-treatment response among genotype-1 infected patients treated with peginterferon 1.0- or 1.5-μg/kg varied considerably as a function of baseline HCV RNA level, in that 43% and 50% of patients with lower levels of HCV RNA experienced an end-of-treatment response, whereas only 20% and 35% of patients with higher levels of HCV RNA responded. Virologic relapse after discontinuation of treatment also varied by baseline viral level, in that 17% and 36% of patients with lower HCV RNA levels relapsed after treatment was discontinued, whereas 63% and 80% of those with higher HCV RNA levels developed virologic relapse.

Because previous studies have shown that an early response to interferon treatment is associated with sustained virologic response in patients with chronic hepatitis C,[2,16-19] the time at which HCV RNA was first negative (<100 copies/mL serum) was analyzed in relationship to subsequent development of sustained virologic response. In each treatment group, the likelihood of an SVR occurring was highest in subjects whose first negative HCV RNA occurred at treatment week 4 (77%-86%), compared with those in whom HCV RNA was first negative at treatment week 12 (32%-52%), and those whose HCV RNA was first negative at treatment week 24 (13%-20%). For the interferon alfa-2b group as well as the peginterferon treatment groups, nearly all (93% to 100%) patients who eventually became sustained responders had developed undetectable serum HCV RNA by treatment week 24. These data confirm previous observations that early virologic response during treatment is associated with a higher likelihood of sustained response. The sensitivity of a negative serum HCV RNA result at treatment week 4 was low, however (49% in the

TABLE 4. Virologic Response by Baseline HCV RNA Level (Million Copies/mL) and Genotype

	Number (%) of Subjects			
	Peginterferon Alfa-2b 0.5 μg/kg QW	Peginterferon Alfa-2b 1.0 μg/kg QW	Peginterferon Alfa-2b 1.5 μg/kg QW	Interferon Alfa-2b 3 MIU TIW
End of treatment (week 48)				
Genotype 1 (All)	52/211 (25)	50/199 (25)*	87/223 (39)*	32/217 (15)
≤2 million	20/52 (38)	18/42 (43)	28/56 (50)	17/48 (35)
>2 million	32/159 (20)	32/157 (20)†	59/167 (35)†	15/169 (9)
Genotypes 2/3 (All)	47/88 (53)	63/83 (76)	56/73 (77)	41/81 (51)
≤2 million	14/24 (58)	16/21 (76)	17/22 (77)	12/25 (48)
>2 million	33/64 (52)	47/62 (76)	39/51 (76)	29/56 (52)
Genotypes 4/5/6 (All)	3/10 (30%)	6/13 (46)	4/5 (80)	0/4
≤2 million	3/6 (50)	4/8 (50)	3/4 (75)	0/2
>2 million	0/4	2/5 (40)	1/1 (100)	0/2
Week 72				
Genotype 1 (All)	22/211 (10)	28/199 (14)	31/223 (14)	14/217 (6)
≤2 million copies	14/52 (27)	16/42 (38)	19/56 (34)	10/48 (21)
>2 million copies	8/159 (5)	12/157 (8)	12/167 (7)	4/169 (2)
Genotypes 2/3 (All)	31/88 (35)	39/83 (47)	36/73 (49)	23/81 (28)
≤2 million copies	14/24 (58)	13/21 (62)	15/22 (68)	9/25 (36)
>2 million copies	17/64 (27)	26/62 (42)	21/51 (41)	14/56 (25)
Genotypes 4/5/6 (All)	2/10 (20)	4/13 (31)	3/5 (60)	0/4
≤2 million copies	2/6 (33)	4/8 (50)	3/4 (75)	0/2
>2 million copies	0/4	0/5	0/1	0/2

*$P = .002$ for the comparison with 1.0 μg/kg QW and 1.5 μg/kg QW.
†$P = .003$ for the comparison with 1.0 μg/kg QW and 1.5 μg/kg QW.

interferon alfa-2b group and 46% to 65% in the peginterferon alfa-2b groups). Negative predictive values (the likelihood that a sustained response would occur if HCV RNA was not detected) for treatment week 4 were calculated for subjects treated with 1.0 μg/kg and those treated with 1.5 μg/kg, and were 85% and 77% respectively. The positive predictive value (the likelihood that a sustained response would not occur if HCV RNA was detected) for HCV RNA at treatment week 4 in these 2 treatment groups was 84% and 90%.

Safety Evaluation. With respect to safety and tolerability, peginterferon alfa-2b (all doses) was comparable to interferon alfa-2b. No new or unexpected adverse events specific to peginterferon alfa-2b were reported. The incidence and severity of adverse events were similar between peginterferon alfa-2b 0.5 μg/kg and 3 MIU interferon alfa-2b, whereas profiles for the higher doses of peginterferon alfa-2b (1.0 μg/kg and 1.5 μg/kg) were similar to each other (Table 6) and associated with a somewhat higher frequency of fever and chills. As has previously been seen with interferon alfa-2b, the most common adverse events with peginterferon alfa-2b were flu-like symptoms including headache, myalgia, fatigue, rigors, and fever. Compared with interferon alfa-2b, the incidence of injection site reactions was increased approximately twofold in patients receiving peginterferon alfa-2b. In all cases, the characteristics of the reaction were similar for both interferon alfa-2b and peginterferon alfa-2b: the event was generally mild, not treatment-limiting, and characterized by localized erythema.

As previously reported for interferon alfa-2b, leukocyte, neutrophil, and platelet counts decreased from baseline during the first few weeks of treatment in all groups, stabilized during the remainder of treatment, and reverted to baseline levels upon cessation of treatment (data not shown). For all 3 hematological parameters, the profile over time for peginterferon alfa-2b was similar to that of interferon alfa-2b. Dose reduction for neutropenia occurred infrequently with both peginterferon alfa-2b and interferon alfa-2b, but was more common in the 1.5 μg/kg treatment group (5%) compared with the other treatment groups (2% to 3%). Dose reduction for thrombocytopenia was more common in the peginterferon treatment groups (2% to 3%) compared with the interferon alfa-2b group (0.3%).

As shown in Table 6, the incidence of dose reduction increased with higher doses of peginterferon alfa-2b, and was higher than for interferon alfa-2b. However, discontinuation rates were comparable in all 3 peginterferon alfa-2b groups (9%-11%) and were slightly higher than in the interferon alfa-2b group (6%).

TABLE 5. Relapse Rate in Patients Treated With Peginterferon Alfa-2b by Baseline HCV RNA Level (Million Copies/mL) and Genotype

	Number (%) of Subjects	
	Peginterferon Alfa-2b 1.0 μg/kg QW	Peginterferon Alfa-2b 1.5 μg/kg QW
Relapse rate		
Genotype 1 (All)	23/50 (46)*	57/87 (66)*
≤2 million	3/18† (17)	10/28‡ (36)
>2 million	20/32 (63)	47/59 (80)
Genotypes 2/3 (All)	24/63 (38)	20/56 (36)
≤2 million	3/16 (19)	2/17 (12)
>2 million	21/47 (45)	18/39 (46)

*$P = .026$ for the comparison with 1.0 μg/kg QW and 1.5 μg/kg QW.
†Of the 18 patients who had an end-of-treatment response, 15 had undetectable HCV RNA at Week 72; an additional patient who had detectable HCV RNA at Week 48 had undetectable HCV RNA at Week 72.
‡Of the 28 patients who had an end-of-treatment response, 18 had undetectable HCV RNA at Week 72; an additional patient who had detectable HCV RNA at Week 48 had undetectable HCV RNA at Week 72.

TABLE 6. Rates of Discontinuation of Treatment, Dose Reduction, and Incidence of Adverse Events During Treatment

	Percentage of Patients			
	Peginterferon Alfa-2b 0.5 μg/kg QW (N = 315)	Peginterferon Alfa-2b 1.0 μg/kg QW (N = 297)	Peginterferon Alfa-2b 1.5 μg/kg QW (N = 304)	Interferon Alfa-2b 3 MIU TIW (N = 303)
Discontinuation	9	11	9	6
Dose Reduction	9	14	19	6
Influenza-Like Symptoms				
Headache	61	64	64	58
Fatigue	43	51	45	50
Chills	34	40	44	33
Fever	31	45	44	30
Myalgia	48	54	61	53
Musculoskeletal pain	19	28	20	22
Gastrointestinal Symptoms				
Nausea	21	26	25	20
Anorexia	10	20	25	17
Psychiatric Symptoms				
Irritability	19	18	17	24
Insomnia	17	23	20	23
Dermatologic Symptoms				
Alopecia	20	22	34	22
Injection site inflammation	44	42	40	16

DISCUSSION

Peginterferon alfa-2b, a pegylated formulation of interferon alfa-2b, was developed to decrease the rapid clearance of interferon alfa-2b. Hepatitis C viral infection is an ideal setting in which to use peginterferon alfa-2b because maintaining constant antiviral pressure on hepatitis C virus is crucial during therapy because of the short virion half-life (2.7 hours) and estimated production and clearance rate of 10^{12} virions/day.[20] Nonpegylated interferon alfa-2b is undetectable after approximately 24 hours of administration (Laughlin, M., unpublished data, 1995) thus permitting viral breakthrough and the development of resistance. Because the plasma half-life of peginterferon alfa-2b in humans is approximately 10-fold longer than that of interferon alfa-2b (Laughlin, M., unpublished data, 1995), the pegylated form intensifies interferon therapy by maintaining effective plasma drug concentrations over time. In addition, the weekly dosing schedule with peginterferon alfa-2b may positively affect patient compliance and quality of life.

In this international, randomized, active-controlled, parallel-group, double-blind, dose-finding study, we have shown that peginterferon alfa-2b is superior to and as safe as interferon alfa-2b for the initial treatment of adult patients with compensated chronic hepatitis C.

This study had the following major findings: (1) All peginterferon alfa-2b doses (0.5, 1.0, and 1.5 μg/kg QW) significantly improved end-of-treatment virologic responses and sustained virologic responses compared with interferon alfa-2b 3 MIU TIW. Whereas the end-of-treatment virologic response was dose-related, the proportion of subjects with sustained virologic responses was similar for the 1.0- and 1.5-μg/kg peginterferon alfa-2b dose groups. (2) Both the 1.0-μg/kg and 1.5-μg/kg doses of peginterferon alfa-2b were superior to interferon alfa-2b with regard to combined virologic and biochemical response after treatment and after follow-up. (3) Overall, the higher efficacy of the 1.0-μg/kg and 1.5-μg/kg dose of peginterferon alfa-2b, compared with 0.5-μg/kg peginterferon alfa-2b or interferon alfa-2b, was maintained across all treatment subgroups, including those stratified by HCV genotype or baseline virus level. (4) The proportion of subjects who experienced an improvement in hepatic inflammation and hepatic fibrosis was higher among subjects with sustained responses in each treatment group, as compared with subjects who experienced a relapse or showed no response. (5) Finally, all peginterferon alfa-2b doses were safe and well tolerated, with a safety profile comparable with that of interferon alfa-2b and no new or unexpected adverse events attributable to peginterferon alfa-2b were reported.

This database further substantiates the profound influence of hepatitis C viral genotype and HCV RNA level on response to alpha interferon, and emphasizes the importance of further research to identify the mechanisms of viral resistance.[21-23] Despite optimization of drug delivery, HCV genotype and viral load had a major impact on the sustained response rate. Patients receiving 1.0 or 1.5 μg/kg peginterferon alfa-2b had sustained virologic response rates ranging from 62% to 68% in those infected with genotype 2/3 and ≤2 million copies HCV RNA/mL serum compared with 7% to 8% in those infected with genotype 1 and >2 million copies HCV RNA/mL serum. These data underscore the importance of patient selection in clinical trials designed to evaluate interferon-based treatment regimens, not only because of the effect on response endpoints, but also because of the applicability of the data to the larger patient population. Our cohort of subjects is highly representative of the patient population in Europe and North America,[2,13-15] because the majority of subjects had high baseline HCV RNA levels (74% >2 million copies/mL serum) and infection with HCV genotype 1 (70%).

The influence of viral genotype was a significant factor in the finding that the virologic response rate at the end of treatment was greater in the 1.5-μg/kg peginterferon alfa-2b dose group than in the 1.0-μg/kg dose group (49% and 41%), but the proportion of subjects with sustained virologic responses was similar for the 2 groups (23% and 25%). The higher dose of peginterferon alfa-2b induced a response in a significantly greater proportion of patients infected with HCV genotype 1

but this response was not maintained following the end of treatment.

Comparative response between pegylated interferon and unpegylated interferon and safety data from our study are similar to those recently reported from a multinational study[24] in which 531 patients with chronic hepatitis C were randomized to receive peginterferon alfa-2a, a 40-kd branched chain polyethylene glycol moiety, or interferon alfa-2a. The sustained virologic response rate in the group treated with peginterferon alfa-2a was approximately double that in the group treated with interferon alfa-2a (39% vs. 19%, $P = .001$). Sixty-two percent of patients were infected with HCV genotype 1, and subanalyses of virologic response by genotype and viral level are not reported. Flat, rather than weight-based dosing was used, the average weight of the subjects was 74.7 and 76.5 kg, and a smaller body-surface area was determined to be one of the factors which independently and significantly increased the odds of a sustained virological response. Finally, baseline liver biopsies demonstrated bridging fibrosis or cirrhosis in 13% of patients in this study, and an absence of cirrhosis or bridging fibrosis was also determined to be one of the factors that independently and significantly increased the odds of a sustained virological response. Because the percentage of patients with important baseline variables which negatively influence response (genotype 1 infection, presence of bridging fibrosis or cirrhosis on liver biopsy) are higher in our study, results of the 2 studies cannot be compared. Appropriate comparison of efficacy between these 2 peginterferon alfas will require a randomized controlled trial. Of importance, however, is that the safety profile of peginterferon alfa-2a as measured by rate of discontinuation (7%) and dose modification (19%) is very similar to that seen in our study with peginterferon alfa-2b. In another recently published study, peginterferon alfa-2a therapy was compared with interferon alfa-2a therapy in HCV patients with cirrhosis or bridging fibrosis.[25] As could be anticipated in this population with more advanced liver disease and cytopenia, rates of discontinuation and dose modification were somewhat higher.

Results from our study are very useful in defining strategies for more effective antiviral therapy against hepatitis C virus. End-treatment response and sustained response rates have been conventionally used to describe results in clinical trials since they were proposed at the NIH Consensus Development Conference on Hepatitis C in 1997.[26] Since that time, it has been shown that sustained virological response (SVR) is associated with the greatest long-term clinical benefit.[27-29] Sustained virological response is a function of both the end-treatment response rate and the degree of posttreatment relapse, each of which can be differentially affected by a treatment regimen. Based on antiviral pharmacodynamic studies, it appears that clearance of hepatitis C virus from serum and intracellular compartments is important during therapy.[3,20] We have shown that the rate of virologic relapse varies considerably among patient subpopulations treated with the same peginterferon monotherapy regimens, and this may reflect a differential clearance rate from intracellular compartments. Relapse rates are lower and sustained virological response rates higher in patients treated with the combination of ribavirin and interferon alfa-2b for 48 weeks compared with those treated with interferon alfa-2b alone.[1,2] This has been confirmed in a recent study in which ribavirin was combined with peginterferon alfa-2b treatment, and the SVR rate was 54% in patients who received peginterferon alfa-2b 1.5 μg/kg once weekly and ribavirin 800 mg daily, compared with 47% in patients treated with alfa-2b 3 MIU TIW and ribavirin 1,000-1,200 mg daily.[30]

Based on the higher SVR rates shown when ribavirin is combined with interferon alfa-2b or peginterferon alfa-2b, it is anticipated that peginterferon alfa-2b monotherapy will potentially be most beneficial in the subgroup of patients who cannot tolerate the hemolytic effects of ribavirin. In such patient populations, longer courses of peginterferon alfa-2b should be evaluated in patients infected with genotype 1 and in those with genotype 2/3 and high levels of HCV RNA in light of the data from our study, showing higher relapse rates in these subgroups.

Finally, we have shown that peginterferon alfa-2b is associated with improvement in hepatic histology, even in patients who do not develop a sustained virological response. In light of its safety profile and ease of administration, peginterferon alfa-2b is therefore an optimal agent for clinical trials designed to evaluate the potential benefit of long-term interferon therapy on histologic endpoints in HCV patients who have not virologically responded to interferon-based therapies.

Acknowledgment: Karen L. Lindsay and Christian Trepo contributed equally to this project.

APPPENDIX

Other Investigators From the Hepatitis Interventional Therapy Group: B. Bacon, St. Louis University, St. Louis, MO; L. Balart, Tenet Physician Services, New Orleans, LA; K.G. Benner, Oregon Health Sciences University, Portland, OR; R. Barcena, Hospital Ramon y Cajal, Madrid, Spain; M. Bourliere, Hôpital St. Joseph, Marseille, France; H. Brunner, Lainz der Stadt Wien, Vienna, Austria; W. Carey, Cleveland Clinic Foundation, Cleveland, OH; V. Carreno, Fundacion Jimenez Diaz, Madrid, Spain; R.L. Carithers, Jr., University of Washington, Seattle, WA; W. Caselmann, Rheinisch Friedrich-Wilhems-Universitat, Bonn, Germany; W.G.E. Cooksley, Royal Brisbane Hospital, Herston, Australia; G.L. Davis, University of Florida, Gainesville, FL; J.L. Deinstag, Massachusetts General Hospital, Boston, MA; J. Donovan, University of Nebraska, Omaha, NE; G.T. Everson, University of Colorado, Denver, CO; R. H. Fried, Kantonsspital Basel, Basel, Switzerland; D. R. Ganger, Rush North Shore Medical Center, Skokie, IL; R. Gish, California Pacific Medical Center, San Francisco, CA; N. Gitlin, Emory University, Atlanta, GA; S. Hadziyannis, Evgenidion Hospital, Athens, Greece; I. Jacobson, Cornell Medical College, New York, NY; R. S. Koff, MetroWest Medical Center, Framingham, MA; D. R. LaBrecque, University of Iowa, Iowa City, IA; W.M. Lee, UT Southwestern Medical Center at Dallas, Dallas, TX; C. Liddle, Westmead Hospital, Westmead, Australia; P. Marcellin, Hopital Beaujon, Clichy, France; P. Martin, University of California, Los Angeles, Los Angeles, CA; T. J. McGarrity, Penn State Hershey Medical Center, Hershey, PA; J.G. McHutchison, Scripps Clinic, La Jolla, CA; T. Morgan, VA Medical Center, Long Beach, CA; R.P. Perrillo, Ochshner Clinic, New Orleans, LA; T. Poynard, Hopital Pitie-Salpetriere, Paris, France; J. Rakela, Presbyterian University Hospital, Pittsburgh, PA; R. Reindollar, Charlotte Clinic for GI and Liver Disease, Charlotte, NC; E. Renner, University Hospital, Zurich, Switzerland; L. Rodrigo, Hospital Central de Asturias, Oviedo, Spain; R.A. Rubin, Atlanta Gastroenterology Associates, Atlanta, GA; V. K. Rustgi, Institute of Research and Education INOVA Fairfax Hospital, Falls Church, VA; S. Ryder, Queens Medical Centre University Hospital, Nottingham, UK; C. Smith, Minnesota Clinical Research Cen-

ter, St. Paul, MN; H.M. Steffen, Universitaetskliniken Koeln, Koeln, Germany; C. Tamburro, (deceased) University of Louisville School of Medicine, Louisville, KY; N. Tassopoulos, Western Attica General Hospital, Athens, Greece; T. Wright, Veterans Administration Medical Center, San Francisco, CA; R. Zachoval, Ludwig-Maximilians-Universitaet, Muenchen, Germany; J. P. Zarski, Hôpital Nord Michallon La Tronche, Grenoble, France.

REFERENCES

1. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk G, Ideo G, Bain V, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352: 1426-1432.
2. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339:1485-1492.
3. Zeuzem S, Schmidt JM, Lee J-H, Ruster B, Roth WK. Effect of interferon alfa on the dynamics of hepatitis C virus turnover *in vivo*. HEPATOLOGY 1996;23:366-371.
4. Lam NP, Neumann AU, Gretch DR, Wiley TE, Perelson AS, Layden TJ. Dose-dependent acute clearance of hepatitis C genotype 1 virus with interferon alfa. HEPATOLOGY 1997;26:226-231.
5. Katre NV. Immunogenicity of recombinant IL-2 modified by covalent attachment of polyethylene glycol. J Immunol 1990;144:209-213.
6. Inada Y, Furukawa M, Sasaki H, Kodera Y, Hiroto M, Nishimura H, Matsushima A. Biomedical and biotechnological applications of PEG- and PM-modified proteins. Trends Biotechnol 1995;13:86-91.
7. Wang Q-C, Pai LH, Debinski W, FitzGerald DJ, Pastan I. Polyethylene glycol-modified chimeric toxin composed of transforming growth factor alpha and *Pseudomonas* exotoxin. Cancer Res 1993;53:4588-4594.
8. He X-H, Shaw P-C, Tam S-C. Reducing the immunogenicity and improving the in vivo activity of trichosanthin by site-directed pegylation. Life Sci 1999;65:355-368.
9. Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, Jacobs S, et al. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. HEPATOLOGY 2000;32:647-653.
10. Lurie Y, Dusheiko G, Rouzier-Panis R, Glue P. Assessment of optimal dosing frequency of pegylated interferon alfa-2b (PegIntron®) in chronic hepatitis C [Abstract]. HEPATOLOGY 2000;32:444A.
11. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. HEPATOLOGY 1981;1:431-435.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214.
13. Bukh J, Miller RH, Purcell RH. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. Semin Liver Dis 1995;15:41-63.
14. Lau JYN, Davis GL, Prescott LE, Maertens G, Lindsay KL, Qian KP, Mizokami M, et al. Distribution of hepatitis C virus genotypes determined by line probe assay in patients with chronic hepatitis C seen at tertiary referral centers in the United States. Ann Intern Med 1996;124: 868-876.
15. Mutchnick M, Tamburro C, Hassanein T, Tong M, Herrera J, Conrad A, Russell J, et al. Analysis of HCV RNA concentrations by a multi-cycle RT-PCR assay in 3538 untreated chronic HCV patients: assessment of RNA titer by HCV genotype [Abstract]. HEPATOLOGY 1997;26:186A.
16. Kleter GE, Brouwer JT, Heijtink RA, Schalm SW, Quint WGV. Detection of hepatitis C virus RNA in patients with chronic hepatitis C virus infections during and after therapy with alpha interferon. Antimicrob Agents Chemother 1993;37:595-597.
17. Orito E, Mizokami M, Suzuki K, Ohba K-i, Ohno T, Mori M, Hayashi K, et al. Loss of serum HCV RNA at week 4 of interferon-alpha therapy is associated with more favorable long-term response in patients with chronic hepatitis C. J Med Virol 1995;46:109-115.
18. Hino K, Okuda M, Konishi T, Ishiko H, Okita K. Serial assay of hepatitis C virus RNA in serum for predicting response to interferon-alpha therapy. Dig Dis Sci 1995;40:14-20.
19. Lee WM, Reddy KR, Tong MJ, Black M, van Leeuwen DJ, Hollinger FB, Mullen KD, et al. Early hepatitis C virus-RNA responses predict interferon treatment outcomes in chronic hepatitis C. HEPATOLOGY 1998;28: 1411-1415.
20. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ, Perelson AS. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-α therapy. Science 1998;282:103-107.
21. Gale MJ, Korth MJ, Tang NM, Tan S-L, Hopkins DA, Dever, TE, Polyak SJ, et al. Evidence that hepatitis C virus resistance to interferon is mediated through repression of the PKR protein kinase by the nonstructural 5A protein. Virology 1997;230:217-227.
22. Taylor DR, Shi ST, Romano PR, Barber GN, Lai MC. Inhibition of the interferon-inducible protein kinase PKR by HCV E2 protein. Science 1999;285:107-110.
23. Brechot C. The direct interplay between HCV NS5A protein and interferon transduction signal: from clinical to basic science. J of Hepatology 1999;30:1152-1154.
24. Zeuzem S, Feinman SV, Rasenack J, Heathcote J, Lai M-Y, Gane E, O'Grady J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-1672.
25. Heathcote EJ, Shiffman ML, Cooksley GE, Dusheiko GM, Lee SS, Balart L, Reindollar R, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673-1680.
26. Lindsay KL. Therapy of hepatitis C: overview. HEPATOLOGY 1997; 26(Suppl 1):71S-77S.
27. Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, Kilani A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Annals of Internal Medicine 1997; 127:875-881.
28. Lau DT, Kleiner DE, Ghany MG, Park Y, Schmid P, Hoofnagle JH. 10-year follow-up after interferon-α therapy for chronic hepatitis C. HEPATOLOGY 1998;28:1121-1127.
29. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, Kuroki T, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Annals Int Med 2000;132:517-524.
30. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, et al. Peginterferon alfa-2b in combination with ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: results of a randomized trial. Lancet 2001 (in press).