Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

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See editorial on page 1525.

Background & Aims: **Liver fibrosis is an important prognostic factor in patients with hepatitis C. The effect of pegylated (PEG) interferon alone or its combination with ribavirin on fibrosis has not been established.** ***Methods:*** **We pooled individual data from 3010 naive patients with pretreatment and posttreatment biopsies from 4 randomized trials. Ten different regimens combining standard interferon, PEG interferon, and ribavirin were compared. The impact of each regimen was estimated by the percentage of patients with at least 1 grade improvement in the necrosis and inflammation (METAVIR score), the percentage of patients with at least 1 stage worsening in fibrosis METAVIR score, and by the fibrosis progression rate per year.** ***Results:*** **Necrosis and inflammation improvement ranged from 39% (interferon 24 weeks) to 73% (optimized PEG 1.5 and ribavirin; $P < 0.001$). Fibrosis worsening ranges from 23% (interferon 24 weeks) to 8% (optimized PEG 1.5 and ribavirin; $P < 0.001$). All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment. The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis. Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (odds ratio [OR] = 0.12; $P < 0.0001$), sustained viral response (OR = 0.36; $P < 0.0001$), age < 40 years (OR = 0.51; $P < 0.001$), body mass index < 27 kg/m^2 (OR = 0.65; $P < 0.001$), no or minimal baseline activity (OR = 0.70; $P = 0.02$), and viral load < 3.5 millions copies per milliliter (OR = 0.79; $P = 0.03$).** ***Conclusions:*** **PEG-interferon and ribavirin combination significantly reduces the rate of fibrosis progression in patients with hepatitis C.**

Approximately 170 million people worldwide are infected with chronic hepatitis C virus (HCV).[1] The degree of histologic fibrosis is an important marker of the stage of the disease[2] because the natural history of hepatitis C involves the gradual progression of hepatic fibrosis that can eventually lead to cirrhosis. Most of the complications related to chronic infection occurs in patients who have established cirrhosis.[3–5] Treatments that could halt or diminish the progression of fibrosis would theoretically be beneficial.[6]

We have previously reported that the combination regimen of interferon and ribavirin slows progression of liver fibrosis and even leads to regression in a proportion of patients. The impact on fibrosis was related both to the response to therapy and the duration of interferon treatment.[7]

Recently, it has been shown that the pegylated form of interferon (PEG-interferon) has a significantly higher efficacy in achieving sustained response in comparison to standard interferon. This greater efficacy has been observed both for monotherapy[8–10] or in combination with ribavirin.[11] The effect of these new regimens on histological changes has not been well characterized.[8–11]

The aim of this study was to compare the efficacy of these different regimens (PEG-interferon alone or in combination with ribavirin) on fibrosis progression and on the necrosis and inflammatory features and to identify risk factors for these changes. This analysis was undertaken to determine the impact of therapy in patients who eradicate the virus, and also in patients who do not eradicate the virus during therapy.

Materials and Methods

The individual data from 4 randomized trials of PEG-interferon alfa-2b alone (Pegintron, Schering Plough, Kenilworth, NJ),[8] or in combination with ribavirin,[11] or of the combination

Abbreviations used in this paper: PEG, pegylated; TIW, three times per week.

0016-5085/02/$35.00
doi:10.1053/gast.2002.33023

interferon alfa-2b and ribavirin (Rebetron, Schering Plough)[12–13] were obtained. Patients with serologic confirmation of chronic hepatitis C were included if they had both pretreatment and posttreatment liver biopsies. Patients were excluded if they had HBV or human immunodeficiency virus infection, a daily alcohol consumption greater than 50 g, or other forms of liver disease (hemochromatosis, autoimmune, α_1-antitrypsin, steatohepatitis). In all trials, a signed informed consent was obtained after the nature and possible consequences of the studies were explained. All these pivotal trials were prospectively similarly designed with identical and centralized histologic and viral methods.[8,11–13]

A database combining all 4 studies was created that contained the following: gender, age at first biopsy, age at infection, body mass index, presumed mode of infection (parenteral, usually intravenous drug use, transfusion, other, or unknown), type of treatment (PEG-interferon ribavirin, interferon-ribavirin, PEG-interferon, interferon), duration of treatment (24 or 48 weeks), METAVIR fibrosis stage, and activity grade at first and second biopsy, time elapsed between the 2 biopsies in months, quantification of viral load before treatment, at the end of treatment, at the end of follow-up (6 months after the end of treatment), and HCV genotype. The 10 following regimens were compared: standard interferon (alpha 2b 3 MU 3 times per week [TIW]) 24 weeks, standard interferon 48 weeks, PEG interferon 0.5 (0.5 mcg per kg) 48 weeks, PEG interferon 1.0 48 weeks, PEG 1.5 48 weeks, standard interferon and ribavirin (1000 mg, if weight <75 kg, 1200 mg >= 75 kg) 24 weeks, standard interferon-ribavirin 48 weeks, 1.5 PEG interferon 1 month then 0.5 PEG and ribavirin (1000 mg, if weight <75 kg, 1200 mg >= 75 kg) (this regimen is designated combination 0.5 PEG interferon and ribavirin), a low ribavirin (10.6 mg or less per kg), and 1.5 PEG interferon combination, and a high-dose ribavirin (more than 10.6 mg per kg) and 1.5 PEG interferon combination. The high-dose ribavirin (more than 10.6 mg per kg) and 1.5 PEG interferon combination regimen is the recommended regimen in recent European approvals because it has been shown that ribavirin was less effective when administered at a dose of 10.6 mg per kg or less.[11] Of these regimens, 3 were not fully adjusted by weight: interferon monotherapy 24 and 48 weeks and combination of low-dose ribavirin and 1.5 PEG. As there was no randomized group without treatment, the first approved regimen (standard interferon alpha 2b 3 MU TIW 24 weeks) was considered as a control group and the other 9 regimens as "reinforced."

Liver biopsies were processed using standard techniques and evaluated for stage of fibrosis and grade of activity according to the METAVIR scoring system.[14,15] Fibrosis was staged on a scale of 0 to 4: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3= numerous septa without cirrhosis, and F4= cirrhosis. Reproducibility of results between pathologists using this method has been established.[14] Progression of fibrosis from normal liver or portal fibrosis (F0/F1) to outside the portal tract with formation of septa (F2/F3/F4) (called "significant fibrosis" throughout this article) represents a critical threshold of progressive disease caused by HCV, the last step being the constitution of cirrhosis (F4). The grading of activity, previously described[15] (the intensity of necroinflammatory activity mostly based on necrosis), was scored as follows: A0 = no histological activity, A1 = mild activity, A2 = moderate activity, and A3= severe activity. One pathologist (Zachary Goodman) reviewed the biopsies at the time these individual studies were undertaken without any information concerning the clinical, biological, or treatment characteristics during the conduct of each study.

Serum HCV RNA levels had been assessed in all 4 studies, and were determined by a single central laboratory (NGI, Los Angeles, CA). A quantitative reverse-transcription multicycle polymerase chain reaction was used, with a lower limit of detection of 50 IU/mL (100 copies/mL).[16] The median observed 3.5 millions copies/mL is equivalent to 1.300.000 IU/mL.[17] HCV genotyping was performed as previously described.[18]

Assessment of Fibrosis Progression

Progression of Fibrosis Was Analyzed by 3 Methods

First, we compared the impact of the different treatment regimens on the percentage of patients who improve by at least 1 fibrosis stage, remained stable, or worsened by at least 1 stage.

Secondly, we compared the different treatment regimens according to the fibrosis progression rates per year before and after treatment. These estimates have been extensively detailed and validated previously.[2,6,19]

The fibrosis progression rate after treatment was defined as the ratio between the difference in fibrosis stage expressed in METAVIR units between the 2 biopsies (before and after treatment) and the interval between the 2 biopsies in years. The progression rate before treatment was the ratio between the fibrosis stage in METAVIR units at the biopsy before treatment and the estimated duration of infection in years. Because of the nonnormal distribution of these estimates and the uncertainty of linearity, only medians and nonparametric tests were used. In a previous study, we had validated our estimate by comparison with paired biopsy estimates (our cohort and meta-analysis of control groups).[2]

Third, we assessed the impact of the different treatment regimens adjusted by other risk factors in multivariate analyses. The end point was the percentage of patients with significant fibrosis at the second biopsy.

Evolution of activity (necrosis and inflammation) was analyzed by assessing for each regimen the percentage of patients who improve by at least 1-grade activity, remain stable, or worsen by at least 1 grade. We selected a 1-grade improvement in the necrosis and inflammation METAVIR scoring system as its represent a major change. One grade in METAVIR is equivalent to 4 grades in the Knodell index.[14–15] This is twice the usual definition of histological improvement.

Finally, we tested the hypothesis that the reinforced regimens (9 regimens with interferon monotherapy pegylated or not for 48 weeks or combination with ribavirin) can reverse cirrhosis (change in fibrosis score based on the biopsy sample) in comparison with the "control" regimen (standard interferon alpha 2b 3 MU TIW 24 weeks which obtained only 5% of sustained virological response). If there were more reversal versus the control regimen this would strongly suggest an even

more significant effect versus an absence of treatment. For this purpose, we compared the percentage of patients with baseline cirrhosis reversal between control and reinforced regimens and control regimen. To take into account the sampling error we compared the biopsy sizes between groups.

Statistical Methods

Four randomized trials with 3 to 4 arms were included (Table 1). The same regimen can be found in different randomized trials. Therefore, some comparisons can be made between randomized arms ("directly compared," e.g., IFN-R 48w vs. IFN 48w in Poynard trial) or by pooling arms (IFN-R 48w of Poynard, Hutchison, and Manns versus IFN 48w of Poynard, Hutchison, and Lindsay-Trepo). Therefore, we performed analyses twice, one between "directly randomized" arms and between pooled arms. Table 2 gives the details of each arm in each trial. Univariate comparisons used Student *t* test, Mann–Whitney test, and Kruskal–Wallis test on ranks

Table 1. Characteristics of All Patients Randomized in Trials and of Patients With Paired Biopsies Included in the Present Analysis

Characteristics	Interferon-ribavirin		Interferon-ribavirin		PEG-interferon		PEG-interferon ribavirin		Total with paired biopsies
First author (ref)	Poynard[12]		McHutchison[13]		Lindsay-Trepo[8]		Manns[13]		
	All N = 832	Paired biopsies N = 562	All N = 912	Paired biopsies N = 670	All N = 1219	Paired biopsies N = 744	All N = 1530	Paired biopsies N = 1034	N = 3010
Treatment received (N)									
IFN 24 weeks	0	0	231	176	0	0	0	0	176
IFN 48 weeks	278	191	225	158	303	191	0	0	540
IFN + ribavirin 24 weeks	281	204	228	179	0	0	0	0	383
IFN + ribavirin 48 weeks	278	167	228	157	0	0	505	334	658
PEG-IFN 0.5 48 weeks	0	0	0	0	315	198	0	0	198
PEG-IFN 1.0 48 weeks	0	0	0	0	297	178	0	0	178
PEG-IFN 1.5 48 weeks	0	0	0	0	304	177	0	0	177
PEG 0.5 -ribavirin 48 weeks	0	0	0	0	0	0	514	361	361
PEG 1.5 -ribavirin 48 weeks	0	0	0	0	0	0	511	339	339
Age, mean (*yrs*)	41	41	44	44	43	43	43	43	43
Gender, male sex (*%*)	65	65	65	67	65	65	66	65	65
Weight, mean (*kg*)	74	74	83	83	80	80	82	83	80
Body mass index (kg/m^2)	25	25	27	27	27	27	27	27	27
Source of infection (*%*)									
Transfusion	25	26	22	23	21	21	21	22	23
Intravenous drug	42	42	52	52	48	49	64	64	53
Other or unknown source	34	32	26	25	31	30	15	14	24
Duration of infection									
Information available (*%*)	81	81	84	84	74	74	100	100	83
Median years	14	14	19	19	18	18	17	17	18
Duration between biopsies									
Mean month	19	19	18	18	21	21	21	21	20
Size baseline biopsy (*mm*)	14	14	16	16	16	16	16	16	16
Histology at first biopsy									
Mean METAVIR fibrosis stage	1.3	1.3	1.5	1.5	1.3	1.3	1.5	1.5	1.4
No fibrosis (F0) (*%*)	2	2	2	2	4	3	1	1	2
Portal fibrosis (F1)	79	78	69	70	77	76	70	68	73
Few septa (F2)	9	9	14	14	9	11	17	17	13
Many septa (F3)	6	6	10	10	6	6	6	7	7
Cirrhosis (F4)	4	5	5	5	4	3	6	7	5
Mean METAVIR activity grade	2.0	2.0	2.2	2.2	2.0	2.0	2.3	2.3	2.2
No activity (A0)	2	2	1	1	3	2	1	1	2
Mild (A1)	26	25	22	23	23	22	16	16	21
Moderate (A2)	40	40	34	33	44	44	38	36	39
Severe (A3)	32	33	43	43	30	32	45	47	38
Virologic assessment (*%*)	100	100	100	100	100	100	100	100	100
Genotype determination (*%*)									
1	59	60	72	71	70	70	68	70	69
2 or 3	36	35	26	27	27	27	29	28	28
Other	6	5	2	2	3	3	3	2	3
Initial serum HCV RNA									
Median (*millions IU/mL*)	1.6	1.6	1.9	1.9	1.7	1.7	1.4	1.4	1.5

Table 2. Impact of PEG Interferon and Ribavirin Combination Regimen on Fibrosis Progression Between Baseline and Posttreatment Biopsies

Groups	Number	Improved	Stabilized	Worsened
All patients	3010	590 (20%)	1955 (65%)	465 (15%)
Sustained responders[a]	1094	277 (25%)	740 (68%)	77 (7%)
Relapsers	464	74 (16%)	311 (67%)	79 (17%)
Nonresponders	1452	239 (17%)	904 (62%)	309 (21%)
PEG 1.5 -ribavirin 48w[b]	339	78 (23%)	206 (61%)	55 (16%)
High-dose ribavirin	117	28 (24%)	79 (68%)	10 (8%)
Low-dose ribavirin	222	50 (23%)	57 (57%)	45 (20%)
PEG 0.5 -ribavirin 48w	361	82 (23%)	242 (67%)	37 (10%)
Interferon-ribavirin 48w	658	132 (20%)	437 (66%)	89 (14%)
Poynard trial	167	31 (19%)	111 (66%)	25 (15%)
McHutchison trial	157	28 (18%)	102 (65%)	27 (17%)
Manns trial	334	73 (22%)	224 (67%)	37 (11%)
Interferon-ribavirin 24w	383	76 (20%)	252 (66%)	55 (14%)
Poynard trial	204	45 (22%)	137 (67%)	22 (11%)
McHutchison trial	179	31 (17%)	115 (64%)	33 (19%)
PEG 1.5 48w	177	30 (17%)	115 (65%)	32 (18%)
PEG 1.0 48w	178	38 (21%)	111 (62%)	29 (16%)
PEG 0.5 48w	198	43 (22%)	122 (62%)	33 (17%)
Interferon 48w	540	89 (16%)	356 (66%)	95 (18%)
Poynard trial	191	34 (18%)	125 (65%)	32 (17%)
McHutchison trial	158	29 (18%)	100 (64%)	29 (18%)
Lindsay-Trepo trial	191	26 (14%)	131 (69%)	34 (18%)
Interferon 24w[c]	176	22 (12%)	114 (65%)	40 (23%)

NOTE. Poynard trial has 3 arms: interferon-ribavirin 48 weeks, interferon-ribavirin 24 weeks, and interferon 48 weeks. McHutchison trials has same 3 arms plus 24-week interferon therapy. Lindsay-Trepo trial has 4 arms: PEG 1.5 48 weeks, PEG 1.0 48 weeks, PEG 0.5 48 weeks, and interferon 48 weeks. Manns trial has 3 arms: PEG 1.5 -ribavirin 48 weeks, PEG 0.5 -ribavirin 48 weeks, and interferon-ribavirin 48 weeks. There was no significant difference between randomized arms in a single trial.

[a] The percentage of patients with worsening fibrosis was lower in responders vs. nonresponders ($P < 0.001$) and vs. relapsers ($P < 0.001$), as well as between relapsers vs. nonresponders ($P = 0.046$).

[b] The percentage of patients with worsening fibrosis was lower in patients treated 48 weeks by PEG-interferon 1.5 and high-dose ribavirin (dose ribavirin greater than 10.0 mg per kg) in comparison with combination with low-dose ribavirin ($P = 0.005$). There were significantly fewer patients with worsening fibrosis among patients treated 48 weeks by PEG-interferon 1.5 and high-dose ribavirin combination vs. interferon 24 weeks ($P = 0.001$), vs. interferon 48 weeks ($P = 0.02$), vs. PEG interferon 0.5 48 weeks ($P = 0.04$), vs. PEG interferon 1.0 48 weeks ($P = 0.05$), vs. PEG interferon 1.5 48 weeks ($P = 0.03$), vs. interferon-ribavirin 24 weeks ($P = 0.02$), vs. interferon-ribavirin 48 weeks ($P = 0.006$), vs. PEG interferon 0.5 ribavirin 48 weeks ($P = 0.05$).

[c] The percentage of patients with worsening fibrosis was higher in patients treated 24 weeks by interferon vs. interferon-ribavirin 24 weeks combination ($P = 0.02$), vs. interferon-ribavirin 48 weeks combination ($P = 0.003$) and vs. PEG-interferon 0.5 and ribavirin combination ($P = 0.003$) and vs. PEG-interferon 1.5 and high-dose ribavirin combination ($P = 0.001$).

for quantitative factors with nonequal variance (Bonferroni method for multiple comparisons), Fisher exact test for qualitative factors, and Wilcoxon signed-rank test for difference in medians.[20] *P* values were 2-sided. Multivariate analysis used logistic regression analysis.[20] Independent factors associated with the percentage of patients without significant fibrosis at the posttreatment biopsy were assessed by logistic regression model. The following factors were assessed in the model: ribavirin combination therapy (yes or no), duration of treatment (24 or 48 weeks), PEG interferon or not, age at first biopsy (younger than 40 years), gender, genotype (2 of 3 or other for first analyses, then genotype 3 or other because genotype 3 was associated with steatosis and fibrosis), baseline viral load (lower than 1.3 millions IU/mL or higher which was the median value), fibrosis stage (F0/F1 or F2/F3/F4), and activity grade (A0/A1 or A2/A3) at first biopsy, sustained response (yes or no), relapse (yes or no), the body mass index (lower than 27 or not which was the median value), and the total size of the 2 paired biopsies as a covariate to minimize the sampling error (>30 mm or not which was the median value). A sustained response was defined as a negative serum HCV RNA (<50 IU/mL) at the end of treatment and 24 weeks after the end of treatment, and a nonresponse as a positive HCV RNA either at the end of the treatment or 24 weeks later.

Results

Of the 4493 naive patients enrolled in the 4 trials, 3010 had paired biopsies available with a 20-month mean duration between the biopsies (Table 1). There were no statistically significant differences between the original population and the population of patients with paired biopsies included in this analysis. At baseline, 2243 patients had no significant fibrosis (75%) and 767 significant fibrosis (25%), 673 (22%) had no significant activity, and 2337 (78%) significant activity. The mean weight of 1880 patients in the United States was 84 kg

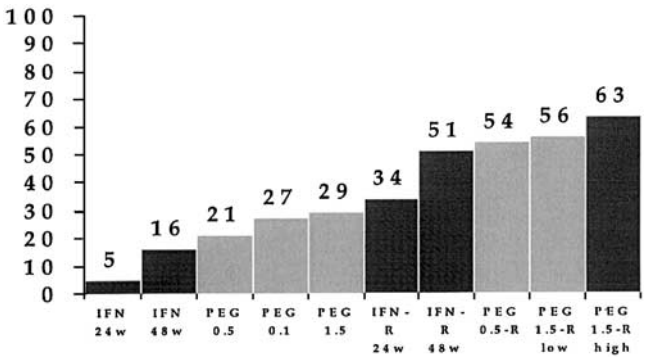

Figure 1. Sustained response rates observed in the 10 different regimens. The sustained response rate varied significantly from 5% to 63% according to regimen. 5% for interferon 24 weeks (9 of 176), 16% for interferon 48 weeks (86 of 540), 21% for PEG 0.5 (41 of 198), 27% for PEG 1.0 (48 of 178), 29% for PEG 1.5 (52 of 177), 34% for interferon-ribavirin 24 weeks (131 of 383), 51% for interferon-ribavirin 48 weeks (334 of 658), 54% for 0.5 PEG-ribavirin (194 of 361), 56% for the low ribavirin dose and 1.5 PEG combination (125 of 222), and 63% for the high ribavirin (more than 10.6 mg/kg) and 1.5 PEG interferon combination (74 of 117). *Black boxes* are the regimen approved in European or U.S. drug agencies.

vs. 74 kg for the 1330 patients not in the United States ($P < 0.0001$).

Sustained Viral Response Rate According to Regimen

The sustained response rate varied significantly from 5% to 63% according to regimen (Figure 1). These rates were not significantly different than those of the overall population.

Overall Histologic Response

Fibrosis stage was improved in 20% of patients, stable in 65%, and worsened in 15% (Tables 2 and 3). Most of the differences were a 1 stage change: 16% 1 stage and 4% 2 or 3 stages for those biopsy pairs that improved; 12% 1 stage, and 3% 2 or 3 stages for those that worsened. The activity grade improved in 55%, remained stable in 31%, and worsened in 14%. At the second biopsy, cirrhosis was observed in 175 patients (6%) of 2834 patients treated with reinforced regimens and in 18 of 176 patients treated with control regimen (10%; $P = 0.03$).

Histologic Response According to Virologic Response

Among patients who achieved a virologic sustained response, there was less frequently worsening of fibrosis (7%) in comparison with relapsers (17%) or nonresponders (21%) ($P < 0.001$ for both comparisons; Table 2), as well as more activity improvement (86% vs. 43% and 36%, $P < 0.001$ for both comparisons, respectively; Table 3). When relapsers were compared with nonresponders, the differences were also significant ($P = 0.046$ and $P = 0.009$, respectively).

Histologic Response According to Regimen

Between randomized different treatment arms there was a significant difference in 2 separate trials for activity grade improvement in favor of interferon–ribavirin 48 weeks in comparison with interferon alone 48 weeks or 24 weeks (Tables 2 and 3). There was no significant difference between randomized arms for fibrosis.

Between regimens there were also highly significant differences. Fibrosis worsening ranged from 8% in patients receiving the PEG 1.5 and ribavirin high-dose combination to 23% in patients treated with interferon for 24 weeks (Table 2 and Figure 2). Activity improvement ranges from 73% in patients receiving the PEG 1.5 and high-dose ribavirin combination to 39% in patients treated by interferon 24 weeks (Table 3 and Figure 3).

Comparison Between Fibrosis Progression Rates per Year Before and After Treatment

All rates were lower after treatment than before both in responders and in nonresponders (all $P < 0.001$; Table 4). There were no significant differences between different treatments ($P = 0.48$). There was a significant difference between responders and nonresponders ($P < 0.001$).

Factors Associated With the Absence of Significant Fibrosis at the End of Follow-up in Multivariate Analysis

Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage, sustained viral response, age younger than 40 years, body mass index lower than 27 kg/m^2, no or mild baseline activity, and viral load lower than 3.5 millions copies/mL (Table 5).

Factors Associated With Histological Improvement in Patients Without Sustained Virologic Response

The same risk factors were associated with significant fibrosis in patients without sustained virologic response (relapsers and nonresponders). In comparison with the other regimens, PEG 0.5 and ribavirin combination had a better impact on fibrosis and on activity: 21% had demonstrable fibrosis improvement vs. 12% for interferon 24 weeks ($P = 0.04$) and vs. 15% for interferon 48 weeks (Table 6); 50% improvement of activity vs. interferon 24 weeks (37%, $P = 0.02$), vs. interferon

Table 3. Impact of PEG Interferon and Ribavirin Combination Regimen on Activity Progression Between Baseline and Posttreatment Biopsies

Groups	Number	Improved	Stabilized	Worsened
All patients	3010	1660 (55%)	924 (31%)	426 (14%)
Sustained responders[a]	1094	944 (86%)	131 (12%)	19 (2%)
Relapsers	464	200 (43%)	168 (36%)	96 (21%)
Nonresponders	1452	516 (36%)	625 (43%)	311 (21%)
PEG 1.5 -ribavirin 48w	339	230 (68%)	75 (22%)	34 (10%)
High-dose ribavirin[b]	117	85 (73%)	25 (21%)	7 (6%)
Low-dose ribavirin	222	145 (65%)	50 (23%)	27 (12%)
PEG 0.5 -ribavirin 48w	361	254 (70%)	85 (24%)	22 (6%)
Interferon-ribavirin 48w[c]	658	424 (64%)	158 (24%)	76 (12%)
Poynard trial	167	103 (62%)	41 (25%)	23 (14%)
McHutchison trial	157	91 (58%)	46 (29%)	20 (13%)
Manns trial	334	230 (69%)	71 (21%)	33 (10%)
Interferon-ribavirin 24w	383	193 (51%)	131 (34%)	59 (15%)
Poynard trial	204	102 (50%)	72 (35%)	30 (15%)
McHutchison trial	179	91 (51%)	59 (33%)	29 (16%)
PEG 1.5 48w	177	86 (49%)	59 (33%)	32 (18%)
PEG 1.0 48w	178	88 (49%)	63 (36%)	27 (15%)
PEG 0.5 48w	198	95 (48%)	69 (35%)	34 (17%)
Interferon 48w	540	221 (41%)	216 (40%)	103 (19%)
Poynard trial	191	70 (37%)	77 (40%)	44 (23%)
McHutchison trial	158	57 (36%)	71 (45%)	30 (19%)
Lindsay-Trepo trial	191	94 (49%)	68 (36%)	29 (15%)
Interferon 24w	176	69 (39%)	68 (39%)	39 (22%)

NOTE. There were significant differences between randomized arms in McHutchison trial with higher percentage of patients with activity improvement in patients treated by combination interferon-ribavirin 48 weeks vs. interferon 24 weeks ($P = 0.0006$, vs. interferon 48 weeks $P = 0.0001$; combination 24 weeks vs. interferon 48 weeks $P = 0.006$, vs. interferon 24 weeks $P = 0.03$). There were significant differences between randomized arms in Poynard trial with higher percentage of patients with activity improvement in patients treated by combination interferon-ribavirin 48 weeks vs. interferon 48 weeks ($P < 0.001$) and vs. combination 24 weeks ($P = 0.02$); combination 24 weeks vs. interferon 48 weeks, $P = 0.007$.

[a] The percentage of patients with activity improvement was higher in responders vs. nonresponders ($P < 0.001$) and vs. relapsers ($P < 0.001$), as well as between relapsers vs. nonresponders ($P = 0.009$).

[b] The percentage of patients with activity improvement was higher in patients treated 48 weeks by PEG-interferon 1.5 and high-dose ribavirin combination vs. interferon 24 weeks ($P < 0.0001$), vs. interferon 48 weeks ($P < 0.0001$), vs. PEG interferon 0.5 48 weeks ($P < 0.0001$), vs. PEG interferon 1.0 48 weeks ($P < 0.0001$), vs. PEG interferon 1.5 48 weeks ($P < 0.0001$), vs. interferon-ribavirin 24 weeks ($P < 0.0001$).

[c] The percentage of patients with activity improvement was higher in patients treated 48 weeks by interferon and ribavirin combination vs. interferon 24 weeks ($P < 0.0001$), vs. interferon 48 weeks ($P < 0.0001$), vs. PEG interferon 0.5 48 weeks ($P < 0.0001$), vs. PEG interferon 1.0 48 weeks ($P = 0.0003$), vs. PEG interferon 1.5 48 weeks ($P = 0.0001$), vs. interferon-ribavirin 24 weeks ($P < 0.0001$).

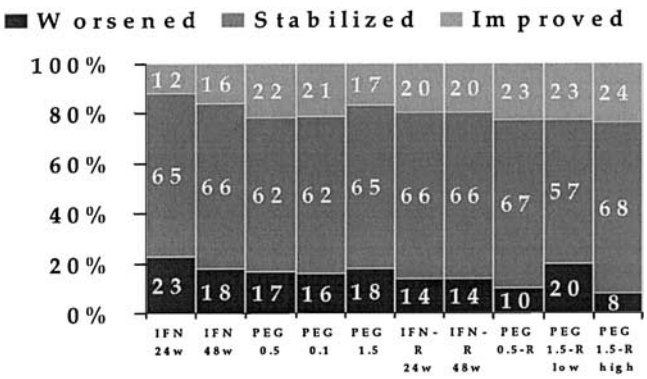

Figure 2. Impact of the 10 different regimens on fibrosis stage. Fibrosis worsening ranged from 8% in patients receiving the PEG 1.5 and ribavirin high dose combination to 23% in patients treated with interferon for 24 weeks. Details and statistical comparisons are given in Table 2.

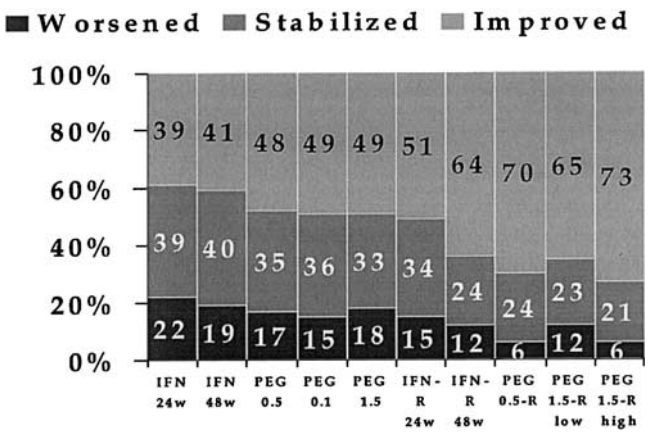

Figure 3. Sustained response rates observed in the 10 different regimens. Activity improvement ranges from 73% in patients receiving the PEG 1.5 and high dose ribavirin combination to 39% in patients treated with interferon 24 weeks. Details and statistical comparisons are given in Table 3.

Table 4. Impact of PEG-Interferon and Ribavirin Combination Regimen on Fibrosis Progression Rate

		Estimated fibrosis progression rate per year	
		Before treatment	During and after treatment
Groups	Number	Median (95% CI)	Median (95% CI)
All patients	2579	0.073 (0.070;0.076)	0.0 (0;0)
F0/F1	1900	0.056 (0.054;0.059)	0 (0;0)
Sustained responders	771	0.063 (0.060;0.068)	0 (0;0)
Nonresponders	1129	0.053 (0.051;0.055)	0 (0;0)
F2/F3/F4	679	0.137 (0.129;0.144)	−0.488 (−0.522;−0.491)
Sustained responders	210	0.139 (0.127;0.149)	−0.591 (−0.627;−0.550)
Nonresponders	469	0.135 (0.127;0.149)	0 (−0.443;0)
F0/F1 at first biopsy			
PEG 1.5 -ribavirin	236	0.054 (0.051–0.061)	0 (0;0)
High-dose ribavirin	90	0.055 (0.052;0.067)	0 (0:0)
Low-dose ribavirin	146	0.054 (0.048;0.061)	0 (0;0)
Sustained responders	151	0.056 (0.051;0.063)	0 (0;0)
Nonresponders	85	0.054 (0.048;0.056)	0 (0;0)
PEG 0.5 -ribavirin	246	0.055 (0.052–0.065)	0 (0;0)
Sustained responders	142	0.065 (0.055;0.078)	0 (0;0)
Nonresponders	104	0.049 (0.043;0.054)	0 (0;0)
PEG 1.5	105	0.053 (0.047–0.061)	0 (0;0)
Sustained responders	36	0.084 (0.056;0.111)	0 (0;0)
Nonresponders	69	0.124 (0.092;0.189)	0 (0;0)
PEG 1.0	106	0.052 (0.044–0.057)	0 (0;0)
Sustained responders	25	0.055 (0.044;0.066)	0 (0;0)
Nonresponders	81	0.053 (0.044;0.061)	0 (0;0)
PEG 0.5	105	0.060 (0.055–0.070)	0 (0;0)
Sustained responders	26	0.080 (0.053;0.167)	0 (−0.417;0)
Nonresponders	79	0.059 (0.050;0.069)	0 (0;0)
F2/F3/F4 at first biopsy			
PEG 1.5 -ribavirin	101	0.130 (0.110–0.147)	−0.492 (−0.556;0)
High-dose ribavirin	27	0.137 (0.103;0.162)	−0.569 (−1.02;0)
Low-dose ribavirin	74	0.127 (0.106;0.157)	−0.448 (−0.550;0)
Sustained responders	47	0.139 (0.104;0.160)	−0.594 (−0.492;−0.667)
Nonresponders	54	0.122 (0.105;0.141)	0 (−0.515;0)
PEG 0.5 -ribavirin	113	0.138 (0.126–0.163)	−0.484 (−0.530;0)
Sustained responders	50	0.147 (0.116;0.195)	−0.515 (−0.571;−0.382)
Nonresponders	63	0.132 (0.109;0.163)	−0.432 (−0.524;0)
PEG 1.5	24	0.113 (0.092–0.146)	−0.205 (−0.563;0)
Sustained responders	2	0.084 (0.056;0.111)	−0.488 (−0.563;−0.414)
Nonresponders	22	0.124 (0.092;0.189)	0 (−0.571;0)
PEG 1.0	25	0.120 (0.094–0.160)	−0.524 (−0.649;0)
Sustained responders	5	0.160 (0.068;0.244)	−0.910 (−1.773;−0.634)
Nonresponders	20	0.107 (0.067;0.159)	−0.480 (−0.618;0)
PEG 0.5	40	0.113 (0.091–0.140)	−0.243 (−0.628–0)
Sustained responders	6	0.105 (0.074;0.138)	−1.063 (−1.395;−0.629)
Nonresponders	34	0.117 (0.091;0.155)	0 (−0.533;0)

NOTE. All rates were lower after treatment than before (all Wilcoxon signed-rank test for difference in medians $P < 0.001$). There was no significant difference between treatments (Kruskal–Wallis variance analysis $P = 0.48$). There was significant difference between responders and nonresponders ($P < 0.001$). Impact was analyzed according to treatment regimen, baseline fibrosis stage and virologic response, in naive patients with known duration of infection.

48 weeks (33%, $P = 0.0001$), vs. PEG interferon 0.5 for 48 weeks (35%, $P = 0.02$), vs. PEG interferon 1.0 48 weeks (35%, $P = 0.007$), vs. PEG interferon 1.5 48 weeks (37%, $P = 0.02$), vs. interferon-ribavirin 24 weeks (34%, $P = 0.0008$), and vs. interferon-ribavirin 48 weeks (40%, $P = 0.03$; Table 7).

There was a significant association between fibrosis and activity changes but with low concordance rates in all patients. This was also observed in nonresponders (data not shown).

Treatment of Patients With Cirrhosis

A total of 153 patients had cirrhosis at the time of the first biopsy before treatment. The "reversal" of cirrhosis (change in fibrosis score based on the biopsy sample) was observed in 75 patients (49 %), none in the

Table 5. Factors Associated With the Absence of Significant Fibrosis (F2/F3/F4) After Treatment (Logistic Regression Model) in all Patients

Factor	Odds ratio Exp (B)	Lower 95% confidence limit	Upper 95% confidence limit	Significance
Baseline fibrosis stage F0/F1	0.12	0.10	0.15	$P < 0.0001$
Sustained viral response	0.36	0.28	0.47	$P < 0.0001$
Age younger than 40 years	0.51	0.40	0.64	$P < 0.0001$
Body mass index < 27	0.65	0.53	0.79	$P < 0.0001$
Baseline activity grade A0/A1	0.70	0.53	0.94	$P = 0.02$
Viral load < 3.5 millions	0.79	0.64	0.98	$P = 0.03$
Female gender	0.81	0.65	1.01	$P = 0.07$
Relapse	0.84	0.63	1.11	$P = 0.23$
Treatment duration of 48 weeks	0.91	0.68	1.21	$P = 0.48$
PEG-interferon	0.99	0.79	1.24	$P = 0.50$
Genotype 3	1.08	0.79	1.49	$P = 0.61$
Combination with ribavirin	1.16	0.93	1.44	$P = 0.19$
Total biopsies size > 30 mm	0.97	0.79	1.19	$P = 0.80$

NOTE. A total of 2861 patients had all the data, and 685 had significant fibrosis (F2/F3/F4) at the second biopsy. The R squared correlation coefficient was 0.21 ($P < 0.001$).

control regimen (Table 8). One third of patients with cirrhosis reversal were sustained responders; they were also younger and had significant improvement in the activity grade in comparison to patients without cirrhosis reversal. The size of the biopsies (at baseline or at the second biopsy) were not different between patients with or without cirrhosis reversal. Among the 75 patients with cirrhosis reversal, the second biopsy sample was graded stage 3 in 23 patients, stage 2 in 26, stage 1 in 23, and no fibrosis in 3. The mean fibrosis score at the second biopsy was 1.9 ± 0.9 (SD), and the mean activity grade improved from 2.5 ± 0.7 to 1.6 ± 0.9 ($P < 0.01$).

Discussion

This overview of 4 pivotal randomized trials has permitted us to assess the incremental benefit of 10 different regimens on the histological features of patients infected with hepatitis C virus. These regimens given for 24 or 48 weeks allowed us to observe an improvement of necrosis and inflammation grades and a reduction of fibrosis progression at least during the 2 years' histological follow-up. This analysis has also demonstrated that the histological improvement was related both to the viral response and to several baseline factors. The combination of PEG-interferon and ribavirin eradicates the virus in more than 50% of patients, and therefore potentially can prevent cirrhosis, amplifying our previous

Table 6. Impact of PEG Interferon and Ribavirin Combination Regimen in Patients Without Sustained Virologic Response (Nonresponders or Relapsers) on Fibrosis Progression Between Baseline and Posttreatment Biopsies

Groups	Number	Improved	Stabilized	Worsened
PEG 1.5 -ribavirin 48w	140	25 (18%)	77 (55%)	38 (27%)
High-dose ribavirin	43	8 (19%)	27 (62%)	8 (19%)
Low-dose ribavirin	97	17 (17%)	50 (52%)	30 (31%)
PEG 0.5 -ribavirin 48w[a]	167	35 (21%)	107 (64%)	25 (15%)
Interferon-ribavirin 48w	324	54 (17%)	207 (64%)	63 (19%)
Interferon-ribavirin 24w	252	42 (16%)	163 (65%)	47 (19%)
PEG 1.5 48w	125	18 (14%)	80 (64%)	27 (22%)
PEG 1.0 48w	130	22 (17%)	79 (61%)	29 (22%)
PEG 0.5 48w	157	27 (17%)	98 (62%)	32 (20%)
Interferon 48w	454	69 (15%)	298 (66%)	87 (19%)
Interferon 24w	167	21 (12%)	106 (64%)	40 (24%)

[a] The percentage of patients with fibrosis worsening was lower in patients treated 48 weeks by PEG-interferon 0.5 and ribavirin combination vs. interferon 24 weeks ($P = 0.04$), and vs. interferon 48 weeks ($P < 0.0001$).

Table 7. Impact of PEG Interferon and Ribavirin Combination Regimen in Patients Without Sustained Virologic Response (Nonresponders or Relapsers) on Activity Progression Between Baseline and Posttreatment Biopsies

Groups	Number	Improved	Stabilized	Worsened
PEG 1.5 -ribavirin 48w	140	55 (39%)	54 (39%)	31 (22%)
High-dose ribavirin	43	19 (44%)	17 (40%)	7 (16%)
Low-dose ribavirin	97	36 (37%)	37 (38%)	30 (25%)
PEG 0.5 -ribavirin 48w[a]	167	84 (50%)	63 (38%)	20 (12%)
Interferon-ribavirin 48w[b]	324	130 (40%)	124 (38%)	70 (22%)
Interferon-ribavirin 24w	252	85 (34%)	110 (44%)	57 (23%)
PEG 1.5 48w	125	46 (37%)	51 (41%)	28 (22%)
PEG 1.0 48w	130	45 (35%)	58 (45%)	27 (20%)
PEG 0.5 48w	157	58 (37%)	67 (40%)	32 (23%)
Interferon 48w	454	151 (33%)	200 (44%)	103 (23%)
Interferon 24w	167	62 (37%)	66 (40%)	39 (23%)

[a] The percentage of patients with activity improvement was higher in patients treated 48 weeks by PEG-interferon 0.5 and ribavirin combination vs. interferon 24 weeks ($P = 0.02$), vs. interferon 48 weeks ($P = 0.0001$), vs. PEG interferon 0.5 48 weeks ($P = 0.02$), vs. PEG interferon 1.0 48 weeks ($P = 0.007$), vs. PEG interferon 1.5 48 weeks ($P = 0.02$), vs. interferon-ribavirin 24 weeks ($P = 0.0008$) and vs. interferon-ribavirin 48 weeks ($P = 0.03$). The significant differences were observed both for relapsers and nonresponders.

[b] The percentage of patients with activity improvement was higher in patients treated 48 weeks by interferon and ribavirin combination vs. interferon 48 weeks ($P = 0.049$).

Table 8. Treatment of 153 Patients With Baseline Cirrhosis: Factors Associated With Change in Fibrosis Score Based on the Biopsy Sample (Cirrhosis Reversal)

Factor	No more cirrhosis n = 75	Persistent cirrhosis n = 78	Significance
Regimen[a]			$P = 0.003$
48 weeks IFN or combination	75 (100%)	69 (89%)	
24 weeks IFN 3 MU TIW	0 (0%)	9 (11%)	
Sustained viral response[b]	25 (33%)	12 (15%)	$P = 0.01$
Relapse	12 (16%)	13 (17%)	$P = 0.91$
Age	44.7 ± 7.4	47.2 ± 7.8	$P = 0.045$
Body mass index	29.0 ± 6.3	30.2 ± 6.4	$P = 0.26$
Female gender	18 (24%)	24 (31%)	$P = 0.37$
Baseline activity grade A0/A1	9 (12%)	7 (9%)	$P = 0.60$
Follow-up activity grade A0/A1	34 (45%)	18 (23%)	$P = 0.004$
Viral load < 3.5 millions	30 (41%)	32 (41%)	$P = 1.00$
Genotype 3	18 (24%)	13 (17%)	$P = 0.31$
Baseline weight	87 ± 20	90 ± 21	$P = 0.11$
Baseline biopsy size > 15 mm	28 (37%)	27 (35%)	$P = 0.73$
Follow-up biopsy size > 15 mm	20 (27%)	27 (28%)	$P = 0.83$
Duration between biopsies month	21 ± 4	21 ± 4	$P = 0.72$
Duration of infection	20.5 ± 10.0	21.0 ± 10.1	$P = 0.75$

[a]Standard interferon 3 million units 3 times per week for 24 weeks was considered as the control regimen and the other regimen as reinforced regimen.

[b]In multivariate logistic regression analysis, only sustained response was significantly associated with cirrhosis reversal (odds ratio = 0.39; 95% confidence interval, 0.17–0.85; $P = 0.02$).

results with standard interferon plus ribavirin combination.[7] Also, half of the patients with baseline cirrhosis treated with the reinforced regimen had a disappearance of cirrhosis at the time of the subsequent follow-up biopsy.

Compared with our prior analyses, a new factor, the body mass index, was strongly associated with fibrosis progression even after adjustment for the 3 main factors previously identified, viral response, fibrosis stage, and age.[7] Gender was probably a confounding factor, which disappears when body mass index was taken into account. Alcohol consumption was not assessed during the treatment and follow-up periods in all of these trials. This is a limitation of the present study. High alcohol consumption was an exclusion criterion, but changes in alcohol consumption may have influenced fibrosis progression. However, the regimens were randomized, which precluded a major risk of bias.

This analysis combining individual data has 3 main methodological weaknesses: (1) paired biopsy was not available for all included patients; (2) the absence of direct comparisons by randomization of the 10 different regimens in a single prospective trial; and (3) the absence of a control group without treatment. A bias related to patient's selection could be reasonably excluded, as there were no different characteristics between all patients randomized versus patients who had paired biopsies (Table 1). The direct comparisons by randomization of the 10 different regimens in a single prospective trial were in practice impossible. Each new trial included in its design the previous standard regimen. The PEG interferon monotherapy trial was started in 1997, before the end of the standard interferon-ribavirin combination trials in 1998. Despite the absence of randomization between the 10 regimens, a randomization was always performed versus the standard treatment at this time. Furthermore, the pooling of data was possible because all the 4 trials were designed prospectively together with centralized endpoints, and all known prognostic factors were taken into account in univariate and multivariate analyses. The individual data from the first trials comparing interferon monotherapy versus controls without treatment were not available. However, the first approved regimen (interferon 3 MU TIW for 24 weeks) had already an impact on the natural history of chronic hepatitis C as demonstrated in meta-analysis of randomized trials[21] and in historical or randomized comparisons.[2,6,22–23] Among 70 nontreated patients (when interferon was not available) with 2 biopsies assessed retrospectively we observed an improvement of activity in 17% and a worsening of fibrosis in 64% of patients.[2,6] In the present study, interferon monotherapy for 24 weeks was associated with an improvement of activity grade in 37% and a worsening of fibrosis stage in 24% of treated patients. Even if in a conservative approach this first approved regimen was considered as the control regimen group, very significant breakthroughs have been obtained thereafter. The last approved regimen, the PEG-interferon and high-dose ribavirin combination, had the highest histological benefit ever observed: an activity improvement was observed

in 73% of patients and a worsening of fibrosis stage was observed in only 8%.

The different regimens were more and more effective on viral response with 63% of sustained response with the PEG 1.5 high-dose ribavirin combination that is 58% more than the 5% achieved with the first approved regimen. When a sustained response was achieved, the histological impact was the same whatever the regimen: activity improvement was observed in 86% of patients with only 7% of patients with worsening fibrosis.

The percentage of patients with reversal of cirrhosis after treatment was surprisingly high among patients receiving the reinforced regimen (52%). Before a generalized conclusion that cirrhosis can be cured, several limitations of our study must be underlined.[24] Cirrhosis reversal was defined as a change in fibrosis score based on the biopsy sample. A sampling error is possible especially between stage 3 (extensive fibrosis) and stage 4 (cirrhosis), particularly with biopsies of small size. However, there was no difference in biopsy sizes between patients with cirrhosis reversal and those whose biopsies did not change. If we analyzed stage 3 and stage 4 together, there was also a very significant improvement rate in fibrosis in 50% of cases (data not shown). One concordant fact is the association between activity improvement and cirrhosis reversal: twice as many patients had none or mild necroinflammatory features at the follow-up biopsy in comparison with patients who still had cirrhosis. A sampling error cannot explain the significant association between cirrhosis reversal and virologic response and activity improvement. The patients with cirrhosis reversal were younger, and it is possible that early cirrhosis is easier to reverse than more established cirrhosis. These large prospective studies with repeated biopsies have finally identified a new category of extensive fibrosis that could be named a "reversible cirrhotic stage." Because the follow-up in these trials was less than 48 weeks after the end of the treatment, the possibility of a continued decrease in fibrosis among patients with a sustained virologic response should be evaluated with long-term histologic and virologic follow-up studies. Recent noninvasive biochemical markers of fibrosis may also be useful.[25]

In virologic nonresponders, there was less fibrosis regression and more fibrosis progression than in responders. However, it may be incorrect to conclude that the combination regimen or interferons alone are valueless in virologic nonresponders. By comparing the fibrosis progression rate of virologic nonresponders after interferon to their estimated progression before treatment and to nonrandomized matched untreated patients, we and other investigators have previously observed[6,7,23] that interferon slowed the natural fibrosis progression observed before treatment (although the impact was weaker than in sustained responders). This has been confirmed by a randomized trial for necrosis and inflammation.[23] In the present study, we also observed a reduction of fibrosis progression rates in comparison to estimates before treatment, especially among patients with initial significant fibrosis. Because there is no certainty concerning the linearity of the fibrosis progression, we used only medians and nonparametric methods for all comparisons. It seems unfair not to take into account information based on 17 years of disease evolution. The fibrosis stage at the first biopsy for each patient represents an excellent abstract of this balance between extracellular matrix formation and degradation. One weakness of the fibrosis progression rate estimated during and after treatment is the short time elapsed between biopsies with a mean of 20 months. This argues against the concept of stopping treatment too early in patients without a sustained virologic response.[26] The antifibrotic and histologic efficacy of these regimens should be carefully considered before prematurely stopping treatment, especially in patients who have significant fibrosis. In a patient with a rapid fibrosis progression rate, it may be clinically relevant to prevent fibrosis progression and cirrhosis complications even if the virus is still detectable.[27] The retrospective analyses of these randomized trials suggested 2 options for maintenance therapy, either PEG-1.0 monotherapy which is the simplest and well-tolerated regimen or the combination PEG-0.5-ribavirin, which was the most effective regimen in nonresponders on necrosis and inflammation. These options should be validated prospectively.

This study permitted us to identify body mass index as a major factor associated with significant fibrosis even in treated patients. There are at least 2 factors explaining this association. First, the viral efficacy of both interferon and ribavirin is related to a correct dosage adjusted on the patient's weight.[11] Secondly, there is a strong relationship between fibrosis progression and metabolism. Recently, we observed that the liver fibrosis risk was increased in overweight patients particularly when the body mass index was greater than 27.[28] Since the beginning of these pivotal studies the mean weight is increasing particularly in patients in the United States. The percentage of patients in the United States with a body mass index greater than 27 was 43% in the first combination trial (1995), 51% in the second (1997), and 57% in the last (1998). In a trial of patients not in the United States, these percentages were 28%, 28%, and 32%, respectively.

We conclude that the combination of PEG interferon-ribavirin has the potential to reduce the morbidity and mortality of chronic hepatitis C by reducing fibrosis progression and the incidence of cirrhosis. This effect was most prominent in patients who achieved a virologic response, which is best achieved by the combination of PEG-interferon and high-dose ribavirin. Independent of achieving a sustained viral response to treatment, patients without extensive fibrosis at baseline, younger than 40 years of age, and with body mass index lower than 27 had a much lower progression of liver fibrosis. Cirrhosis reversal seems possible in patients with chronic hepatitis C.

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Received August 27, 2001. Accepted January 3, 2002.

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Supported by research grants from Schering Plough Research Institute, Kenilworth, New Jersey, by Direction de la Recherche Clinique Assistance Publique Hôpitaux de Paris, by Association pour la Recherche contre le Cancer, and by Association pour la Recherche sur les Maladies Hepatiques Viroles, Paris, France.

The authors thank all the investigators of PEG-FIBROSIS project including the investigators of the randomized trials.