2008

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ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

In patients with chronic hepatitis C who do not have a response to antiviral treatment, the disease may progress to cirrhosis, liver failure, hepatocellular carcinoma, and death. Whether long-term antiviral therapy can prevent progressive liver disease in such patients remains uncertain.

METHODS

We conducted a randomized, controlled trial of peginterferon alfa-2a at a dosage of 90 μg per week for 3.5 years, as compared with no treatment, in 1050 patients with chronic hepatitis C and advanced fibrosis who had not had a response to previous therapy with peginterferon and ribavirin. The patients, who were stratified according to stage of fibrosis (622 with noncirrhotic fibrosis and 428 with cirrhosis), were seen at 3-month intervals and underwent liver biopsy at 1.5 and 3.5 years after randomization. The primary end point was progression of liver disease, as indicated by death, hepatocellular carcinoma, hepatic decompensation, or, for those with bridging fibrosis at baseline, an increase in the Ishak fibrosis score of 2 or more points.

RESULTS

We randomly assigned the patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. The level of serum aminotransferases, the level of serum hepatitis C virus RNA, and histologic necroinflammatory scores all decreased significantly (P<0.001) with treatment, but there was no significant difference between the groups in the rate of any primary outcome (34.1% in the treatment group and 33.8% in the control group; hazard ratio, 1.01; 95% confidence interval, 0.81 to 1.27; P=0.90). The percentage of patients with at least one serious adverse event was 38.6% in the treatment group and 31.8% in the control group (P=0.07).

CONCLUSIONS

Long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, who had not had a response to initial treatment with peginterferon and ribavirin. (ClinicalTrials.gov number, NCT00006164.)

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*The other investigators participating in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial are listed in the Appendix.

MORE THAN 3 MILLION AMERICANS and 170 million persons worldwide are chronically infected with hepatitis C virus (HCV),[1,2] which can result in progressive hepatic injury and fibrosis, culminating in cirrhosis and end-stage liver disease.[3] Among adults in the Western world, chronic hepatitis C is a major cause of cirrhosis and a major indication for liver transplantation. Chronic hepatitis C has contributed also to the increasing incidence of hepatocellular carcinoma, for which few satisfactory therapies exist.[4]

Therapy with peginterferon and ribavirin for 24 to 48 weeks leads to a sustained loss of serum HCV RNA (termed a sustained virologic response), with resolution of chronic hepatitis in approximately half of patients.[5,6] Unfortunately, treatment options are few for the half of treated patients who do not have a sustained virologic response. Several new, potent HCV protease and polymerase inhibitors have been described recently,[7,8] but none are currently available for therapeutic use.

An approach to management of chronic hepatitis C in patients who do not have a sustained virologic response to initial therapy is long-term, maintenance peginterferon therapy. The rationale is that treatment with interferon can lead to suppression of HCV RNA levels and decreases in serum aminotransferase levels and improvements in liver histologic findings, even without eradication of the virus.[9] In addition, several reports suggest that interferon therapy can reduce the frequency of hepatocellular carcinoma; however, most of these studies were retrospective and were confounded by lead-time bias.[10,11] Whether long-term therapy with interferon results in improvements in histologic and clinical outcomes of hepatitis C has yet to be shown. Therefore, we conducted a large, prospective, randomized, controlled trial of long-term peginterferon therapy in adult patients with advanced hepatitis C who had not had a sustained virologic response to a previous course of interferon-based therapy.[12]

METHODS

PATIENTS

The design of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial has been described previously.[12] Briefly, patients meeting the following criteria were entered into this study from 10 study centers in the United States between August 2000 and August 2004: lack of a sustained virologic response to previous therapy, advanced hepatic fibrosis according to liver biopsy (an Ishak fibrosis score[13] of 3 or more; scores range from 0 to 6, with higher scores indicating greater degrees of fibrosis and scores of 5 or 6 indicating cirrhosis), no history of hepatic decompensation or hepatocellular carcinoma, and absence of exclusion criteria (e.g., liver disease other than hepatitis C, uncontrolled medical or psychiatric conditions, or contraindications to interferon treatment). The patients were stratified according to their Ishak fibrosis score. The noncirrhotic-fibrosis stratum consisted of 622 patients with a score of 3 or 4, and the cirrhosis stratum consisted of 428 patients with a score of 5 or 6. The patients provided written informed consent for participation in the trial.

During the lead-in phase of the trial, all patients underwent treatment with 180 μg of subcutaneous pegylated interferon alfa-2a weekly (Pegasys, Roche; the drug had not yet been approved by the Food and Drug Administration [FDA] when the trial began) and oral ribavirin (1000 to 1200 mg daily, according to body weight) for at least 24 weeks before undergoing randomization (Fig. 1). Randomization was stratified according to clinical center and the presence or absence of cirrhosis and was performed centrally by computer with the use of permuted blocks of random size. Patients with detectable serum HCV RNA levels at treatment week 20 were classified as having no response (<1 $\log_{10}$ IU per milliliter decrease in HCV RNA level from baseline) or a partial response (≥1 $\log_{10}$ IU per milliliter decrease in HCV RNA level from baseline) and were assigned for the next 3.5 years to either the maintenance-therapy group (90 μg of peginterferon alfa-2a weekly, without ribavirin) or the untreated control group. For treated patients who had unacceptable side effects, the weekly peginterferon dose was reduced to 45 μg or even lower, as needed.

Patients with undetectable serum HCV RNA at week 20 continued therapy for an additional 48 weeks, as reported previously.[14] If HCV RNA was detected in a patient again after week 20, either during treatment (breakthrough) or after cessation of treatment (relapse), the patient was
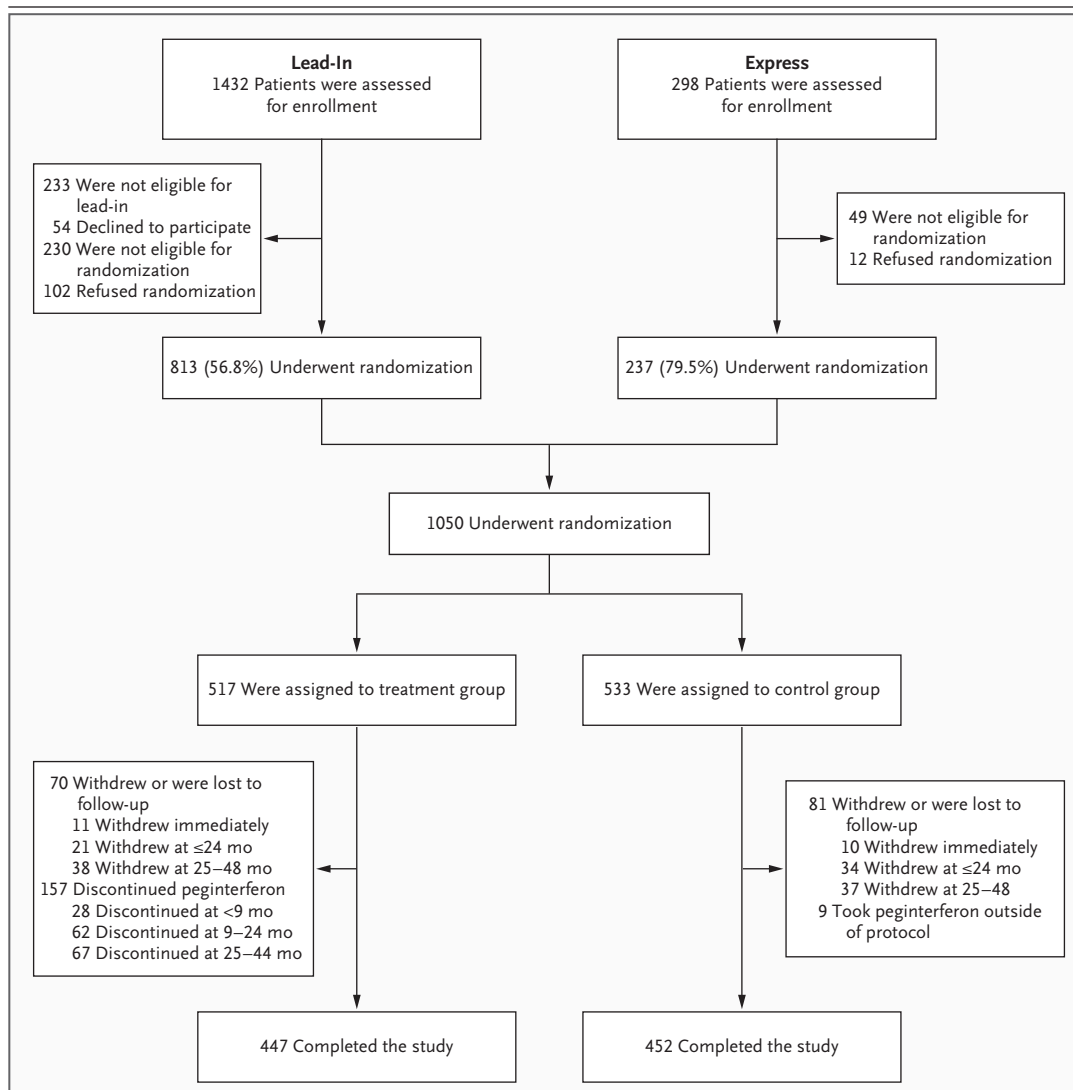
Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

Patients were enrolled either in the lead-in cohort of patients who underwent another course of antiviral treatment with peginterferon and ribavirin within the study or in the express cohort of patients who were initially treated outside the study. They were then randomly assigned to either the treatment or the control group and were followed up to monitor for clinical outcomes and histologic evidence of progression of liver disease.

offered the opportunity to undergo randomization in the controlled phase of the trial (the "breakthrough or relapse" cohort). During the trial, after pegylated interferons became available for treating hepatitis C, we amended the protocol to allow patients who had been treated with peginterferon plus ribavirin outside the study but had not had a sustained virologic response to treatment to undergo randomization to the treatment or control group (the "express" cohort).

OUTCOMES

The primary outcome variable was progression of liver disease within 1400 days (3.83 years) after randomization, as indicated by death, hepatic decompensation (variceal hemorrhage; ascites, which may include hepatic hydrothorax; spontaneous bacterial peritonitis; or hepatic encephalopathy), hepatocellular carcinoma,[15] a Child–Turcotte–Pugh score[16] of 7 or more on two consecutive study visits (the score measures hepatic decom-

pensation and ranges from 5 to 15, with higher numbers indicating greater decompensation), or for patients with noncirrhotic fibrosis at baseline, an increase in the Ishak hepatic fibrosis score of at least 2 points according to assessment of a liver-biopsy specimen obtained during the study. An outcome committee whose members were unaware of the treatment assignments reviewed and adjudicated the validity of each primary clinical outcome. The prespecified secondary end points were a change in quality of life, serious adverse events, events requiring dose reduction (a decrease in the platelet or neutrophil count or an increase in the serum alanine aminotransferase level), an increase in the Ishak fibrosis score from baseline to the follow-up biopsies, and the development of presumed hepatocellular carcinoma.

During the randomized phase of the trial, the patients were seen every 3 months for history taking, physical examination, and laboratory testing to monitor the effects of peginterferon therapy and to assess for clinical end points and adverse events. The patients underwent hepatic ultrasound examination every 12 months to screen for hepatocellular carcinoma, as well as liver biopsy at baseline and at 1.5 and 3.5 years after randomization. The stage of histologic fibrosis was interpreted according to the Ishak score[13] by consensus face-to-face vote of the 10 study-site pathologists and a coordinating pathologist from the Armed Forces Institute of Pathology. All reported clinical outcomes had to meet predetermined criteria and be certified by majority vote of a rotating committee of three investigators.

Routine blood chemical studies and hematologic tests were performed in local clinical laboratories at each of the 10 clinical sites. The serum HCV RNA level and HCV genotype were determined in a single central laboratory at the University of Washington, Seattle; the HCV RNA level was determined by the Roche Cobas Monitor assay, and samples with negative test results according to this assay were retested with the more sensitive Roche Cobas Amplicor assay. HCV genotyping was performed by line-probe assay (Inno-LiPA, Innogenetics).

STATISTICAL ANALYSIS

Statistical analyses were performed at the data coordinating center with the use of SAS software, release 9.1. We estimated that 900 patients would need to be followed for 3.5 years[12] on the basis of a power of 90%, a two-sided significance level of 5%, annual estimated rates of progression of 6% in the control group and 3% in the treatment group, and an anticipated 10% loss to follow-up. After adjustments for nonadherence to the study protocol, we estimated the outcome rates would be 18.7% in the control group and 10.6% in the treatment group at the end of 3.5 years. The decision to include patients who had a relapse after the end of the lead-in phase resulted in 1050 patients who underwent randomization.

Baseline variables in the two treatment groups were compared with the use of chi-square tests, the t-test, or the Wilcoxon rank-sum test. The primary analysis of the primary outcome involved comparison of the survival curves with the use of the log-rank test (SAS Proc Lifetest) with patients stratified according to the presence of noncirrhotic fibrosis or of cirrhosis. Secondary analyses of the primary outcome included Cox proportional-hazards regression with patients stratified according to the presence of noncirrhotic fibrosis or of cirrhosis and according to clinical center and Kaplan–Meier estimates of the event rates 1400 days after randomization. Data were censored at the patient's last follow-up visit or at 1400 days (3.83 years) after randomization, whichever occurred first. The progress of the trial was reviewed every 6 months by a data and safety monitoring board. Three interim analyses for efficacy were planned with the use of O'Brien–Fleming boundaries (East, version 4, Cytel) when approximately 25%, 50%, and 75% of events had occurred. The data and safety monitoring board decided that the third interim analysis was not necessary. Data from patients who dropped out were censored at the time of withdrawal from the trial, and these patients were not considered to have reached an end point. Patients classified as having noncirrhotic fibrosis who did not undergo any follow-up biopsies and for whom no clinical outcome was recorded were not included in the analyses. All reported P values are two-sided. We performed a post hoc exploratory analysis to examine the heterogeneity of treatment effect according to the guidelines of the *Journal*.[17]

The study was designed by a steering committee composed of one representative from each of the participating institutions. Data were entered by the site coordinators into a central database

maintained by the New England Research Institutes, which also performed the statistical analyses. All investigators vouch for the accuracy and completeness of the reported findings. The study was approved by the ethics committee of each participating institution.

RESULTS

PATIENTS

We randomly assigned 1050 patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. Patients were enrolled in three cohorts consisting of 662 patients with no response or a partial response to lead-in therapy (63.0%); 151 patients who had a breakthrough or relapse and in whom HCV RNA became detectable again after week 20, during the lead-in phase of treatment (14.4%); and 237 "express" patients who were treated outside the study but did not have a sustained virologic response to treatment (22.6%).

The treatment and control groups were well matched with regard to clinical, biochemical, virologic, and histologic characteristics (Table 1). The mean age of the patients was 51 years; 71.0% were men; 71.6% were non-Hispanic whites, 8.0% were Hispanic whites, 18.2% were blacks, and 2.2% were Asian Americans or members of other racial or ethnic groups. Among 984 patients for whom the time of infection could be estimated, the mean duration of infection was 28 years. Serum alanine aminotransferase levels were elevated in 83.0% of the patients, and the mean alanine aminotransferase level was 2.1 times the upper limit of normal. The mean serum HCV RNA level at baseline was 6.4 $\log_{10}$ IU per milliliter. Approximately 40% of the patients in each group had cirrhosis, according to the liver biopsy (Ishak fibrosis score, 5 or 6), and the remainder had bridging hepatic fibrosis (Ishak fibrosis score, 3 or 4).

SERUM LEVELS OF ALANINE AMINOTRANSFERASE AND HCV RNA DURING TREATMENT

Serum alanine aminotransferase levels declined between baseline and 1.5 years by 0.45 times the upper limit of the normal range among treated patients, as compared with only 0.21 times the upper limit of normal among control patients, a difference of 0.24 times the upper limit of the normal range (95% confidence interval [CI], 0.09 to 0.39; P=0.002). At 3.5 years after baseline, the decline among treated patients was 0.47 times the

upper limit of the normal range, as compared with 0.19 times among control patients, a difference of 0.28 times the upper limit of the normal range (95% CI, 0.12 to 0.44; P<0.001). At the time of randomization, 17.0% of all patients had normal serum alanine aminotransferase levels; 3.5 years after randomization, 35.1% of treated patients and 22.6% of control patients had normal alanine aminotransferase levels (P<0.001).

Serum HCV RNA levels fell by 0.81 $\log_{10}$ IU per milliliter in the treatment group at 1.5 years, as compared with 0.07 $\log_{10}$ IU per milliliter in the control group, a difference of 0.74 $\log_{10}$ IU per milliliter (95% CI, 0.61 to 0.87; P<0.001). Similar changes were seen at 3.5 years: the decrease was 0.71 $\log_{10}$ IU per milliliter in the treatment group and 0.12 $\log_{10}$ IU per milliliter in the control group, a difference of 0.59 $\log_{10}$ IU per milliliter (95% CI, 0.45 to 0.72; P<0.001). A sustained virologic response occurred in 18 treated patients (3.5%) but in only 1 control patient (who was enrolled on the basis of an isolated positive sample at week 20 but in whom HCV RNA was actually undetectable at randomization).

CLINICAL AND HISTOLOGIC END POINTS

At 3.5 years after randomization, a primary clinical or histologic outcome had occurred in 157 patients in the treatment group and 157 patients in the control group (Table 2 and Fig. 2A). The Kaplan–Meier survival estimates of the proportion of patients with an outcome at 1400 days were 34.1% (95% CI, 29.8 to 38.5) in the treatment group and 33.8% (95% CI, 29.4 to 38.1) in the control group; the hazard ratio was 1.01 (95% CI, 0.81 to 1.27; P=0.90). There was no significant interaction between treatment group and the presence of noncirrhotic fibrosis or of cirrhosis (P=0.66). Among patients with cirrhosis, the Kaplan–Meier estimates of the proportion of patients with an outcome at 1400 days were 30.2% for treated patients and 31.2% for control patients (hazard ratio, 0.97; 95% CI, 0.68 to 1.38); among those with noncirrhotic fibrosis, the estimates were 36.7% for treated patients and 35.5% for control patients (hazard ratio, 1.05; 95% CI, 0.78 to 1.39).

The percentage of patients with a clinical outcome, as assessed by Kaplan–Meier survival analysis, was similar in treated and control patients with cirrhosis (Fig. 2B). Among patients with noncirrhotic fibrosis, clinical outcomes were more frequent in treated patients than in control pa-

Table 1. Baseline Demographic, Biochemical, and Histologic Features of the Patients.*

Variable	Treatment Group (N=517)	Control Group (N=533)	P Value†
Cohort (% of patients)‡			0.90
Lead-in (no response)	30.2	30.8	
Lead-in (partial response)	33.5	31.7	
Lead-in (breakthrough or relapse)	13.7	15.0	
Express	22.6	22.5	
Age (yr)	51.1±7.3	50.1±7.0	0.02
Duration of exposure to HCV (yr)	28.8±7.9	27.4±8.0	0.004
Female sex (% of patients)	30.0	28.1	0.51
Race or ethnic group (% of patients)§			0.70
White	72.0	71.3	
Black	18.8	17.6	
Hispanic	7.5	8.4	
Other	1.7	2.6	
Body-mass index¶	29.7±5.3	30.0±5.6	0.44
Diabetes (% of patients)	24.4	24.0	0.89
Lifetime alcohol consumption (median no. of drinks)	7229	7537	0.43
HCV genotype — % of patients			0.02‖
1	95.2	91.6	
2	1.2	2.8	
3	2.1	4.1	
4 or 6	1.6	1.5	
Baseline serum HCV RNA (log_{10} IU/ml)	6.42±0.54	6.44±0.51	0.62
Serum alanine aminotransferase (U/liter)	104±74	110±80	0.24
Ratio of the patient's alanine aminotransferase level to the upper limit of normal	2.07±1.53	2.18±1.70	0.27
Total serum bilirubin (mg/dl)**	0.79±0.41	0.78±0.39	0.75
Serum albumin (g/dl)	3.88±0.38	3.86±0.40	0.44
Prothrombin time (INR)	1.04±0.12	1.04±0.11	0.99
Cirrhosis on biopsy (% of patients)	40.2	41.3	0.73
Ishak fibrosis score††	4.08±1.25	4.13±1.28	0.55
Ishak inflammation score‡‡	7.55±2.10	7.54±2.02	0.91
Mean length of biopsy specimen — cm	1.8±1.0	1.8±0.8	0.24
Esophageal varices (% of patients)	24.3	27.0	0.32

* Percentages may not total 100 because of rounding. Plus–minus values are means ±SD. HCV denotes hepatitis C virus, and INR international normalized ratio.
† The P values were determined with the use of the t-test or the chi-square test, except for the P value for lifetime alcohol consumption, which was determined with the use of the Wilcoxon rank-sum test.
‡ The 813 lead-in patients were classified as having had no response to lead-in therapy if they had a decrease in the serum HCV RNA level of less than 1 log_{10} IU per milliliter from baseline to lead-in week 20, as having had a partial response if they had a decrease in HCV RNA of at least 1 log_{10} IU per milliliter from baseline to week 20 and detectable HCV RNA at week 20, and as having had a breakthrough or relapse if they had undetectable HCV RNA at week 20 and then had detectable HCV RNA either during or after treatment. The 237 "express" patients underwent randomization after having received treatment with peginterferon plus ribavirin outside the study but without having had a sustained virologic response.
§ Race or ethnic group was self-reported.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ The P value is given for the comparison of the frequency of genotype 1 with the frequencies of genotypes 2, 3, and 4.
** To convert values for bilirubin to micromoles per liter, multiply by 17.1.
†† The Ishak fibrosis score measures structural changes associated with fibrosis and cirrhosis and ranges from 0 to 6, where 0 indicates no fibrosis and 6 indicates cirrhosis.
‡‡ The Ishak inflammation score measures several components of necroinflammatory changes in the liver-biopsy specimen and ranges from 0 to 18, with 18 being the worst score.[18]

Table 2. First Primary Outcome in Treated and Control Patients with Noncirrhotic Fibrosis or Cirrhosis at Baseline.*

Outcome	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
Death — no.	8	2	5	6	13	8
Hepatocellular carcinoma — no.	8	5	4	10	12	15
Ascites — no.	6	0	7	8	13	8
Hepatic encephalopathy — no.	1	4	4	3	5	7
Variceal hemorrhage — no.	1	2	2	4	3	6
Spontaneous bacterial peritonitis — no.	0	0	0	1	0	1
Child–Turcotte–Pugh score ≥7 on 2 consecutive visits — no.†	10	10	37	32	47	42
Progression of fibrosis — no.	64	70	NA	NA	64	70
Patients with primary outcome — no. (%)	98 (31.7)	93 (29.7)	59 (28.4)	64 (29.1)	157 (30.4)	157 (29.5)
Kaplan–Meier estimate of rate — %	36.7	35.5	30.2	31.2	34.1	33.8

* NA denotes not applicable.
† The Child–Turcotte–Pugh score assesses the presence and degree of hepatic decompensation, with scores for hypoalbuminemia, hyperbilirubinemia, hypoprothrombinemia, ascites, and hepatic encephalopathy. The score ranges from 5 to 15, with 15 being the worst. Patients with scores of 7 or less are classified as having class A liver disease, those with scores of 8 to 11 as having class B disease, and those with scores of 12 or more as having class C disease. Class A disease is compensated, and class B and class C disease are associated with worsening degrees of hepatic decompensation.[16]

tients (11.9% vs. 8.3%), but the difference was not significant (P=0.13).

The most common clinical outcome was an increase of 2 or more points in the Child–Turcotte–Pugh score (documented on two consecutive visits), which occurred in 109 patients (10.4%). Other hepatic-decompensation outcomes included ascites in 59 patients (5.6%), hepatic encephalopathy in 37 patients (3.5%), variceal hemorrhage in 16 patients (1.5%), and spontaneous bacterial peritonitis in 6 patients (0.6%). Hepatocellular carcinoma occurred in 29 patients (2.8%), 13 in the noncirrhotic-fibrosis stratum (2.1%) and 16 in the cirrhosis stratum (3.7%). Fifty-three patients (5.0%) died, 31 in the treatment group (15 of liver-related causes) and 22 in the control group (12 of liver-related causes) (P=0.18). At 3.8 years, the overall death rate was 6.6% among patients who received peginterferon and 4.6% among control patients (P=0.18). There was a significant difference in mortality between the treatment and control groups among patients with noncirrhotic fibrosis (5.0% and 1.9%, respectively; P=0.04), but not among patients with cirrhosis (9.1% and 8.4%, respectively; P=0.93).

Among patients with noncirrhotic fibrosis, 86.4% had either undergone a biopsy or had a clinical outcome by the 1.5-year time point, and 80.0% had either undergone a biopsy or had a clinical outcome by the 3.5-year time point. The rate of progression to cirrhosis (defined as an increase of at least 2 points in the Ishak fibrosis score) among patients with noncirrhotic fibrosis was similar in the treatment and control groups (28.2% [95% CI, 22.8 to 33.9] and 31.9% [95% CI, 26.0 to 37.8], respectively; P=0.46). Among patients with noncirrhotic fibrosis, the mean Ishak fibrosis score increased by 0.38 and 0.42 points at year 3.5 in the treatment and control groups, respectively, a difference of 0.04 (95% CI, −0.27 to 0.20; P=0.77), despite a significant mean reduction in the necroinflammatory score in the treatment group as compared with the control group (−1.03 vs. −0.03; difference, −1.00; 95% CI, −1.46 to −0.55; P<0.001). Among patients with cirrhosis, a similar, significant decrease in the necroinflammatory score occurred in treated patients as compared with control patients (−1.38 vs. −0.33; difference, −1.05; 95% CI, −1.66 to −0.44; P<0.001). In a post hoc exploratory analysis, we did not observe heterogeneity of treatment effect according to baseline characteristics (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Figure 2. Kaplan–Meier Analysis of Time to the Primary Outcome and the First Clinical Outcome.

Panel A shows the time to the first primary outcome (death, hepatic decompensation, hepatocellular carcinoma, or histologic progression) according to group assignment (treatment or control). The large steps in the plot reflect liver biopsies performed for the study. Panel B shows the time to the first clinical outcome (death, hepatic decompensation, or hepatocellular carcinoma) according to group assignment and with patients stratified according to the presence or absence of cirrhosis.

ADVERSE EVENTS AND DRUG DISCONTINUATION

In the treatment group, 3991 adverse events occurred among 486 patients, as compared with 3129 adverse events among 492 patients in the control group; 330 patients had at least one serious adverse event (Table 3). A higher proportion of patients in the treatment group than in the control group had at least one serious adverse event (38.6% [95% CI, 33.8 to 43.3] vs. 31.8% [95% CI, 27.6 to 36.1] by Kaplan–Meier analysis), but this difference was not significant (P=0.07). Infectious complications, predominantly bacterial infections, were the most frequent adverse events.

During the trial, 157 treated patients discontinued therapy, including 43 who dropped out of the study and 114 who stopped therapy but agreed

to follow-up monitoring. The reasons for stopping therapy included anemia, neutropenia, or thrombocytopenia (25 patients); depression (22 patients); other adverse events (65 patients); and patient refusal (72 patients). Some patients had more than one reason for discontinuing treatment. Dose modifications for adverse events were frequent; by year 3.5, only 58.9% of patients who were still in the study and had not had a clinical outcome were receiving the full 90-μg prescribed weekly dose of peginterferon (Fig. 3). Nine patients assigned to the control group sought and received antiviral therapy with peginterferon, with or without ribavirin, outside the study for some period during the randomized phase.

DISCUSSION

The HALT-C trial assessed whether patients with chronic hepatitis C who had not had a sustained virologic response after optimal therapy with peginterferon and ribavirin would benefit from peginterferon maintenance therapy at a lower and perhaps better-tolerated dose.[12] The outcome measure in most trials of antiviral therapy for chronic hepatitis C has been a sustained virologic response (i.e., undetectable HCV RNA in the serum 6 months after the cessation of therapy[5]), which has been shown to be associated with long-term improvement in disease.[6] In this trial, among patients who had not had a sustained virologic response after previous therapy, the criteria for efficacy of therapy were the prevention of progression to cirrhosis (among patients with noncirrhotic fibrosis at baseline) and the prevention of clinical progression of disease. To test the efficacy of long-term maintenance therapy, we randomly assigned 1050 patients with advanced fibrosis who had not had a response to peginterferon and ribavirin to several years of treatment or no treatment.

When the trial began, peginterferon was not approved by the FDA, and many patients who had been treated with standard interferon had not received concomitant ribavirin. Therefore, to ensure that we were assessing maintenance therapy in a cohort of patients who had not had a sustained virologic response to optimal therapy, we required a lead-in phase of retreatment with a regimen of peginterferon and ribavirin that had been shown to be superior to standard interferon with ribavirin.[19] This lead-in phase

provided not only a well-pedigreed cohort of uniformly documented patients who had not had a response to treatment but also a thoroughly evaluated group of patients highly motivated for such a demanding, long-term trial.

Maintenance peginterferon therapy was associated with significant decreases in serum HCV RNA levels, serum alanine aminotransferase levels, and histologic necroinflammatory scores. Nevertheless, therapy was not associated with a reduction in clinical outcomes or in the progression of fibrosis. Progression of liver disease (the primary study outcome) occurred in 34.1% of the treatment group and 33.8% of the control group. Among patients with bridging fibrosis at baseline, cirrhosis developed by year 3.5 in similar percentages of treated and control patients (28.2% and 31.9%, respectively). The high rate of clinical outcomes among patients with noncirrhotic fibrosis at baseline was not predicted and is worthy of note. A possible explanation for this finding is that liver biopsy underestimates the presence of cirrhosis, as evidenced by the presence of varices in some patients classified as having noncirrhotic fibrosis. Nonetheless, it is clear that patients with chronic hepatitis C and bridging fibrosis detected on biopsy appear to be at substantial risk for clinical outcomes, including hepatocellular carcinoma. The finding of excess deaths at 3.5 years among treated patients with noncirrhotic fibrosis at baseline was unexpected and is not well explained by other findings (i.e., changes in laboratory-test results and the rate of development of cirrhosis). All patients in this study continue to be followed prospectively, and it is important to assess whether this difference in mortality between treated patients and control patients will persist.

Our findings contradict the results of several previous studies, but those studies either were not prospective, randomized trials or relied on end points other than clinical outcomes.[9-11] Several reports have suggested that interferon-based therapy in patients with chronic hepatitis C, even with a course as brief as 6 months and even with no sustained virologic response, can reduce the frequency of hepatocellular carcinoma; however, these nonrandomized studies were based on retrospective analyses.[10,11] In contrast, a recent small study involving 102 patients with hepatitis C and cirrhosis who had not had a response to previous therapy with peginterferon and ribavirin and

Table 3. Serious Adverse Events in Treated and Control Patients with Noncirrhotic Fibrosis or Cirrhosis at Baseline.*

Event	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
	number of patients					
Any serious adverse event†	96	83	79	72	175	155
Blood and lymphatic	1	3	6	2	7	5
Anemia	0	3	3	2	3	5
Thrombocytopenia or pancytopenia	1	0	3	0	4	0
Cardiovascular and circulatory	12	10	6	9	18	19
Atherosclerotic disease	9	5	7	4	16	9
Arrhythmia	2	5	1	3	3	8
Other cardiovascular or circulatory event	2	1	2	4	4	5
Digestive system	12	13	6	13	18	26
Nonvariceal gastrointestinal bleeding	2	3	2	6	4	9
Hernia or intestinal obstruction	4	1	1	2	5	3
Other digestive system event	6	10	5	5	11	15
Endocrine and metabolic	7	5	2	5	9	10
Electrolyte, mineral, or water imbalance	4	2	2	5	6	7
Diabetes and its complications	1	1	0	1	1	2
Thyroid disease	2	2	0	0	2	2
Genitourinary and reproductive	8	4	4	6	12	10
Renal or urinary diseases	8	5	3	3	11	8
Gynecologic, menstrual, or sexual disorders	1	1	1	4	2	5
Hepatobiliary	14	6	6	12	20	18
Gallbladder disease	9	6	4	9	13	15
Other pancreatic or biliary disorders	5	1	2	4	7	5
Liver-disease events other than primary or secondary outcomes	1	0	0	1	1	1
Infection and infectious diseases	18	17	26	27	44	44
Mucocutaneous	2	6	7	10	9	16
Respiratory tract	9	2	10	9	19	11
Systemic	3	1	7	3	10	4
Other infections or infectious-disease events	5	10	10	9	15	19
Injury or poisoning	3	5	5	6	8	11
Injury	3	4	1	6	4	10
Drug reaction	0	2	4	0	4	2
Liver-biopsy complication	4	6	4	5	8	11
Musculoskeletal	16	14	11	10	27	24
Musculoskeletal surgery	18	13	7	8	25	21
Arthritis or back pain	5	3	4	3	9	6
Neoplasm	6	8	3	3	9	11
Malignant	5	7	3	3	8	10
Benign	1	3	0	0	1	3
Neurologic	1	5	5	1	6	6
Cerebral aneurysm, infarct, or stroke	1	4	2	0	3	4
Other neurologic event	0	1	3	1	3	2
Psychiatric	8	4	5	4	13	8
Affective disorders or delirium	7	2	1	2	8	4
Suicidal ideation or attempt	0	2	4	2	4	4
Substance abuse	2	1	1	0	3	1

Table 3. (Continued.)

Event	Noncirrhotic Fibrosis		Cirrhosis		Total	
	Treatment Group (N=309)	Control Group (N=313)	Treatment Group (N=208)	Control Group (N=220)	Treatment Group (N=517)	Control Group (N=533)
	number of patients					
Respiratory	1	4	1	3	2	7
Benign skin and nail disorders	0	1	0	1	0	2
Signs or symptoms‡	16	13	12	13	28	26
Cardiovascular	5	3	5	3	10	6
Hepatobiliary	6	3	2	3	8	6
Neurologic	5	2	2	4	7	6
Digestive	3	3	1	0	4	3
Other	1	4	3	4	4	8

* Patients are counted only once in each row of the table but may appear in more than one row.
† The percentage of patients with at least one serious adverse event, as estimated by Kaplan–Meier analysis, was 38.6% (95% CI, 33.8 to 43.3) in the treatment group and 31.8% (95% CI, 27.6 to 36.1) in the control group. The hazard ratio, adjusted for the presence or absence of cirrhosis, was 1.22 (95% CI, 0.99 to 1.52; P=0.07 by Cox regression).
‡ These clinical signs and symptoms are not associated with a specific diagnosis but are still classified as a serious adverse event. After serious adverse events related to death or other study-related clinical outcomes were excluded, 284 serious adverse events were recorded among 175 patients in the treatment group and 283 serious adverse events were recorded among 155 patients in the control group.

who were randomly assigned to receive either standard interferon or no treatment for 24 months yielded results similar to those of our trial.[20]

Several reports have suggested that interferon-based therapy in patients with chronic hepatitis C may reduce the risk of hepatocellular carcinoma among those patients with a sustained virologic response.[10,11] The HALT-C trial was a large-scale, randomized, controlled assessment of the effect of interferon on the incidence of hepatocellular carcinoma, and our findings show definitively that, even when maintained for several years, peginterferon therapy does not reduce the incidence of hepatocellular carcinoma in patients with advanced fibrosis and persistent viremia.

In the HALT-C trial, we used half the recommended dose of peginterferon alfa-2a (90 μg rather than 180 μg per week) because of concern about adverse events that may be associated with full-dose, long-term peginterferon therapy. Indeed, in this study, which was conducted among highly motivated patients, the starting peginterferon dose was maintained for the full 3.5 years in only 59% of patients. Higher doses of peginterferon might have been more effective in suppressing HCV replication and might have prevented disease progression. In addition, patients in the HALT-C trial did not receive long-term

ribavirin with peginterferon, which might have been more potent than monotherapy in suppressing HCV RNA levels and improving clinical outcomes; however, the preliminary data suggesting that long-term antiviral therapy improves histologic results were generated in trials of interferon monotherapy. Furthermore, the rate of adverse events associated with maintenance therapy would almost certainly have been higher had ribavirin or full-dose peginterferon been included in the maintenance regimen.

Shiffman et al.[9] found that among patients who did not have a viral response to interferon therapy but who had a histologic response after 6 months, extended treatment suppressed HCV RNA levels, with reductions in necroinflammation and fibrosis. Unfortunately, the degree of virologic suppression in the HALT-C trial did not result in a diminished rate of disease progression, although theoretically, maintenance therapy that is associated with more marked suppression of serum HCV RNA levels might be more effective. We conclude that long-term maintenance therapy with half-dose peginterferon is ineffective in preventing clinical and histologic disease progression and is not indicated in patients with hepatitis C–associated advanced fibrosis, with or without cirrhosis, who have not had a response to a

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Figure 3. Changes in Dose or Discontinuation of Peginterferon among Patients in the Treatment Group.

The figure shows the proportion of patients who had a clinical outcome and stopped treatment, received a full dose of peginterferon (90 μg per week), decreased their dose of peginterferon (to either 45 to 89 μg or 22 to 44 μg per week), withdrew from the study, or stopped treatment but continued to be followed for assessment of outcomes.

standard course of peginterferon and ribavirin therapy.

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