

CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Effect of HCV RNA Suppression During Peginterferon Alfa-2a Maintenance Therapy on Clinical Outcomes in the HALT-C Trial

MITCHELL L. SHIFFMAN,* CHIHIRO MORISHIMA,† JULES L. DIENSTAG,§ KAREN L. LINDSAY,|| JOHN C. HOEFS,¶ WILLIAM M. LEE,# ELIZABETH C. WRIGHT,** DEEPA NAISHADHAM,†† GREGORY T. EVERSON,§§ ANNA S. LOK,||| ADRIAN M. DI BISCEGLIE,¶¶ HERBERT L. BONKOVSKY,###,***,††† MARC G. GHANY,§§§ and the HALT-C Trial Group

*Hepatology Section, Virginia Commonwealth University Medical Center, Richmond, Virginia; †Virology Division, Department of Laboratory Medicine, University of Washington, Seattle, Washington; ‡Gastrointestinal Unit (Medical Services), Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts; §Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, California; ¶Division of Gastroenterology, University of California-Irvine, Irvine, California; #Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, Texas; **Office of the director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; ††New England Research Institutes, Watertown, Massachusetts; §§Section of Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, Colorado; |||Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, Michigan; ¶¶Division of Gastroenterology and Hepatology, St. Louis University School of Medicine, St. Louis, Missouri; ###Department of Medicine, ***Department of Molecular and Structural Biology, and †††The Liver-Biliary-Pancreatic Center, University of Connecticut Health Center, Farmington, Connecticut; and §§§Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

This article has an accompanying continuing medical education activity on [page 2159](#). Learning Objective: Upon completion of reading this article, successful learners will be able to determine the role of peginterferon alfa-2b maintenance therapy on the management of patients with chronic HCV and advanced fibrosis.

BACKGROUND & AIMS: The Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial demonstrated that low-dose peginterferon maintenance therapy was ineffective in preventing clinical outcomes in patients with chronic hepatitis C, advanced fibrosis, and failure to achieve a sustained virologic response during lead-in phase treatment with standard dose peginterferon/ribavirin. This analysis was performed to determine whether suppressing HCV RNA during the trial was associated with a reduction in clinical outcomes. **METHODS:** Seven hundred sixty-four patients treated during the lead-in phase of HALT-C trial were randomized to either peginterferon alfa-2a (90 μ g/week) maintenance therapy or no treatment (control) for 3.5 years. Clinical outcomes included an increase in Child-Turcotte-Pugh score, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatocellular carcinoma, and mortality. **RESULTS:** During the lead-in, ≥ 4 -log₁₀ decline in serum HCV RNA occurred in 178 patients; 82% of whom lost detectable HCV RNA and later broke through or relapsed. These patients had significantly ($P = .003$) fewer clinical outcomes whether randomized to maintenance therapy or control. Following randomization, serum HCV RNA increased significantly in all 90 control patients and in 58 of 88 receiving maintenance therapy. Only 30 patients had persistent suppression of HCV RNA by ≥ 4 log₁₀ during maintenance therapy. No significant reduction in clinical out-

comes was observed in these patients. **CONCLUSIONS:** **Viral suppression by ≥ 4 log₁₀ with full-dose peginterferon/ribavirin is associated with a significant reduction in clinical outcomes. Continuing low-dose peginterferon maintenance therapy, even in patients with persistent viral suppression, does not lead to a further decline in clinical outcomes.**

Peginterferon and ribavirin therapy results in a sustained virologic response (SVR) in approximately 50% of patients.^{1,2} Unfortunately, patients with advanced fibrosis or cirrhosis respond less well to this treatment. Because these patients are at increased risk for hepatic decompensation, hepatocellular carcinoma (HCC), and mortality, new approaches for managing chronic hepatitis C are needed.^{3,4} Although liver transplantation is an option, disease recurrence is universal.^{5,6}

Patients with SVR following treatment of hepatitis C have an improvement in liver histology and a reduction

Abbreviations used in this paper: CO-PILOT, Colchicine Versus Peginterferon Long-term Therapy; CTP, Child-Turcotte-Pugh; EPIC, Evaluation of Peginterferon in Control of Hepatitis C Cirrhosis; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

© 2009 by the AGA Institute

0016-5085/09/\$36.00

doi:10.1053/j.gastro.2009.08.067

in liver-related mortality.^{4,7-9} Some studies have suggested that even nonresponders to interferon treatment have a reduced risk of HCC and mortality.^{10,11} Moreover, patients with chronic hepatitis C virus (HCV) who have a decline in serum HCV RNA during interferon therapy achieve histologic improvement, and these improvements can be maintained by continuing treatment.¹² These collective observations led to the hypothesis that continuing interferon long-term as maintenance therapy could reduce the risk of hepatic decompensation, HCC, and mortality.

The Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial was a randomized, controlled study designed to determine whether low-dose peginterferon alfa-2a maintenance therapy (90 $\mu\text{g}/\text{week}$) over 3.5 years could reduce hepatic decompensation, HCC, and mortality in patients with bridging fibrosis or cirrhosis who failed to achieve an SVR following peginterferon and ribavirin treatment.¹³ The primary results of this trial demonstrated that peginterferon maintenance therapy provided no overall benefit.¹⁴ However, it remains unclear whether patients who achieved profound viral suppression during maintenance therapy had a reduction in outcomes. This secondary analysis of data from the HALT-C trial was therefore performed to determine whether viral suppression with standard dose peginterferon and ribavirin followed by low-dose peginterferon maintenance therapy benefited patients with chronic hepatitis C and advanced fibrosis or cirrhosis.

Patients and Methods

Patients and Study Design

The design of the HALT-C trial has been described previously.¹³ Briefly, 1050 subjects with bridging fibrosis or cirrhosis (Ishak fibrosis score, 3–6) who were nonresponders to prior treatment with interferon (with or without ribavirin) were re-treated with standard dose peginterferon alfa-2a and ribavirin. Subjects with detectable HCV RNA at week 20 were defined as nonresponders and randomized to receive either 90 $\mu\text{g}/\text{week}$ of peginterferon alfa-2a as maintenance therapy or to stop treatment and be followed as the control group. Subjects with undetectable HCV RNA at treatment week 20 received up to 48 weeks of peginterferon and ribavirin. The SVR rate achieved in this population (18%) was previously reported.¹⁵ Patients in whom virologic breakthrough occurred after week 20 or in whom relapse occurred after 48 weeks of treatment were offered entry into the HALT-C trial and randomly assigned to receive maintenance therapy or no treatment. Both nonresponders and breakthrough/relapsers were followed for 3.5 years after randomization. The current analysis was restricted to 764 of the 813 patients treated during the lead-in phase and who entered the randomized HALT-C trial. The 49 excluded patients either had no follow-up after randomiza-

tion, refused to remain on peginterferon if randomized to maintenance therapy, or were treated with peginterferon outside the trial despite being randomized to the control group. The 237 patients who entered the randomized HALT-C trial after receiving peginterferon and ribavirin treatment outside the formal HALT-C trial lead-in phase (express patients) were also excluded because their quantitative HCV RNA response to treatment had not been assessed in the HALT-C virology core laboratory. Clinical and other laboratory data were collected from all subjects according to standard protocol-defined procedures.¹³ Institutional review boards at all participating institutions approved the study protocol and all amendments. Written informed consent was obtained from all subjects prior to treatment.

Virologic Testing

Serum samples were obtained from all subjects at regular intervals, frozen at -70°C at each clinical site, and shipped at periodic intervals on dry ice to the virology core laboratory. HCV RNA was measured with both the quantitative Roche COBAS Amplicor HCV Monitor Test, v. 2.0 assay (lower limit of detection, 600 IU/mL; Roche Molecular Systems, Branchburg, NJ) and, if negative, by the Roche COBAS Amplicor HCV Test, v. 2.0 assay (lower limit of detection, 100 IU/mL) as described previously.¹⁶ HCV genotypes were determined with the INNO-LiPA HCV II kit (Siemens Medical Solutions Diagnostics, Tarrytown, NY).

For this retrospective analysis, patients were classified into 3 groups according to the decline from pretreatment baseline in HCV RNA levels during the lead-in phase and after randomization: $<2\text{-log}_{10}$ decline, 2 to $<4\text{-log}_{10}$, and $\geq 4\text{-log}_{10}$ decline in HCV RNA. The baseline \log_{10} HCV RNA level was the mean of the screening and pretreatment \log_{10} HCV RNA values. The \log_{10} HCV RNA level during maintenance therapy was the mean of values obtained at months 6, 12, 18, 24, 30, and 36 after randomization. Patients were also grouped according to their mean serum HCV RNA level after randomization as follows: $\geq 100,000$ IU/mL, $<100,000\text{--}1000$ IU/mL, and <1000 IU/mL. Patients who were HCV RNA negative by Roche Amplicor Monitor but positive by the Roche COBAS Amplicor HCV assay were assigned a value of \log_{10} 2.78 (600 IU/mL), and patients who were negative by both assays were assigned a value of \log_{10} 2.00.

Liver Histology

All patients underwent liver biopsy within 12 months prior to initiating peginterferon and ribavirin treatment in the lead-in phase and at 18 and 42 months after randomization. All biopsy specimens were reviewed by a team of 11 pathologists representing each of the clinical centers and a central lead pathologist. Each biopsy specimen was assigned a consensus Ishak inflammatory and fibrosis score at group review sessions.¹⁷

Definition of Outcomes

Protocol-defined clinical outcomes included an increase in the Child–Turcotte–Pugh (CTP) score to ≥ 7 points on 2 consecutive study visits 3 months apart; development of ascites, hepatic encephalopathy, variceal bleeding, or spontaneous bacterial peritonitis; the occurrence of HCC; or death from any cause. For patients with bridging fibrosis (Ishak fibrosis scores of 3 or 4) at study entry, a histologic end point, an increase by ≥ 2 points in the Ishak fibrosis score at either of the 2 follow-up biopsies (18 or 42 months after randomization) was also a primary outcome.

Statistical Analyses

Analyses were performed with SAS (Statistical Analysis Software, Cary, NC) version 9.1. Baseline variables in the 2 treatment groups were compared with χ^2 tests or *t* tests. Mixed models were used to evaluate the changes in HCV RNA over time. Kaplan–Meier estimators were used to estimate clinical outcomes at 1400 days (3.83 years) after randomization and the rate of a ≥ 2 -point increase in Ishak fibrosis score. Cox proportional hazards regression analyses were performed to test the effects of lead-in treatment and maintenance treatment on clinical outcomes. Complementary log-log regression analyses were performed to assess the effect of these treatments on the time to first 2-point increase in Ishak fibrosis score. Analyses of clinical outcomes and changes in serum HCV RNA level after randomization were restricted to patients who either had an outcome or were followed for at least 36 months after randomization.

Results

Patient Groups

Table 1 summarizes the clinical, biochemical, virologic, and histologic characteristics of the HALT-C trial patients included in this analysis grouped by randomization status to the maintenance therapy arm or control arm. All patients received 24 weeks of peginterferon and ribavirin during the lead-in phase, prior to randomization; 618 had detectable HCV RNA in serum at week 20 and were classified as nonresponders, and 146 had undetectable HCV RNA in serum at week 20 and entered the HALT-C trial only after breakthrough developed ($n = 30$) or they relapsed ($n = 116$). The mean duration of peginterferon and ribavirin in the breakthrough/relapse group was 48 weeks. The features of these 764 patients were not significantly different from those of the entire HALT-C trial cohort.¹⁴

Figure 1 illustrates mean serum HCV RNA levels during the lead-in phase and after randomization throughout the HALT-C trial for patients with nonresponse or breakthrough/relapse. Of the 618 nonresponders who entered the trial, 261 were still being followed in the maintenance group and 253 in the control group by

Table 1. Clinical Characteristics of the Patient Population

	Control	Maintenance	P value
No.	386	378	
Age, y	49.5 \pm 7.3	50.8 \pm 7.3	.01
Male (%)	70	72	.65
Race (% white)	70	72	.49
Baseline ALT (IU/L)	116 \pm 87	107 \pm 78	.14
Baseline WBC (cells/mm ³)	5.7 \pm 1.8	5.9 \pm 1.9	.19
Baseline platelet count (cells/mm ³)	167 \pm 68	166 \pm 62	.87
Genotype 1 (%)	92	95	.09
Baseline log ₁₀ HCV RNA (IU/mL)	6.44 \pm 0.48	6.46 \pm 0.45	.45
Cirrhosis (%)	40	40	.95
Virologic response during lead-in phase: (%)			
Nonresponse	80	82	.55
Breakthrough or relapse	20	18	

NOTE. Values are given as means \pm standard deviation or as the percentage of patients in each group.

ALT, alanine aminotransferase; WBC, white blood cells.

month 42. Nonresponders had a mean decline in serum HCV RNA of 1.5-log₁₀ IU/mL by the end of the 20-week lead-in phase (Figure 1A). In patients randomized to stop therapy, the mean serum HCV RNA level returned to the pretreatment baseline. Patients randomized to remain on peginterferon maintenance therapy had a significant reduction in serum HCV RNA levels compared with the control group ($P < .0001$); however, this reduction was only 0.56-log₁₀ IU/mL (95% confidence interval [CI]: 0.50–0.63) below the pretreatment baseline. Patients with breakthrough/relapse ($n = 146$) had undetectable HCV RNA in serum by week 20 in the lead-in phase and remained on peginterferon and ribavirin until either breakthrough viremia developed before week 48 or HCV RNA reappeared in serum after completing treatment. These patients were randomized at variable times after the initiation of treatment depending on the time of HCV RNA recurrence. Forty-two months after randomization, 73 patients remained in the control group and 59 patients in the maintenance therapy group. With breakthrough or relapse, the level of serum HCV RNA increased to a mean of log₁₀ 6.0 IU/mL at the time of randomization. Breakthrough/relapse patients randomized to stop treatment had a further increase in serum HCV RNA back toward pretreatment baseline levels (Figure 1B). In contrast, patients with breakthrough or relapse who initiated peginterferon maintenance therapy had a decline in mean serum HCV RNA level that averaged 2.5 log₁₀ (95% CI: 2.21–2.78) below the pretreatment baseline throughout the maintenance phase. This decline was significantly different than the change in serum HCV RNA level in the breakthrough/relapse patients randomized to stop treatment ($P < .0001$). During the 3.5 years of maintenance therapy, the mean serum HCV RNA level drifted up gradually relative to the

Figure 1. Change in serum HCV RNA level over time. During the lead-in phase (*shaded area*), patients were treated with peginterferon alfa-2a 180 $\mu\text{g}/\text{mL}$ and ribavirin. (A) Nonresponder group: patients were serum HCV RNA-positive at week 20. At treatment week 24 (month 0), these patients were randomized to either peginterferon alfa-2a 90 $\mu\text{g}/\text{mL}$ maintenance therapy without ribavirin or to the no treatment control group. (B) Breakthrough/relapse group: Patients had undetectable serum HCV RNA at week 20. These patients received up to 48 weeks of treatment and were randomized (month 0) to either peginterferon alfa-2a 90 $\mu\text{g}/\text{mL}$ maintenance therapy or to the no treatment control group after breakthrough or relapse occurred. For simplicity, and for comparison with the nonresponder group, the time listed on the x-axis corresponds to months after randomization. The wider lead-in phase (*shaded area*) along the x-axis in the breakthrough/relapse group reflects the longer duration of treatment these patients received prior to randomization.

pretreatment baseline from a nadir of $\log_{10} -2.9$ to -2.2 ($P = .0001$).

Change in HCV RNA During the Lead-In Phase and Impact on Outcomes

Figure 2 illustrates the distribution of virologic responses observed during the lead-in phase. Compared with their pretreatment baseline levels, 56% of patients had a $<2\text{-log}_{10}$ decline in serum HCV RNA with full-dose peginterferon and ribavirin; 21% had a 2 to $<4\text{-log}_{10}$ decline, and 23% had a $\geq 4\text{-log}_{10}$ reduction. Among patients with a $\geq 4\text{-log}_{10}$ decline in serum HCV RNA, 82% were in the breakthrough/relapse group and had undetectable HCV RNA at week 20.

Figure 3 illustrates clinical outcomes after randomization according to the decline in serum HCV RNA during the lead-in phase. A significant ($P = .003$) reduction in clinical outcomes was observed with increasing degrees of viral suppression (Figure 3A). Clinical outcomes developed in 21% of patients with $<2\text{-log}_{10}$ decline in serum HCV RNA during the lead-in phase (95% CI: 17%–24%); 18% (95% CI: 12%–24%) of patients with a 2 to $<4\text{-log}_{10}$ decline, and 8% (95% CI: 4%–12%) of patients with $\geq 4\text{-log}_{10}$ decline. Clinical outcomes also developed in 8% of the 146 patients with undetectable HCV RNA at the end of the lead-in phase (a subset of the 178 patients with $\geq 4\text{-log}$ decline in HCV RNA). This decline in the 3.5-year incidence of clinical outcomes was not significantly different between the control and maintenance therapy groups ($P = .56$). No effect of viral suppression during the lead-in phase was observed on histologic outcome

(Figure 3B). Overall, a ≥ 2 -point increase in fibrosis score on follow-up liver biopsy was observed in 24% and 33% of control and maintenance patients, respectively, regardless of the degree of viral suppression ($P = .38$). In patients with undetectable HCV RNA at the end of the lead-in phase, fibrosis progression was also observed in 23% and 28% of control and maintenance patients, respectively ($P = .88$).

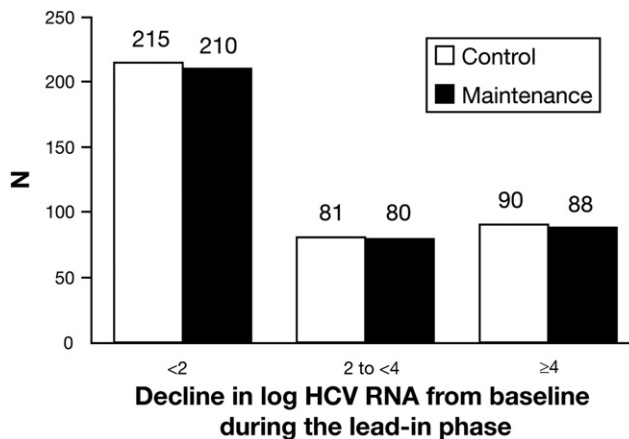


Figure 2. Number of patients who achieved serum HCV RNA suppression to varying degrees during the lead-in phase. Among patients with a $\geq 4\text{-log}_{10}$ decline in serum HCV RNA at the end of the lead-in phase, 77 of 90 (86%) who entered the control arm and 69 of 88 (78%) randomized to maintenance peginterferon had undetectable serum HCV RNA at week 20 and received up to 48 weeks of treatment. Numbers at the top of each bar represent the number of patients in each group.

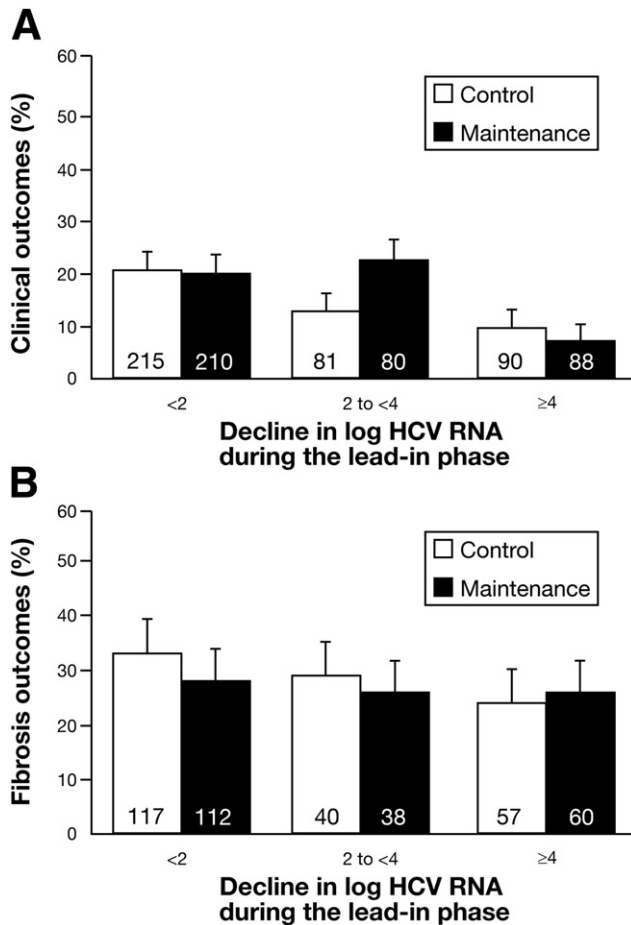


Figure 3. Impact of viral suppression during the lead-in phase on clinical (A) and fibrosis (B) outcomes after randomization. Patients were grouped according to the degree of viral suppression during the lead-in phase. *Panel A:* A significant reduction in clinical outcomes was associated with a decline in serum HCV RNA during the lead-in phase ($P = .003$). No difference in clinical outcomes existed between the control and maintenance therapy groups ($P = .56$). *Panel B:* No significant reduction in fibrosis outcome was associated with a decline in serum HCV RNA during the lead-in phase ($P = .42$). No difference in outcomes existed between the control and maintenance therapy groups ($P = .88$). Numbers at the bottom of each bar represent the number of patients in each group. Error bars indicate the standard error.

Change in HCV RNA With Maintenance Peginterferon and Impact on Outcomes

Patients randomized to the control group had a rapid return in serum HCV RNA back to their pretreatment baseline regardless of their viral response during the lead-in phase (Figure 1). Figure 4 illustrates the impact of continuing peginterferon maintenance therapy, at a reduced dose of 90 $\mu\text{g}/\text{week}$, on viral suppression. Over 97% (204/210) of patients with $<2\text{-log}_{10}$ decline in serum HCV RNA during the lead-in phase had $<2\text{-log}_{10}$ decline during the maintenance phase. In patients with a 2 to $<4\text{-log}_{10}$ decline in HCV RNA during the lead-in phase, 86% had $<2\text{-log}_{10}$ decline in HCV RNA during the maintenance phase. In patients with $\geq 4\text{-log}_{10}$ decline in serum HCV RNA during the lead-in phase, over half (46/88)

could not maintain viral suppression with half-dose peginterferon and failed to maintain HCV RNA at levels $<2\text{ log}_{10}$ below their pretreatment baseline. Only 30 of 88 (34%) patients continued to have marked viral suppression by $\geq 4\text{ log}_{10}$ below their pretreatment baseline levels during the maintenance phase, and all but 1 of these maintained HCV RNA levels $<10,000\text{ IU/mL}$. These 30 patients accounted for 43% of the 69 patients who had undetectable HCV RNA at the end of the lead-in phase.

Figure 5 illustrates clinical and histologic outcomes as a function of the decline in serum HCV RNA during peginterferon maintenance therapy. Overall, no significant impact was observed in clinical outcomes regardless of the degree of viral suppression. Although the lowest frequency of clinical outcomes (13%) was observed in patients who maintained a $\geq 4\text{-log}_{10}$ decline in serum HCV RNA, this was not significantly different ($P = .74$) than that observed in patients with $<4\text{-log}_{10}$ decline in serum HCV RNA during maintenance therapy (18%–23%). Similar results were obtained when clinical outcomes were evaluated with respect to the mean absolute level of HCV RNA during maintenance therapy. Clinical outcomes developed in 17% of patients with a mean serum HCV RNA of $>100,000\text{ IU/mL}$, 29% with a mean serum HCV RNA of $100,000\text{--}1000\text{ IU/mL}$, and 18% with a mean serum HCV RNA of $<1000\text{ IU/mL}$. No significant impact of viral suppression was observed on fibrosis progression ($P = .80$). A histologic outcome was observed in 29% (95% CI: 22%–37%) of patients with $<2\text{-log}_{10}$ decline in serum HCV RNA and in 25% (95% CI: 6%–44%)

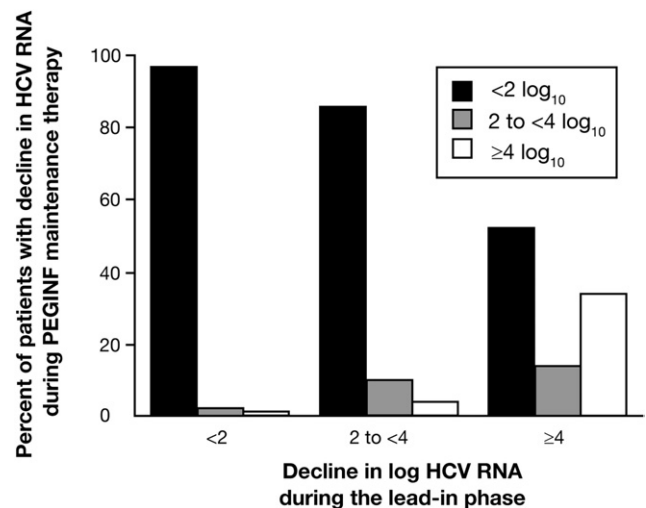


Figure 4. Percent of patients with a decline in serum HCV RNA by various log_{10} amounts from the pretreatment baseline while receiving peginterferon (90 $\mu\text{g}/\text{week}$) maintenance therapy. The mean log_{10} HCV RNA over the first 3 years of maintenance therapy was used for this assessment. Patients were grouped according to their decline in serum log_{10} HCV RNA from the pretreatment baseline during the lead-in phase. Numbers of patients in each group: $<2\text{ log}_{10} = 210$, $2\text{--}4\text{ log}_{10} = 80$, $\geq 4\text{ log}_{10} = 88$.

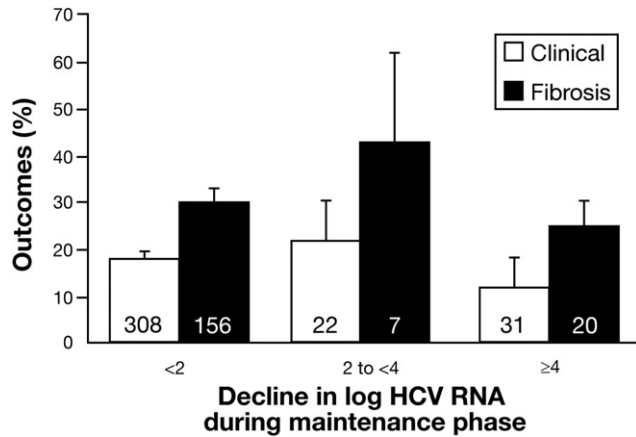


Figure 5. Impact of serum HCV RNA level during peginterferon (90 µg/week) maintenance therapy on clinical and fibrosis outcomes (% ± SE). Patients were grouped according to the mean decline in serum HCV RNA level from the pretreatment baseline after randomization. No significant reductions in clinical outcomes (*P* = .74) or fibrosis outcomes (*P* = .80) were observed with increasing amounts of viral suppression during maintenance therapy. Numbers at the bottom of each bar represent the number of patients in each group.

of patients with >4-log₁₀ decline in HCV RNA during maintenance therapy. Fibrosis progression was observed in 30% of patients when HCV RNA was suppressed to <1000 IU/mL during maintenance therapy.

Table 2 summarizes clinical outcomes that developed in patients who achieved a ≥4-log₁₀ decline in serum HCV RNA during the lead-in phase and various degrees of viral suppression during maintenance therapy. Because achieving a ≥4-log₁₀ reduction in serum HCV RNA level during the lead-in phase was associated with significantly reduced outcomes during the maintenance phase, the clinical outcomes in patients who achieved this profound virologic suppression but were randomized to the control group were also examined. Patients with clinical complications of liver disease and liver-related mortality were separated from those in whom the trial end point reached was only an increase in CTP score without a discrete clinical complication and from patients with non-liver-related death. Patients with a clinical complica-

tion of liver disease were included in the liver-complication category even if they also had a CTP score increase or a non-liver-related death. Overall, complications of liver disease developed in 5.5% of patients with a ≥4-log decline in serum HCV RNA during the lead-in phase who were then randomized to stop treatment and in 4.3% of patients without viral suppression (serum HCV RNA remained <2 logs₁₀ below the pretreatment baseline) despite receiving peginterferon maintenance therapy. A clinical complication of liver disease developed in only 1 of 30 patients (3.3%) who experienced viral suppression by ≥4 logs₁₀ during both the lead-in phase and maintenance therapy. This single patient had undetectable HCV RNA at the end of the lead-in phase and during maintenance therapy. Patients who lost detectable HCV RNA during the lead-in phase with subsequent breakthrough/relapse were treated for 48 weeks (Figure 1). Clinical outcomes developed in 7.5% (11/146) of these patients vs 3 of 32 (9.3%) patients who had a >4-log decline in HCV RNA but failed to clear HCV RNA and were treated for only 24 weeks (*P* = .81).

Of the 69 patients with undetectable HCV RNA at the end of the lead-in phase, 25 were repeatedly (more than 3/7 values between months 12 and 48) HCV RNA undetectable during maintenance therapy. Thirteen (52%) of these patients achieved an SVR, and 5 (20%) relapsed when peginterferon alfa was discontinued after 3.5 years. The remaining patients experienced breakthrough viremia or dropped out of the trial while on maintenance therapy.

Discussion

The HALT-C trial was a prospective, randomized controlled study designed to determine whether continuing peginterferon alfa-2a at a dose of 90 µg/week over 3.5 years could reduce complications of cirrhosis, HCC, and mortality in patients with chronic hepatitis C and advanced bridging fibrosis or cirrhosis who had failed to achieve an SVR following treatment with peginterferon and ribavirin. Unfortunately, no overall reduction in any of these clinical end points was achieved.¹⁴ The results of

Table 2. Outcomes Observed in Patients With a >4-Log₁₀ Decline in Serum HCV RNA During the Lead-In Phase and Varying Degrees of HCV RNA Suppression During Peginterferon Maintenance Therapy

	Control group	Decline in serum HCV RNA by ≥4 logs ₁₀ during the lead-in phase		
		Degree of log ₁₀ decline in serum HCV RNA from the pretreatment baseline during the maintenance phase		
		<2	2 to <4	≤4
No.	90	46	12	30
Death, not liver related, n (%)	0	1 (2.2)	0	1 (3.3)
Increase in CTP score only, n (%)	3 (3.3)	0	0	1 (3.3)
Complication of cirrhosis or liver-related death, n (%)	5 (5.6)	2 (4.3)	0	1 (3.3)

NOTE. Outcomes occurred in 11 of 146 (7.5%) patients with breakthrough/relapse and treated for 48 weeks during the lead-in phase and in 3 of 32 (9.3%) patients without virologic response treated for only 24 weeks.

2 similar studies, Colchicine Versus Peginteron Long-term Therapy (CO-PILOT) and Evaluation of Peginteron in Control of Hepatitis C Cirrhosis (EPIC),³ were also reported recently.^{18,19} In the CO-PILOT trial, no lead-in treatment phase preceded randomization; patients with advanced fibrosis or cirrhosis who were nonresponders to either standard or peginterferon with or without ribavirin were randomized to receive either peginterferon alfa-2b at a dose of 0.5 $\mu\text{g}/\text{kg}/\text{week}$ or colchicine for 4 years. The study design of the EPIC³ trial was similar to that of the HALT-C trial; subjects entered a lead-in treatment phase of peginterferon alfa-2b and weight-based ribavirin after which nonresponders were randomized to receive either peginterferon alfa-2b at a dose of 0.5 $\mu\text{g}/\text{kg}/\text{week}$ or no treatment for up to 3 years. Despite differences in study design, the results of the CO-PILOT and EPIC³ trials were very similar to those observed in the HALT-C trial; no overall benefit of peginterferon maintenance therapy was observed. In EPIC,³ a significant reduction in variceal bleeding was observed in the subset of patients with esophageal varices suggesting that peginterferon may affect portal pressure. A recent substudy of the HALT-C trial has demonstrated that peginterferon alfa-2a 90 $\mu\text{g}/\text{week}$ lowers portal pressure in patients with a baseline portal hypertension and esophageal varices.²⁰ However, maintenance therapy in the HALT-C trial was not associated with a reduction in variceal hemorrhage.

Before these 3 large trials of maintenance therapy were initiated, a preliminary study of maintenance therapy with standard interferon alfa-2b (3 mU 3 times weekly) did suggest that a maintenance approach might be effective.¹² In that study, however, only patients who achieved a histologic response (defined as a 50% decline in the hepatic inflammation score) after 6 months of interferon therapy were eligible for enrollment. This improvement in liver inflammation was associated with a marked decline in serum HCV RNA level.^{9,12} Continuing interferon in these patients maintained both histologic improvement and suppression of serum HCV RNA. Stopping interferon was associated with a rapid rise in serum HCV RNA back to the pretreatment baseline and a worsening in hepatic inflammation scores. Unlike the HALT-C, CO-PILOT, or EPIC³ trials, the majority of patients in this preliminary study did not have advanced fibrosis or cirrhosis, the trial lasted only 2 years, and the impact of treatment on morbidity and mortality was not assessed.

The study designs of the 3 large maintenance therapy trials did not require either prior histologic or virologic responses as criteria for inclusion. In addition, the dose of peginterferon in these trials (half-dose peginterferon alfa-2a and one third the standard dose of peginterferon alfa-2b) was selected based on tolerability over an extended treatment duration, not efficacy in achieving HCV RNA suppression. Only 23% of patients enrolled in the HALT-C trial had profound viral suppression (a $\geq 4\text{-log}_{10}$

decline in serum HCV RNA level) with full-dose peginterferon and ribavirin during the lead-in phase, and only 30 (8%) patients maintained profound viral suppression during maintenance therapy. Serum levels of HCV RNA were not assessed in the CO-PILOT trial, and data on viral suppression during the EPIC³ trial are not currently available. Thus, although the primary analysis of the HALT-C, CO-PILOT, and EPIC³ trials demonstrated that peginterferon maintenance therapy provided no overall benefit to patients with chronic hepatitis C, none of these studies was designed to address whether profound viral suppression with maintenance peginterferon therapy to keep HCV RNA undetectable or near undetectable had the potential to prevent complications of advanced hepatic fibrosis.

The present analysis was performed to investigate the relationship between viral suppression and outcomes during the HALT-C trial. Our results demonstrate that viral suppression with standard doses of peginterferon and ribavirin during the 24-week lead-in phase was associated with a significant reduction in clinical outcomes during the ensuing 3.5 years regardless of whether patients received maintenance peginterferon therapy or not. Several previous studies have suggested that patients who are treated with even a single, brief course of interferon-based therapy have a reduction in HCC and improved mortality.^{10,11} The present study also suggests that profound viral suppression, even for a relatively brief period of time, is associated with clinical benefit.

Data from the present analysis also demonstrated that over half the patients with profound viral suppression during standard dose peginterferon/ribavirin could not maintain this virologic response when ribavirin was stopped and the peginterferon dose was reduced by half. The rate of liver-related outcomes observed in these patients was similar to that observed for patients who also achieved profound virologic suppression during the lead-in phase and were randomized to stop treatment (4.3% vs 5.6%, respectively). Only 30 patients had persistent suppression of HCV RNA by $\geq 4\text{ log}_{10}$ with half-dose peginterferon maintenance therapy. Although a complication of cirrhosis developed in only 1 of these patients (3.3%), the number of patients was not sufficient to demonstrate with any confidence that persistent suppression of HCV RNA, even to undetectable levels, was associated with a reduction in clinical outcomes.

The few patients in this study who appeared to benefit the most from peginterferon maintenance therapy were the ones who responded to full-dose peginterferon and ribavirin during the lead-in phase but experienced either breakthrough or relapse. As has been well established, the relapse rate after antiviral therapy for chronic hepatitis C is inversely proportional to the rapidity with which HCV RNA becomes undetectable during treatment.^{21,22} The vast majority of patients who relapse do not lose detectable HCV RNA until they have received 12–24 weeks of

treatment. Several recent studies have demonstrated that continuing peginterferon and ribavirin for a longer duration, up to 72 weeks, in patients with genotype 1 and delayed clearance of HCV RNA can reduce relapse and increase SVR significantly.^{23,24} Unfortunately, many patients with advanced fibrosis or cirrhosis are unable to tolerate prolonged treatment with full doses of peginterferon and ribavirin. Data from the HALT-C trial suggest that, if such patients could be kept HCV RNA undetectable on half-dose peginterferon maintenance therapy for 3.5 years, an SVR of approximately 52% could be achieved.

The results of this analysis lay the foundation for future studies of maintenance therapy, not with peginterferon, but with potent oral protease and polymerase inhibitors of HCV. Several such agents are currently in various phases of development and, when combined with peginterferon and ribavirin, yield SVR rates that are significantly higher than those observed with peginterferon and ribavirin alone.^{25–27} Despite promising results with these agents, all patients with chronic hepatitis C are unlikely to be cured with a combination of 1 or more oral HCV inhibitors plus peginterferon and ribavirin in the future. Thus, a group of patients with advanced fibrosis or cirrhosis will eventually require multidrug antiviral regimens to achieve long-term suppression of HCV RNA. Whether such patients could achieve an SVR with multidrug oral agents without peginterferon remains to be determined.

In summary, this analysis has demonstrated that profound viral suppression by more than 4 logs₁₀ with full-dose peginterferon and ribavirin was associated with a significant decline in clinical outcomes over the next 3.5 years. Continuing half-dose peginterferon-alfa 2a as maintenance therapy did not affect the development of clinical outcomes regardless of the degree of viral suppression achieved during the lead-in phase. This analysis confirms that no rationale exists for maintenance peginterferon therapy among patients in whom HCV RNA cannot be suppressed to undetectable levels. Our data did show, however, that an SVR of approximately 50% was achieved in the few patients who became HCV RNA undetectable during the lead-in phase, experienced breakthrough or relapse, and then remained persistently HCV RNA negative during maintenance peginterferon for 3.5 years.

References

- Fried MW, Shiffman ML, Reddy KR, et al. Combination of peginterferon alfa-2a (40 kd) plus ribavirin in patients with chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975–982.
- Manns MP, McHutchinson JG, Gordon SC, et al. Peginterferon-alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001;358:958–965.
- Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463–472.
- Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007;147:677–684.
- Forman LM, Lewis JD, Berlin JA, et al. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889–896.
- Shiffman ML, Vargus HE, Everson GT. Controversies in the management of hepatitis C virus infection after liver transplantation. *Liver Transpl* 2003;9:1129–1144.
- Everson GT, Balart L, Lee SS, et al. Histological benefits of virological response to peginterferon alfa-2a monotherapy in patients with hepatitis C and advanced fibrosis or compensated cirrhosis. *Aliment Pharmacol Ther* 2008;27:542–551.
- Poynard T, McHutchinson J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002;122:1303–1313.
- Shiffman ML, Hofmann CM, Thompson EB, et al. Relationship between biochemical, virologic and histologic response during interferon treatment of chronic hepatitis C. *Hepatology* 1997;26:780–785.
- Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2001;357:196–197.
- Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. *Hepatology* 2003;38:493–502.
- Shiffman ML, Hofmann CM, Contos MJ, et al. A randomized, controlled trial of maintenance interferon for treatment of chronic hepatitis C non-responders. *Gastroenterology* 1999;117:1164–1172.
- Lee WM, Dienstag JL, Lindsay KL, et al. Evolution of the HALT-C trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. *Control Clin Trials* 2004;25:472–492.
- Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008;359:2429–2441.
- Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;126:1015–1023.
- Morishima C, Morgan TR, Everhart JE, et al. HCV RNA detection by TMA during the hepatitis C antiviral long-term treatment against cirrhosis (Halt-C) trial. *Hepatology* 2006;44:360–367.
- Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;22:696–699.
- Afdhal NH, Levine R, Brown R, et al. Colchicine versus peginterferon alfa 2b long term therapy: results of the 4 year copilot trial. *J Hepatol* 2008;48(Suppl 2):S4.
- Bruix J, Poynard T, Colombo M, et al. Peginteron maintenance therapy in cirrhotic (Metavir F4) HCV patients, who failed to respond to interferon/ribavirin therapy: final results of the EPIC³ cirrhosis maintenance trial. *J Hepatol* 2009;50(Suppl 1):S22.
- Shiffman ML, Sterling RK, Hofmann C, et al. Low-dose peginterferon alfa-2a maintenance therapy reduces portal pressure in patients with advanced fibrosis and cirrhosis. *Hepatology* 2008;48(Suppl):1045A.
- Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005;43:453–471.
- Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357:124–134.

23. Sánchez-Tapias JM, Diago M, Escartín P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131:451–460.
24. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 2007;46:1688–1694.
25. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med* 2009;360:1827–1838.
26. Kwo P, Lawitz EJ, McCone J, et al. HCV Sprint-1: Boceprevir plus peginterferon alfa-2b/ribavirin for treatment of genotype 1 chronic hepatitis C in previously untreated patients. *Hepatology* 2008;48(Suppl 4):1027A.
27. McHutchison JG, Shiffman ML, Terrault N, et al. A phase 2B study of telaprevir with peginterferon alfa-2a and ribavirin in hepatitis C genotype 1 null and partial responders and relapsers following a prior course of peginterferon alfa-2a/b and ribavirin therapy: prove 3 interim results. *Hepatology* 2008; 48(Suppl 4):431A.

K.L.L.'s current address is Tibotec, Yarlsey, New Jersey.

H.L.B.'s current address is Carolinas Medical Center, Charlotte, North Carolina.

Conflicts of interest

The authors disclose the following: M.L. Shiffman, G.T. Everson, A.S. Lok, and A.M. Di Bisceglie are consultants for Hoffmann-La Roche, Inc. M.L. Shiffman, J.C. Hoefs, G.T. Everson, and A.M. Di Bisceglie are on the speaker's bureau of Hoffmann-La Roche, Inc. M.L. Shiffman, W.M. Lee, G.T. Everson, A.M. Di Bisceglie, and H.L. Bonkovsky receive research support from Hoffmann-La Roche, Inc. K.L. Lindsay was a consultant and received research support during this study and is now an employee of Tibotec (a subsidiary of Johnson and Johnson), Yardsley, NJ. The remaining authors disclose no conflicts.

Funding

Supported by the National Institute of Diabetes and Digestive and Kidney Diseases (contract numbers listed above), the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute, the National Center for Minority Health and Health Disparities, and the General Clinical Research Center and Clinical and Translational Science Center grants from the National Center for Research Resources, and National Institutes of Health (grant numbers are listed above). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. Additional funding to conduct this study was supplied by Hoffmann-La Roche, Inc, through a Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health.

Received April 15, 2009. Accepted August 31, 2009.

Reprint requests

Address requests for reprints to: Mitchell L. Shiffman, MD, Hepatology Section, VCU Health System, Box 980341, Richmond, Virginia 23298. e-mail: mshiffma@vcu.edu; fax: (804) 828-4945.

Acknowledgments

This is publication No. 41 from the HALT-C Trial Group. The HALT-C Trial was registered with clinicaltrials.gov (No. NCT00006164).