12-2009

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Published in final edited form as:
Gastroenterology. 2009 December ; 137(6): 1986–1994. doi:10.1053/j.gastro.2009.08.067.

EFFECT OF HCV RNA SUPPRESSION DURING PEGINTERFERON ALFA-2A MAINTENANCE THERAPY ON CLINICAL OUTCOMES IN THE HALT-C TRIAL

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*The HALT-C Trial was registered with clinicaltrials.gov (#NCT00006164).
This is publication #41 from the HALT-C Trial Group.

CONFLICT OF INTEREST DISCLOSURES

Financial relationships of the authors with Hoffmann-La Roche, Inc., are as follows: M L Shiffman is a consultant, on the speaker's bureau, and receives research support; JC Hoefs is on the speaker's bureau; WM Lee receives research support; GT Everson is a consultant, on the speaker's bureau, and receives research support; AS Lok is a consultant; AM Di Bisceglie is a consultant, on the speaker's bureau, and receives research support; HL Bonkovsky receives research support. KL Lindsay was a consultant and received research support during this study. She is now an employee of Tibotec (a subsidiary of Johnson and Johnson), Yardsley, PA. Authors with no financial relationships related to this project are: C. Morishima, J. L. Dienstag, E. C. Wright, D. Naishadham, and M.G. Ghany.

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Abstract

Background and Aims—The 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 if suppressing HCV RNA during the trial was associated with a reduction in clinical outcomes.

Methods—764 patients treated during the lead-in phase of HALT-C were randomized to either peginterferon alfa-2a (90 mcg/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 $\log_{10}$ 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=0.003) fewer clinical outcomes whether randomized to maintenance therapy or control. Following randomization serum HCV RNA increased significantly in all 90 control patients and 58/88 receiving maintenance therapy. Only 30 patients had persistent suppression of HCV RNA by ≥4 $\log_{10}$ during maintenance therapy. No significant reduction in clinical outcomes was observed in these patients.

Conclusions—Viral suppression by ≥4 $\log_{10}$ 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. Since 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 who SVR following treatment of hepatitis C have an improvement in liver histology and a reduction in liver related mortality (4,7,8,9). 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 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 if low dose peginterferon alfa-2a maintenance therapy (90 mcg/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 if 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, 1,050 subjects with bridging fibrosis or cirrhosis (Ishak fibrosis score 3–6) who were nonresponders to prior treatment with interferon (with or without ribavirin) were retreated 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 mcg/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 randomization, 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 (LLOD) 600 IU/ml; Roche Molecular Systems, Branchburg, NJ) and, if negative, by the Roche COBAS Amplicor HCV Test, v. 2.0 assay (LLOD 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 three groups according to the decline from pretreatment baseline in HCV RNA levels during the lead-in phase and after randomization; <2 $\log_{10}$ decline, 2 to <4 $\log_{10}$, and ≥4 $\log_{10}$ 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: ≥100,000 IU/mL, <100,000-1,000 IU/mL and <1,000 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

Protocl-defined clinical outcomes included an increase in the Child-Turcotte-Pugh (CTP) score to ≥7 points on two 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 endpoint, an increase by ≥2 points in the Ishak fibrosis score at either of the two 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 two treatment groups were compared with chi-square 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 1,400 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 I 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 breakthough/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-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 month 42. Nonresponders had a mean decline in serum HCV RNA of 1.5 $\log_{10}$ 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 to the control group ($p<0.0001$); however, this reduction was only 0.56 $\log_{10}$ IU/ml (95% 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 upon the time of HCV RNA recurrence. 42 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 $\log_{10}$ 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 $\log_{10}$ (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 ($p<0.0001$). During the 3.5 years of maintenance therapy the mean serum HCV RNA level drifted up gradually relative to the pretreatment baseline from a nadir of $\log_{10}$ −2.9 to −2.2 ($p=0.0001$).

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 to their pretreatment baseline levels, 56% of patients had a <2 $\log_{10}$ decline in serum HCV RNA with full-dose peginterferon and ribavirin; 21% had a 2 to <4 $\log_{10}$ decline and 23% had a ≥4 $\log_{10}$ reduction. Among patients with a ≥4 $\log_{10}$ 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 that after randomization according to the decline in serum HCV RNA during the lead-in phase. A significant (p=0.003) reduction in clinical outcomes was observed with increasing degrees of viral suppression (Figure 3A). Clinical outcomes developed in 21% of patients with <2 $\log_{10}$ 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 $\log_{10}$ decline and 8% (95% CI: 4–12%) of patients with ≥4 $\log_{10}$ 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 ≥4 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=0.56). 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=0.38). 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=0.88).

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 mcg/week, on viral suppression. Over 97% (204/210) of patients with <2 $\log_{10}$ decline in serum HCV RNA during the lead-in phase had <2 $\log_{10}$ decline during the maintenance phase. In patients with a 2 to <4 $\log_{10}$ decline in HCV RNA during the lead-in phase, 86% had <2 $\log_{10}$ decline in HCV RNA during the maintenance phase. In patients with ≥4 $\log_{10}$ decline in serum HCV RNA during the lead-in phase over half (46/88) could not maintain viral suppression with half dose pegnterferon and failed to maintain HCV RNA at levels <2 logs_{10} below their pretreatment baseline. Only 30/88 (34%) patients continued to have marked viral suppression by ≥4 logs_{10} below their pretreatment baseline levels during the maintenance phase, all but one of these maintained HCV RNA levels <1,0000 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 ≥4 $\log_{10}$ decline in serum HCV RNA, this was not significantly different (p=0.74) than that observed in patients with <4 $\log_{10}$ 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 IU/mL, 29% with a mean serum HCV RNA of 100,000-1,000 IU/mL and 18% with a mean serum HCV RNA of <1,000 IU/mL. No significant impact of viral suppression was observed on fibrosis progression (p=0.80). A histologic outcome was observed in 29% (95% CI 22%–37%) of patients with <2 $\log_{10}$ decline in serum HCV RNA and in 25% (95% CI 6%–44%) of patients with >4 $\log_{10}$ decline in HCV RNA during maintenance therapy. Fibrosis progression was observed in 30% of patients when HCV RNA was suppressed to <1,000 IU/mL during maintenance therapy.

Table 2 summarizes clinical outcomes that developed in patients who achieved a ≥4 $\log_{10}$ decline in serum HCV RNA during the lead-in phase and various degrees of viral suppression during maintenance therapy. Because achieving a ≥4 $\log_{10}$ 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 endpoint 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 complication 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 $logs_{10}$ below the pre-treatment baseline) despite receiving peginterferon maintenance therapy. A clinical complication of liver disease developed in only 1/30 patients (3.3%) who experienced viral suppression by ≥4 $logs_{10}$ 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 versus 3/32 (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=0.81).

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 12–48) 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 if continuing peginterferon alfa-2a at a dose of 90 mcg/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 endpoints was achieved (14). The results of two similar studies, CO-PILOT and EPIC^3, were also reported recently (18,19). In the CO-PILOT Trial no lead-in treatment phase preceeded 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 mcg/kg/week or colchicine for 4 years. The study design of the EPIC^3 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 mcg/kg/week or no treatment for up to 3 years. Despite differences in study design, the results of the CO-PILOT and EPIC^3 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 mcg/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 three large trials of maintenance therapy were initiated, a preliminary study of maintenance therapy with standard interferon alfa-2b (3 mU three 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 EPIC^3 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 three 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 upon 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 $\log_{10}$ 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 EPIC^3 Trial are not currently available. Thus, although the primary analysis of the HALT-C, CO-PILOT and EPIC^3 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% versus 5.6%). Only 30 patients had persistent suppression of HCV RNA by $\geq$4 $\log_{10}$ 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 in this study 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 loose 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 one 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 multi-drug antiviral regimens to achieve long term suppression of HCV RNA. Whether such patients could achieve an SVR with multi-drug oral agents without peginterferon remains to be determined.

In summary, this analysis has demonstrated that profound viral suppression by more than 4 $\log_{10}$ 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.

Acknowledgments

This study was supported by the National Institute of Diabetes & Digestive & Kidney Diseases (contract numbers are listed below). Additional support was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute, the National Center for Minority Health and Health Disparities and by General Clinical Research Center and Clinical and Translational Science Center grants from the National Center for Research Resources, National Institutes of Health (grant numbers are listed below). 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.

In addition to the authors of this manuscript, the following individuals were instrumental in the planning, conduct and/or care of patients enrolled in this study at each of the participating institutions as follows:

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University of Connecticut Health Center, Farmington, CT: (Grant M01RR-06192) Gloria Borders, RN, Michelle Kelley, RN, ANP

Saint Louis University School of Medicine, St Louis, MO: (Contract N01-DK-9-2324) Bruce Bacon, MD, Brent Neuschwander-Tetri, MD, Elizabeth M. Brunt, MD, Debra King, RN

Massachusetts General Hospital, Boston, MA: (Contract N01-DK-9-2319, Grant M01RR-01066; Grant 1 UL1 RR025758-01, Harvard Clinical and Translational Science Center) Raymond T. Chung, MD, Andrea E. Reid, MD, Atul K. Bhan, MD, Wallis A. Molchen, Cara C. Gooch

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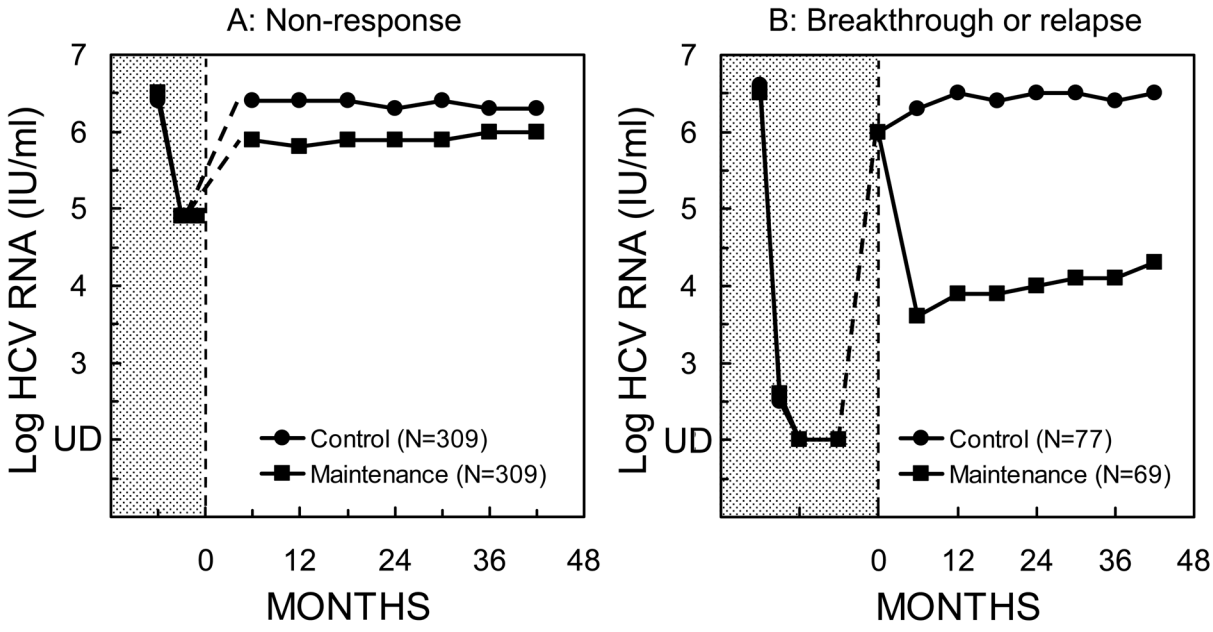

Figure 1.

Change in serum HCV RNA level over time. During the lead-in phase (stippled area) patients were treated with peginterferon alfa-2a 180 mcg/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 mcg/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 mcg/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 (stippled area) along the x-axis in the breakthrough/ relapse group reflects the longer duration of treatment these patients received prior to randomization.

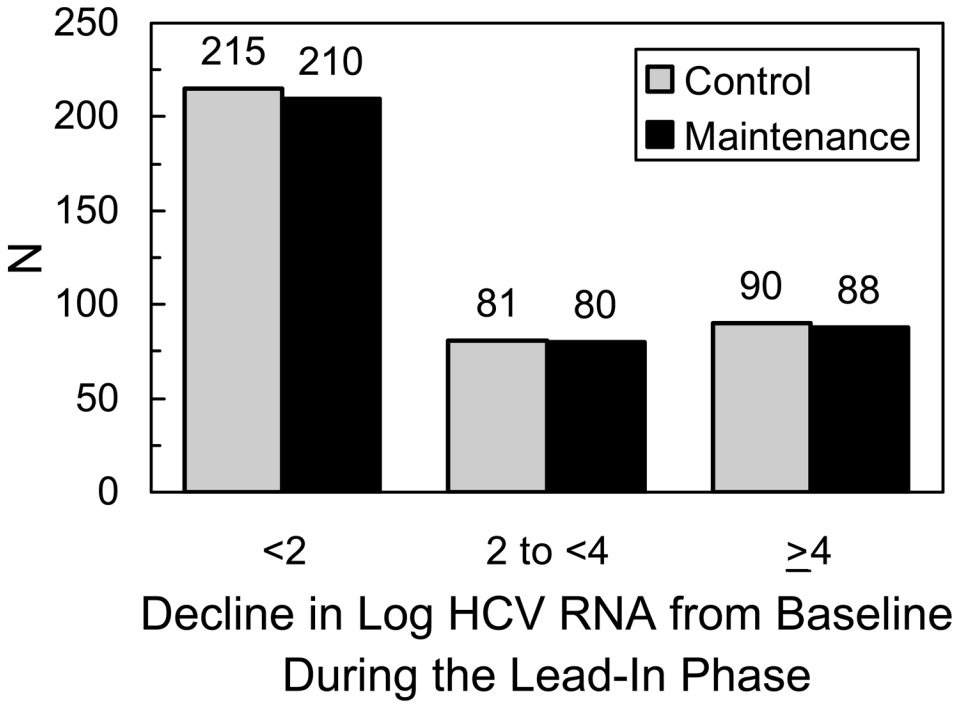

Figure 2.

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

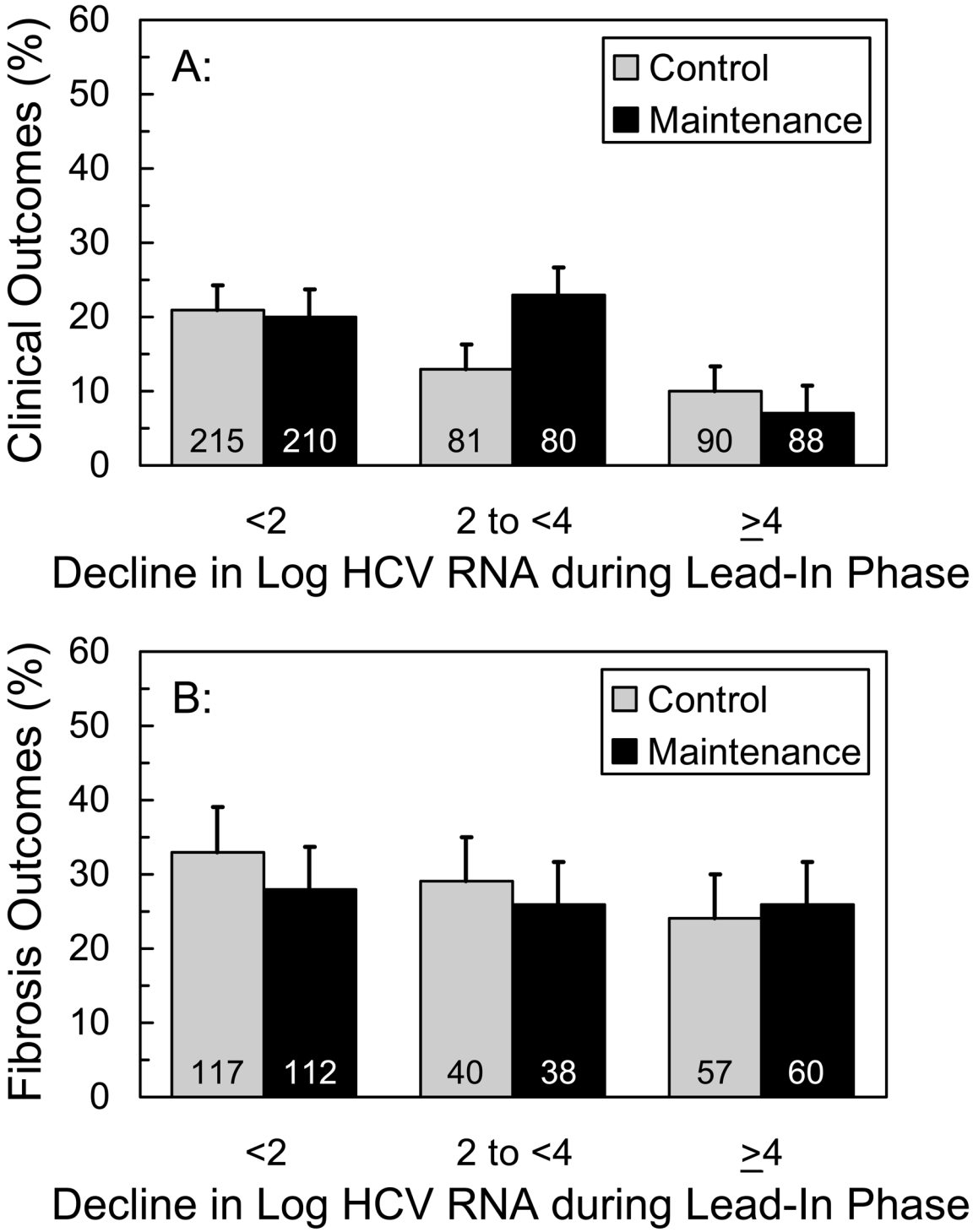

Figure 3.

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=0.003). No difference in clinical outcomes existed between the control and maintenance therapy groups

(p=0.56). Panel B: No significant reduction in fibrosis outcome was associated with a decline in serum HCV RNA during the lead-in phase (p=0.42). No difference in outcomes existed between the control and maintenance therapy groups (p=0.88). Numbers at the bottom of each bar represent the number of patients in each group. Error bars indicate the standard error.

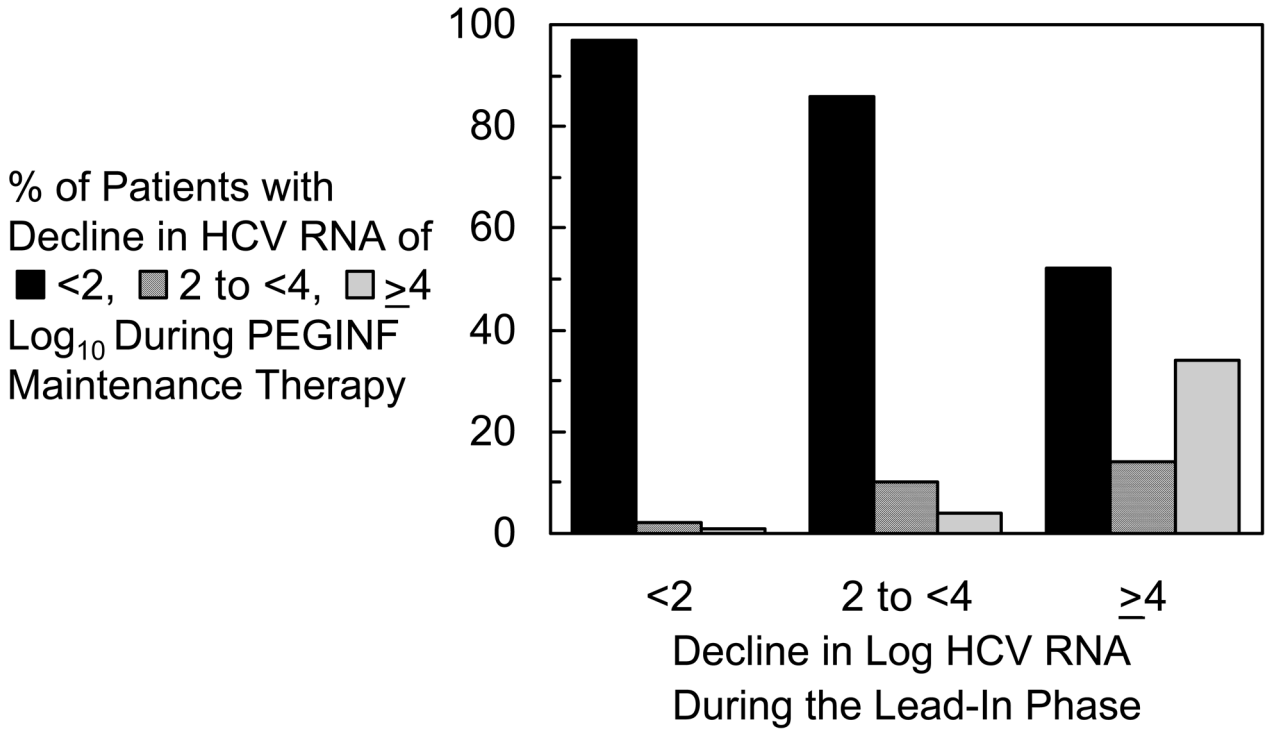

Figure 4.

Percent of patients with a decline in serum HCV RNA by various $\log_{10}$ amounts from the pretreatment baseline while receiving peginterferon (90 mcg/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 pre-treatment baseline during the lead-in phase. Numbers of patients in each group: $< 2 \log_{10} = 210$, 2–4 $\log_{10} = 80$, $\geq 4 \log_{10} = 88$.

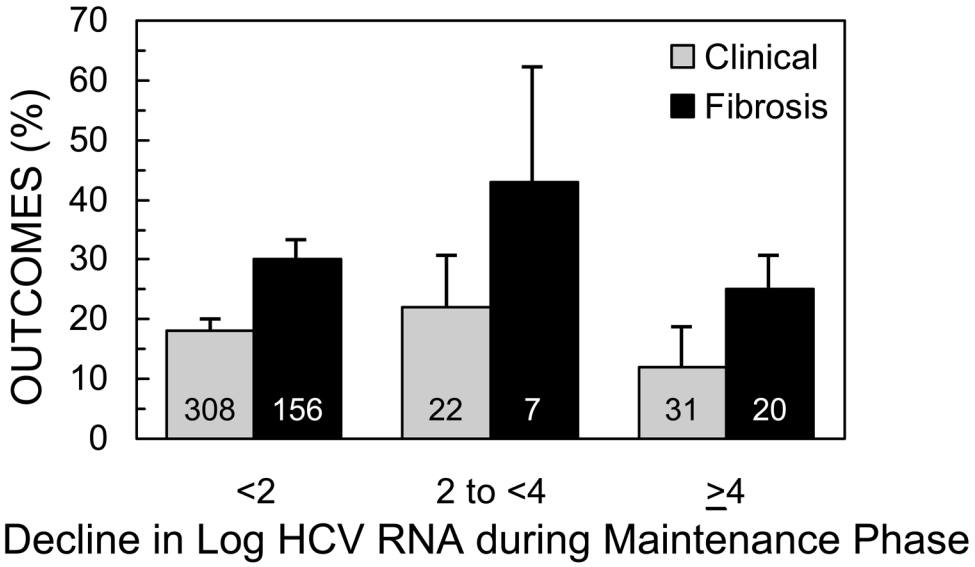

Figure 5.

Impact of serum HCV RNA level during peginterferon (90 mcg/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=0.74) or fibrosis outcomes (p=0.80) 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.

TABLE I

CLINICAL CHARACTERISTICS OF THE PATIENT POPULATION

	Control	Maintenance	p
N	386	378	
Age (years)	49.5 ± 7.3	50.8 ± 7.3	0.01
Male (%)	70%	72%	0.65
Race (%Caucasian)	70%	72%	0.49
Baseline ALT (IU/l)	116 ± 87	107 ± 78	0.14
Baseline WBC (cels/mm^3)	5.7 ± 1.8	5.9 ± 1.9	0.19
Baseline platelet count (cells/mm^3)	167 ± 68	166 ± 62	0.87
Genotype 1 (%)	92%	95%	0.09
Baseline log_{10} HCV RNA (IU/ml)	6.44 ± 0.48	6.46 ± 0.45	0.45
Cirrhosis (%)	40%	40%	0.95
Virologic response during lead-in:			
Non-response (%)	80%	82%	0.55
Breakthrough or relapse (%)	20%	18%	

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

TABLE 2

OUTCOMES OBSERVED IN PATIENTS WITH A >4 LOG_{10} DECLINE IN SERUM HCV RNA DURING THE LEAD-IN PHASE AND VARYING DEGREES OF HCV RNA SUPPRESSION DURING PEGINTERFERON MAINTENANCE THERAPY

	Decline in serum HCV RNA by ≥4 $logs_{10}$ during the lead-in phase			
	Control Group	**Log_{10} decline in serum HCV RNA from the pre-treatment baseline during the maintenance phase by:**		
		<2	**2 to <4**	**≥4**
N	90	46	12	30
Death - not liver related	0	1 (2.2%)	0	1 (3.3%)
Increase in CTP score only	3 (3.3%)	0	0	1 (3.3%)
Complication of cirrhosis or liver related death	5 (5.6%)	2 (4.3%)	0	1 (3.3%)

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