

# **Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection**

**Update #1: Preliminary Scan Report #3**

May 2010

**The Agency for Healthcare Research and  
Quality has not yet seen or approved this report**

**The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.**

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## **OBJECTIVE:**

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

## **Date of Last Update:**

The Original Final Report was completed in May 2007, with searches through July 2006.

## **Date of Last Update Scans:**

Preliminary Update Scan #1: May 2008

Preliminary Update Scan #2: June 2009

## **Scope and Key Questions**

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of regimens of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?
  - a. How does duration of treatment or dosing protocols (including weight-based or maintenance dosing or dosing of ribavirin) affect estimates of comparative effectiveness?
2. What is the comparative tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?
3. Does the comparative effectiveness or tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin vary in patient subgroups defined by demographics (age, racial groups, gender, genotype, markers of disease severity), use of other medications, or presence of co-morbidities (such as HIV infection)?

## Inclusion Criteria

<b>Populations</b>
• Non-pregnant adult outpatients with chronic Hepatitis C infection
<i>Subgroups include:</i>
• HIV-infected persons
• Non-responders or relapsers (including re-treatment)
• Based on gender, race, or age
• Based on genotype
• Based on viral load
• Based on liver function test abnormalities
• Based on degree of fibrosis, inflammation, or cirrhosis on liver biopsy
• Based on other co-morbid conditions, including obesity, addiction, psychiatric illness
<b>Treatments</b>
• Pegylated interferon alfa-2a plus ribavirin
• Pegylated interferon alfa-2b plus ribavirin
<b>Effectiveness outcomes</b>
• Sustained virologic response (SVR)
• Normalization of liver enzyme abnormalities (sustained biochemical response, or SBR)
• Improvement in inflammation or fibrosis on liver biopsy
• Cirrhosis
• Hepatocellular carcinoma
• Need for liver transplant
• Quality of life
• Mortality
• Early virologic response (only for head-to-head trials)
<b>Safety outcomes</b>
• Overall adverse effects
• Withdrawals due to adverse effects
• Serious adverse events (including depression, suicidality)
• <b>Specific adverse events (including myalgias, flu-like symptoms, fevers, chills, neutropenia, dose reduction)</b>
<b>Study designs</b>
• For assessment of effectiveness in general, controlled clinical trials and good-quality systematic reviews were included.
• For assessment of effectiveness for cirrhosis, hepatocellular cancer, need for transplant, and mortality, controlled clinical trials and <i>long-term</i> observational studies were included.
• For assessment of safety, controlled clinical trials and observational studies were included.

## METHODS

### Literature Search

To identify relevant citations, we searched MEDLINE (June 2009 to April Week 3, 2010) using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp->

[mps/medeff/advisories-avis/prof/index-eng.php](https://mps.medeff.advisories-avis.prof/index-eng.php)) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote v X2<sup>®</sup>) and duplicate citations were removed.

## **Study Selection**

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## **RESULTS**

### **Overview**

Searches resulted in 41 citations. Of those, there are 10 new potentially relevant controlled clinical trials (See Appendix A). Four of these are head-to-head trials (Ascione 2010, Laguno 2009, McHutchinson 2009, Rumi 2009). The other trials compared different dosing regimens or treatment durations of the same drug.

Taken together with the 39 trials identified in the previous preliminary update scans, there are now 49 trials that would potentially be added in the event of a full update of this topic, 10 of which are head-to-head trials.

### **New Drugs**

No new drugs were identified.

### **New Indications**

No new indications for included drugs were identified.

### **New Safety Alerts**

No new safety alerts for included drugs were identified.

## APPENDIX A: Abstracts of potentially relevant trials of pegylated interferons for chronic hepatitis C infection (N=10)

Ascione, A., M. De Luca, et al. (2010). "Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection."

Gastroenterology **138**(1): 116-22.

**BACKGROUND & AIMS:** Patients with chronic hepatitis C virus (HCV) infection are frequently treated with a combination of pegylated interferon (peginterferon) and ribavirin. This study compared the efficacy and safety of peginterferon alfa-2a and peginterferon alfa-2b, each in combination with ribavirin. **METHODS:** A total of 320 consecutive, treatment-naïve, HCV RNA-positive patients with chronic hepatitis were randomly assigned to once-weekly peginterferon alfa-2a (180 microg, group A) or peginterferon alfa-2b (1.5 microg/kg, group B) plus ribavirin 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight ≥75 kg) for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3). The primary end point was sustained virological response (SVR) by intention-to-treat. **RESULTS:** More patients in group A than group B achieved an SVR (110/160 [68.8%] vs 87/160 [54.4%]; P = .008). Higher SVR rates were obtained in group A than group B among patients with genotype 1/4 (51/93 [54.8%] vs 37/93 [39.8%]; P = .04), with genotype 2/3 (59/67 [88.1%] vs 50/67 [74.6%]; P = .046), without cirrhosis (96/127 [75.6%] vs 75/134 [55.9%]; P = .005), and with baseline levels HCV RNA >500,000 IU/mL (58/84 [69%] vs 43/93 [46.2%]; P = .002). SVR rates in groups A and B were not statistically different among patients with baseline HCV RNA ≤500,000 IU/mL (52/76 [68.4%] vs 44/67 [65.7%]; P = .727) or in patients with cirrhosis (14/33 [42.4%] vs 12/26 [46.1%]; P = .774). **CONCLUSIONS:** In patients with chronic HCV infection, peginterferon alfa-2a plus ribavirin produced a significantly higher SVR rate than peginterferon alfa-2b plus ribavirin. Copyright 2010 AGA Institute. Published by Elsevier Inc. All rights reserved.

Brady, D. E., D. M. Torres, et al. "Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study." Clinical Gastroenterology & Hepatology **8**(1): 66-71.e1.

**BACKGROUND & AIMS:** Standard of care (SOC) treatment for chronic hepatitis C (CHC) involves weekly pegylated (PEG) interferon plus weight-based ribavirin with resultant sustained virologic response (SVR) rates at or near 50% for genotypes 1 and 4 virus. Induction therapy with higher doses of PEG interferon may improve first-phase viral kinetics and thus improve the overall SVR in genotypes 1 and 4 patients. **METHODS:** This multicenter, randomized, open-label trial enrolled treatment-naïve genotypes 1- and 4-infected CHC patients to either initial induction therapy versus SOC. The induction group received PEG interferon alfa-2b 3.0 mcg/kg/wk for 12 weeks followed by PEG interferon alfa-2b 1.5 mcg/kg/wk for 36 weeks and 13 +/- 2 mg/kg ribavirin daily for 48 weeks. SOC patients received PEG interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks and 13 +/- 2 mg/kg ribavirin daily for 48 weeks. The primary end point was SVR. **RESULTS:** There were 610 patients enrolled throughout the United States. Complete early virologic response was 62.6% versus 57.7% in induction versus SOC (NS). Overall SVR was 32% in induction versus 29% in SOC group (NS). Dose reduction of either PEG interferon (24.1% vs 23.8%) or ribavirin (26.8% vs 25.1%) was similar between the 2 groups. There was a trend toward a significant difference when

comparing the SVR in induction therapy in patients weighing more than 85 kg versus those receiving SOC (38% vs 28%;  $P = .08$ ). **CONCLUSIONS:** Induction therapy does not enhance complete early virologic response or SVR rates in a predominantly genotype 1 CHC population compared with SOC therapy. Copyright (c) 2010 AGA Institute. Published by Elsevier Inc. All rights reserved.

Bressler, B., K. Wang, et al. (2009). "Pharmacokinetics and response of obese patients with chronic hepatitis C treated with different doses of PEG-IFN alpha-2a (40KD) (PEGASYS)." British Journal of Clinical Pharmacology **67**(3): 280-7.

**AIMS:** To evaluate whether higher doses of peginterferon alpha-2a (40KD) [PEG-IFN alpha-2a (40KD)] can compensate for lower exposure observed among obese patients with chronic hepatitis C (CHC) treated with the standard dose of PEG-IFN alpha-2a (40KD). **METHODS:** Noncirrhotic, obese (body mass index  $\geq 30$  kg  $m^{-2}$ ) patients with CHC participated in a single-centre, open-label study. Patients were randomized to 180 or 270 microg week $^{-1}$  PEG-IFN alpha-2a (40KD) + ribavirin (1000/1200 mg day $^{-1}$ ) for 48 weeks. Blood samples were collected predose and up to 168 h after the first dose and at week 12 for pharmacokinetic analysis. Trough serum concentrations (C(trough)) were determined up to week 24. **RESULTS:** In the 180 microg week $^{-1}$  group mean  $\pm$  SD steady-state (week 12) estimates of AUC(0-168) (ng h $^{-1}$  ml $^{-1}$ ), C(max) (ng ml $^{-1}$ ) and CL/F (l h $^{-1}$ ) were 2154  $\pm$  919, 13.8  $\pm$  6.7 and 0.102  $\pm$  0.051, respectively. In the 270 microg week $^{-1}$  group, estimates were 3374  $\pm$  1844, 23.4  $\pm$  10.7 and 0.090  $\pm$  0.042, respectively. The mean (range) C(trough) (ng ml $^{-1}$ ) was 11.2 (4.4-18.5) in the 180 microg week $^{-1}$  group and 16.1 (0.4-44.2) in the 270 microg week $^{-1}$  group. Overall, 14 of 20 (70%) and 16 of 20 (80%) patients in the 180 microg week $^{-1}$  and 270 microg week $^{-1}$  groups were infected with hepatitis C virus genotype 1 or 4. In the 180 microg week $^{-1}$  and 270 microg week $^{-1}$  groups 14 of 20 (70%) and 15 of 19 (79%) patients, respectively, achieved a sustained viral response. Safety was similar between groups. **CONCLUSIONS:** Mean PEG-IFN alpha-2a (40KD) exposure was dose proportional from 180 to 270 microg week $^{-1}$ . Increasing PEG-IFN alpha-2a (40KD) from 180 to 270 microg week $^{-1}$  achieves higher serum drug exposure in obese patients.

Ferenci, P., H. Laferl, et al. "Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response." Gastroenterology **138**(2): 503-12.

**BACKGROUND & AIMS:** This randomized multicenter trial evaluated individualization of treatment duration with peginterferon alfa-2a 180 microg/wk plus ribavirin 1000/1200 mg/day in patients with chronic hepatitis C genotype 1/4 based on the rapidity of virologic response (VR). **METHODS:** Patients with a rapid VR (RVR; undetectable hepatitis C virus [HCV]-RNA level ( $<50$  IU/mL at week 4) were treated for 24 weeks, those with an early VR (EVR; no RVR but undetectable HCV-RNA level or  $\geq 2$ -log(10) decrease at week 12) were randomized to 48 (group A) or 72 weeks of treatment (group B; peginterferon alfa-2a was reduced to 135 microg/wk after week 48). Patients without an EVR continued treatment until week 72 if they had undetectable HCV-RNA levels at week 24. The primary end point was relapse; sustained VR (SVR; undetectable HCV-RNA level after 24 weeks of follow-up evaluation) was a secondary end point. **RESULTS:** Of 551 genotype 1/4 patients starting treatment, 289 were randomized to group A (N = 139) or group B (N = 150). The relapse rate was 33.6% in group A (95%

confidence interval [CI], 24.8%-43.4%) and 18.5% in group B (95% CI, 11.9%-27.6%;  $P = .0115$  vs group A) and the SVR rate was 51.1% (95% CI, 42.5%-59.6%) and 58.6% (95% CI, 50.3%-66.6%;  $P > .1$ ), respectively. The overall SVR rate was 50.4% (278 of 551; 95% CI, 46.2%-54.7%), including 115 of 150 patients with an RVR treated for 24 weeks and 4 of 78 patients without an EVR. CONCLUSIONS: Extending therapy with peginterferon alfa-2a/ribavirin to 72 weeks decreases the probability of relapse in patients with an EVR. If they can be maintained on extended-duration therapy, SVR rates also may improve.

Kawaoka, T., Y. Kawakami, et al. (2009). "Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial." *Journal of Gastroenterology & Hepatology* **24**(3): 366-71.

BACKGROUND AND AIM: To compare the efficacy and safety of pegylated interferon (PEG-I) at 1 and 1.5 microg/kg, and in combination with ribavirin (RBV) for 24 weeks in naive Japanese patients infected with hepatitis C virus genotype 2. METHODS: The present study was an open-label, randomized trial of 55 patients receiving PEG-I (1 or 1.5 microg/kg body weight [BW], subcutaneously, once a week) and RBV for 24 weeks. The patients were followed up for 24 weeks without treatment. RESULTS: The intention-to-treat analyses showed that the proportion of patients with a sustained virological response (SVR) in the 1-microg/kg PEG-I-RBV group (38.5%, 10/26) was lower than that of the 1.5-microg/kg PEG-I-RBV group (74.1%, 20/27;  $P = 0.013$ ). The PEG-I dose was reduced in two of the 26 patients of the 1-microg/kg PEG-I-RBV group (one because of thrombocytopenia at 2 weeks, and one because of generalized fatigue at 20 weeks), and four of the 27 patients of the 1.5-microg/kg PEG-I-RBV group (one because of neutropenia at 20 weeks, and three because of generalized fatigue at 1, 5, and 8 weeks). The multivariate analysis identified age ( $< 60$  years) and dose of PEG-I (1.5 microg/kg) as significant determinants of SVR. CONCLUSION: The dose of PEG-I to be used at the start of therapy should be 1.5-microg/kg BW in naive Japanese patients infected with hepatitis C virus genotype 2.

Laguno, M., C. Cifuentes, et al. (2009). "Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients.[Erratum appears in *Hepatology*. 2009 Mar;49(3):1058]." *Hepatology* **49**(1): 22-31.

Although two pegylated interferons (Peg-IFN) are available to treat chronic hepatitis C virus (HCV) infection, no head-to-head comparative studies have been published. We aim to compare the efficacy and safety of PEG IFN alfa-2b (PEG 2b) versus PEG IFN alfa-2a (PEG 2a), plus ribavirin (RBV). A prospective, randomized, multi-center, open-label clinical trial including 182 human immunodeficiency virus (HIV)-hepatitis C virus (HCV) patients naive for HCV therapy was performed. Patients were assigned to PEG 2b (80-150 mug/week;  $n = 96$ ) or PEG 2a (180 mug/week;  $n = 86$ ), plus RBV (800-1200 mg/day) for 48 weeks. The primary endpoint was sustained virological response (SVR: negative HCV-RNA 24 weeks after completion of treatment). At baseline, both groups were well balanced: 73% male; 63% HCV genotype 1 or [corrected] 4; 29% had fibrosis index of 3 or greater. The overall SVR was 44% (42% PEG 2b versus 46% PEG 2a,  $P = 0.65$ ). Among genotypes 1 or [corrected] 4, SVRs were 28% versus 32% ( $P = 0.67$ ) and 62% versus 71% ( $P = 0.6$ ) in genotypes 2 or [corrected] 3 for PEG 2b and PEG 2a,

respectively. Early virological response (EVR;  $\geq 2$  log reduction from baseline or negative HCV-RNA at week 12) was 70% in the PEG 2b group and 80% in the PEG 2a group ( $P = 0.13$ ), reaching a positive predictive value of SVR of 64% and a negative predictive value of 100% in both arms. Side effects were present in 96% of patients but led to treatment discontinuation in 10% of patients (8% on PEG 2b and 13% on PEG 2a,  $P = 0.47$ ). Conclusion: In patients with HIV, HCV therapy with PEG 2b or PEG 2a plus RBV had no significant differences in efficacy and safety.

McHutchison, J. G., E. J. Lawitz, et al. (2009). "Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1027]." New England Journal of Medicine **361**(6): 580-93.

**BACKGROUND:** Treatment guidelines recommend the use of peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for chronic hepatitis C virus (HCV) infection. However, these regimens have not been adequately compared. **METHODS:** At 118 sites, patients who had HCV genotype 1 infection and who had not previously been treated were randomly assigned to undergo 48 weeks of treatment with one of three regimens: peginterferon alfa-2b at a standard dose of 1.5 microg per kilogram of body weight per week or a low dose of 1.0 microg per kilogram per week, plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 microg per week plus ribavirin at a dose of 1000 to 1200 mg per day. We compared the rate of sustained virologic response and the safety and adverse-event profiles between the peginterferon alfa-2b regimens and between the standard-dose peginterferon alfa-2b regimen and the peginterferon alfa-2a regimen. **RESULTS:** Among 3070 patients, rates of sustained virologic response were similar among the regimens: 39.8% with standard-dose peginterferon alfa-2b, 38.0% with low-dose peginterferon alfa-2b, and 40.9% with peginterferon alfa-2a ( $P=0.20$  for standard-dose vs. low-dose peginterferon alfa-2b;  $P=0.57$  for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). Estimated differences in response rates were 1.8% (95% confidence interval [CI], -2.3 to 6.0) between standard-dose and low-dose peginterferon alfa-2b and -1.1% (95% CI, -5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Relapse rates were 23.5% (95% CI, 19.9 to 27.2) for standard-dose peginterferon alfa-2b, 20.0% (95% CI, 16.4 to 23.6) for low-dose peginterferon alfa-2b, and 31.5% (95% CI, 27.9 to 35.2) for peginterferon alfa-2a. The safety profile was similar among the three groups; serious adverse events were observed in 8.6 to 11.7% of patients. Among the patients with undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively. **CONCLUSIONS:** In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or between the two doses of peginterferon alfa-2b. (ClinicalTrials.gov number, NCT00081770.) 2009 Massachusetts Medical Society

Nagaki, M., M. Shimizu, et al. (2009). "Clinical trial: extended treatment duration of peginterferon-alpha2b plus ribavirin for 72 and 96 weeks in hepatitis C genotype 1-infected late responders." Alimentary pharmacology & therapeutics **30**(4): 343-51.

**BACKGROUND:** The benefits of prolonging peginterferon and ribavirin after 48 weeks of treatment to maximize sustained virological responses (SVR) in hepatitis C virus (HCV) genotype 1-infected patients remain to be understood. **AIM:** To investigate

whether extended treatment longer than 72 weeks may be superior to 72-week treatment. **METHODS:** A total of 120 treatment-naïve or retreated patients with HCV genotype 1 were treated with peginterferon-alpha-2b (1.5 microg/kg/week) plus weight-based ribavirin. We had 34 late responders, in whom HCV RNA first became undetectable at week 12-48, and randomized them into three groups receiving standard-dose peginterferon-alpha-2b plus low-dose ribavirin (200 mg/day) for extended 24 weeks (group A), receiving low-dose peginterferon-alpha-2b (0.75 microg/kg/week) plus low-dose ribavirin for extended 48 weeks (group B) or no extended treatment (group C), and evaluated the outcome according to their virological response. **RESULTS:** Multivariate analysis showed that the treatment for 96 weeks was identified as a significant, independent factor associated with SVR in HCV genotype 1-infected late responders in comparison with group A [odds ratio (OR), 10.002; P = 0.080] and group C (OR, 17.748; P = 0.025). **CONCLUSION:** Extending the treatment duration from 48 weeks to 96 weeks improves SVR rates in genotype 1-infected patients with late virological response to peginterferon-alpha-2b and ribavirin.

Rumi, M. G., A. Aghemo, et al. "Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C." *Gastroenterology* **138**(1): 108-15. **BACKGROUND & AIMS:** Ribavirin (RBV) combined with either pegylated interferon (PegIFN) alpha2a or PegIFNalpha2b is the standard of care for chronic hepatitis C virus (HCV) infection. Due to the lack of head-to-head studies, the 2 PegIFNs have not been directly compared. The endpoints of our study were safety and antiviral efficacy of the 2 regimens. **METHODS:** Treatment-naïve patients with chronic hepatitis C were randomly (1:1) assigned after stratification for HCV genotype to receive either 1.5 mcg/Kg/week PegIFNalpha2b plus RBV 800-1200 mg/day or 180 mcg/week PegIFNalpha2a plus RBV 800-1200 mg/day for 24 or 48 weeks according to HCV genotype. The study was powered to detect a difference of at least 10% in safety and efficacy of the 2 regimens. **RESULTS:** The 212 patients on PegIFNalpha2a and the 219 patients on PegIFNalpha2b had similar baseline characteristics, including cirrhosis (20% vs 18%, respectively). By intention to treat, the 2 groups showed similar rates of treatment-related serious adverse events (1% vs 1%, respectively) and drop out rates for adverse effects (7% vs 6%, respectively). Overall, sustained virologic response (SVR) rate was higher in PegIFNalpha2a than in PegIFNalpha2b patients (66% vs 54%, respectively, P = .02), being 48% vs 32% in the 222 HCV-1 and -4 patients (P = .04), and 96% vs 82%, respectively, in the 143 HCV-2 patients (P = .01). PegIFNalpha2a independently predicted SVR in the logistic regression analysis (odds ratio, 1.88; 95% confidence interval: 1.20-2.96). **CONCLUSIONS:** Although the 2 regimens showed a similar safety profile, the PegIFNalpha2a-based treatment yielded significantly more SVR than PegIFNalpha2b. Copyright 2010 AGA Institute. Published by Elsevier Inc. All rights reserved.

Shiffman, M. L., C. Morishima, et al. (2009). "Effect of HCV RNA suppression during peginterferon alfa-2a maintenance therapy on clinical outcomes in the HALT-C trial." *Gastroenterology* **137**(6): 1986-94.

**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 microg/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,  $\geq 4$ -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 ( $P = .003$ ) 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  $\geq 4$  log(10) during maintenance therapy. No significant reduction in clinical outcomes was observed in these patients. **CONCLUSIONS:** Viral suppression by  $\geq 4$  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.