

Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection

Update #1: Preliminary Scan Report

May 2008

**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.

Roger Chou, MD
Susan Carson, MPH
Benjamin KS Chan, MS
Byron Care, MA

Update scan prepared by Susan Carson, MPH

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director



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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.

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

Populations
• 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
Treatments
• Pegylated interferon alfa-2a plus ribavirin
• Pegylated interferon alfa-2b plus ribavirin
Effectiveness outcomes
• 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)
Safety outcomes
• Overall adverse effects
• Withdrawals due to adverse effects
• Serious adverse events (including depression, suicidality)
• Specific adverse events (including myalgias, flu-like symptoms, fevers, chills, neutropenia, dose reduction)
Study designs
• 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 (2006 to April 11, 2008) 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/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote v 9.0[®]) 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 84 citations. Of those, there are 20 new potentially relevant controlled clinical trials. Titles and abstracts (where available) appear in Appendix A.

One head-to-head trial was identified; it reported only early viral response rates (12 weeks). Preliminary results of the IDEAL study, a head-to-head trial with SVR outcomes, have been publicized in a press release, but no publication is available yet. The press release is available at: http://www.hivandhepatitis.com/hep_c/news/2008/011408_ideal.html.

Other potentially relevant trials:

- 3 trials compared pegylated interferon alfa-2a or pegylated interferon alfa-2b to non-pegylated interferon alfa-2a.
- 2 trials compared pegylated interferon alfa-2a or pegylated interferon alfa-2b plus ribavirin to a control group receiving no treatment.
- 14 trials compared different regimens of the same pegylated interferon.

New Drugs

No new drugs in this class were identified.

New Indications

No new indications were identified.

New Safety Alerts

No new safety alerts were identified.

APPENDIX A: Abstracts of potentially relevant trials of pegylated interferons for chronic hepatitis C infection (N=20)

Head-to-head trial (early viral response only)

1. Di Bisceglie, A. M., R. H. Ghalib, et al. (2007). "Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C." Journal of Viral Hepatitis **14**(10): 721-9.

Patients infected with hepatitis C virus (HCV) genotype 1 and with serum HCV RNA concentrations over 800 000 IU/mL have relatively low rates of virologic response to pegylated interferons. The 2 forms of pegylated interferon have different pharmacokinetic profiles, and pilot studies comparing them have yielded varying results. We compared the virologic response to 12 weeks of treatment with peginterferon alpha-2a plus ribavirin vs peginterferon alpha-2b plus ribavirin in 380 patients who were infected with HCV genotype 1 and had high viral loads. We observed no between-group differences in viral load reduction over time and no differences in the percentage of patients treated with peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin who achieved early virologic response (EVR), defined as ≥ 2 -log reduction in HCV RNA concentration or undetectable HCV RNA at 12 weeks (66% vs 63%). Serum levels of interferon were more frequently below the level of quantitation in patients treated with peginterferon alpha-2b plus ribavirin (58-68%) than in those treated with peginterferon alpha-2a plus ribavirin (1-2%). Patients treated with peginterferon alpha-2b plus ribavirin had higher rates of discontinuation for safety reasons (6% vs 1%). In conclusion, a substantial percentage of patients infected with HCV genotype 1 and high viral load can achieve EVR when treated with peginterferon and ribavirin. The 2 pegylated interferons showed comparable anti-HCV activity during the first 12 weeks of treatment when combined with the same doses of ribavirin (1000-1200 mg/day), but discontinuations for safety reasons were higher in the patients treated with peginterferon alpha-2b plus ribavirin.

Trials of pegylated interferon vs non-pegylated interferon

1. Derbala, M. F., S. R. Al Kaabi, et al. (2006). "Treatment of hepatitis C virus genotype 4 with peginterferon alfa-2a: impact of bilharziasis and fibrosis stage." World Journal of Gastroenterology **12**(35): 5692-8.

AIM: To evaluate pegylated interferon alpha2a (PegIFN-alpha2a) in Egyptian patients with HCV genotype 4, and the impact of pretreatment viral load, co-existent bilharziasis and histological liver changes on response rate. METHODS: A total of 73 naive patients (61 with history of bilharziasis) with compensated chronic HCV genotype 4 were enrolled into: group A (38 patients) who received 180 mg PegIFN-alpha2a subcutaneously once weekly for a year and group B (35 patients) received IFN alpha-2a 3 MU 3 times weekly. Ribavirin was added to each regimen at a dose of 1200 mg. Patients were followed for 72 wk and sustained response was assessed. RESULTS: Significant improvement in both end of treatment response (ETR) ($P < 0.002$) and sustained response (SR) ($P < 0.05$) was noted with pegylated interferon, where ETR was achieved in 29 (76.3%) and 14 patients (40%) in both groups respectively, and 25 patients in group A

(65.8%) and 9 (25.7%) in group B could retain negative viraemia by the end of follow up period. Sustained virological response (SVR) showed a significant negative correlation with age and positive correlation with pretreatment inflammation in patients receiving PegIFN. Viral clearance after 3 mo of therapy was associated with high incidence of ETR and SR ($P < 0.001$), but without significant difference between both forms of interferon. Significant improvement in response was achieved in patients with high grade fibrosis (grade 3 and 4) with PegIFN-alpha2a, where SR was seen in 5 out of 13 patients in group A, but none in group B. There was no significant difference in response between bilharzial and non-bilharzial patients in both groups. In terms of safety and tolerability, neutropenia was the predominant side effect; both drugs were comparable.

CONCLUSION: PegIFN-alpha2a combined with ribavirin results in improvement in sustained response in HCV genotype 4, irrespective of history of bilharzial infestation.

2. Fargion, S., M. Borzio, et al. (2006). "Triple antiviral therapy in HCV positive patients who failed prior combination therapy." World Journal of Gastroenterology 12(33): 5293-300.

AIM: To assess the efficacy of triple therapy (peginterferon or high dose standard interferon, plus ribavirin and amantadine) in nonresponders to prior combination therapy. **METHODS:** A total of 196 patients were enrolled in a multicenter, open, randomized study. Patients were given 180 mug/wk of peginterferon-alpha-2a (40 kDa) plus ribavirin (800-1000 mg/d) and amantadine (200 mg/d) for 48 wk (group A) or interferon-alpha-2a (6 MU/d for 4 wk, 3 MU/d for 20 wk, and 3 MU tiw for 24 wk) plus ribavirin (800-1000 mg/d) and amantadine (200 mg/d) for 48 wk (group B). **RESULTS:** Overall sustained virologic response (SVR) was 26.6% (32.1% and 19.5% in group A and B, $P = 0.057$). Baseline ALT > 120 UI/L (OR 2.4; 95% CI: 1.11 to 5.20; $P = 0.026$) and HCV RNA negativity after 12 wk (OR 8.7; 95% CI: 3.87 to 19.74; $P < 0.0001$) were independently associated with SVR. Therapy discontinuation occurred less frequently in patients treated with peginterferon than standard interferon ($P = 0.036$). **CONCLUSION:** More than 25% of nonresponders to combination therapy can eradicate HCV infection when retreated with triple therapy, especially if they have a high baseline ALT and are treated with pegylated interferon.

3. Sjogren, M. H., R. Sjogren, Jr., et al. (2007). "Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin." Digestive Diseases & Sciences 52(6): 1540-7.

Achieving an antiviral response at a reasonable cost is a challenge in the treatment of patients with chronic hepatitis C. A previous study indicated that consensus interferon with ribavirin had promising activity against hepatitis C virus (HCV) genotype 1. The objective of this study was to determine the virologic response with consensus interferon or pegylated interferon alpha-2b plus weight-ribavirin in patients chronically infected with HCV genotype 1. Intention-to-treat analysis showed response in 37% and 41% of subjects treated with consensus interferon/ribavirin or pegylated interferon/ribavirin, respectively, with response rates of 42% and 44% observed in analysis of the per-protocol population, not a significant difference. Tolerability of the two treatment regimens was similar. In conclusion, both treatment regimens were safe and gave a similar antiviral response. It is possible that if consensus interferon is administered daily rather than three times weekly, eradication of HCV could be achieved in a larger proportion of patients infected with HCV genotype 1.

Trials of pegylated interferon vs no treatment

1. Arora, S., C. O'Brien, et al. (2006). "Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life." Journal of Gastroenterology & Hepatology **21**(2): 406-12.

BACKGROUND: Peginterferon alpha-2a (40 kDa) plus ribavirin is equally effective in chronic hepatitis C patients with normal or elevated alanine aminotransferase (ALT) values. This analysis, in patients with normal ALT levels, compared health-related quality of life (HRQoL) measurements between untreated control patients and treated patients grouped by virological response. HRQoL in the present population was also compared with HRQoL in patients with elevated ALT levels, observed in a previous study. **METHODS:** A total of 491 patients with persistently normal ALT levels were randomized to peginterferon alpha-2a (40 kDa)/ribavirin for 24 (group A) or 48 weeks (group B) or no treatment for 72 weeks (group C). Quality of life was assessed with valid instruments (self-administered Short Form (SF)-36 Health Survey and Fatigue Severity Scale). **RESULTS:** In groups A and B, patients with sustained virological responses after combination therapy had significantly better quality of life and less fatigue than patients without sustained responses. Differences were significant for five SF-36 domains, the SF-36 Physical Component score and both Fatigue Severity Scale scores. Viral clearance was not observed in any untreated patients (group C). Comparison with data from elevated ALT patients revealed little difference in baseline quality of life, although normal ALT patients had significantly higher scores related to mental health than elevated ALT patients. **CONCLUSIONS:** Eradication of HCV with peginterferon alpha-2a (40 kDa) plus ribavirin is associated with better quality of life and less fatigue in normal ALT patients. These patient benefits, coupled with the high probability of eradicating HCV, should be considered in making decisions about treating this population.

2. Iacobellis, A., M. Siciliano, et al. (2007). "Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study.[see comment]." Journal of Hepatology **46**(2): 206-12.

BACKGROUND/AIM: To evaluate long-term outcomes in decompensated HCV-related cirrhotic patients treated with antiviral therapy. **METHODS:** Of 129 eligible patients, 66 received peginterferon alfa-2b and ribavirin for 24 weeks, and 63 were controls. Survival and recurrence of liver failure events after therapy were main outcomes. **RESULTS:** Therapy was tolerated by 27 patients, dose reduced in 26 for toxicity, and discontinued in 13 for intolerance. End-of-therapy and sustained virological response (SVR) rates were 82.6% and 43.5% for HCV 2/3 patients, and 30.2% and 7.0% for HCV 1/4 patients. During therapy, odds ratios for severe infections or deaths due to infection were 2.95 (95% C.I. 0.93-9.3) and 1.97 (95% C.I. 0.40-9.51) in treated patients as compared with controls. During a follow-up of 30 months off-therapy, decompensated events occurred in 52, 33, and 3 of controls, non-responders, and SVR patients. Odds ratios for ascites,

encephalopathy, and oesophageal bleeding in treated patients significantly decreased as compared with controls. Annualized incidence of death was 2.34, 1.91, and 0 per 1000 patient-years, respectively, in controls, non-responders, and SVR patients. Survival curves showed early separation of SVR patients from both non-responders and controls at approximately 6 months. CONCLUSIONS: In decompensated cirrhotics, HCV clearance by therapy is life-saving and reduces disease progression.

Trials of different doses or durations of the same pegylated interferon

1. Bergmann, J. F., J. M. Vrolijk, et al. (2007). "Gamma-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-alpha-2b in chronic hepatitis C non-responders." *Liver International* **27**(9): 1217-25.

BACKGROUND: High-dose peginterferon-alpha (PegIFN-alpha) induction and prolongation of therapy may be an option to improve sustained virological response (SVR) rates among hepatitis C virus (HCV) non-responders, although a higher and a longer dosing of PegIFN-alpha may intensify side effects. **METHODS:** We randomized 53 patients, who previously failed with standard IFN-alpha+/-ribavirin, to a high-dose induction and an extended regimen with PegIFN-alpha-2b [3.0 microg/kg once weekly (q.w.) 12 weeks-->2.0 microg/kg q.w. 12 weeks-->1.5 microg/kg q.w. 48 weeks] or a standard regimen (1.5 microg/kg q.w. 48 weeks). All patients received daily weight-based ribavirin (800-1200 mg/day). The short-form 36 health survey was used to evaluate health-related quality of life (HRQL). **RESULTS:** Intention-to-treat analysis showed no significant difference in SVR rate (44% vs. 37%, $P=0.62$) and relapse rate (9% vs. 31%, $P=0.17$) between experimental and standard treatment. Overall, 80% of the [positive predictive value (PPV)] patients with rapid virological response (RVR, HCV-RNA negativity at week 4) achieved SVR. No significant dose-related differences in HRQL were seen between both groups. At baseline, genotype 2 or 3 [odds ratio (OR): 7.4, 95% confidence interval (CI): 1.4-33.3, $P=0.01$] and gamma-glutamyltransferase (GGT) levels $<2 \times$ ULN (upper limit of normal) (OR: 6.76, 95% CI: 1.5-31.3, $P=0.009$) were significantly associated with SVR. Multivariate logistic regression at week 4 showed that only baseline GGT $<2 \times$ ULN (OR: 7.3, 95% CI: 1.4-38.5, $P=0.01$) and RVR (OR: 15.6, 95% CI: 3.2-76.9, $P<0.001$) were independently predictive for SVR. **CONCLUSION:** Retreatment with PegIFN-alpha-2b and ribavirin for a minimum of 48 weeks should be considered in all patients unresponsive to previous IFN-based therapies. Baseline GGT values and RVR are highly predictive for retreatment outcome.

2. Carr, C., F. Blaine Hollinger, et al. (2007). "Efficacy of interferon alpha-2b induction therapy before retreatment for chronic hepatitis C." *Liver International* **27**(8): 1111-8.

BACKGROUND/AIMS: Chronic hepatitis C (HCV) patients who have failed previous treatment have low sustained viral response (SVR) rates with repeat treatment. We evaluated whether interferon (IFN) induction during retreatment improves response rates. **METHODS:** Two randomized, controlled trials were conducted in chronic HCV patients who failed IFN. In Study 1, patients received IFN 3 MU daily plus ribavirin (RBV) 1000 mg/day for 4 weeks, followed by IFN 3 MU TIW plus RBV 1000 mg/day for 44 weeks

(induction; n=232), or IFN 3 MU TIW plus RBV 1000 mg/day for 48 weeks (non-induction; n=237). In Study 2, patients received IFN 5 MU B.I.D. plus RBV 1000-1200 mg/day for 2 weeks, followed by pegylated IFN (PEG-IFN) 75-150 mug weekly plus RBV 1000-1200 mg/day for 46 weeks (induction; n=201), or PEG-IFN 75-150 mug weekly plus RBV 1000-1200 mg/day for 48 weeks (non-induction; n=206). The primary end point for both trials was SVR. RESULTS: Induction did not increase SVR compared with non-induction, but did increase the on-treatment response among genotype non-1 patients in Study 2. By intention-to-treat (ITT) analysis, SVR in Study 1 was 13% for induction vs. 9% for non-induction (P=NS). In Study 2 (ITT), SVR was 20% for induction vs. 24% for non-induction (P=NS). However, by non-ITT analysis of Study 2, genotype non-1-previous non-responders showed significantly higher response rates with induction than non-induction. CONCLUSION: For chronic HCV patients who have failed IFN, induction with retreatment does not improve SVR, but may be beneficial for patients with genotype non-1 HCV.

3. Dalgard, O., K. Bjoro, et al. (2008). "Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response." *Hepatology* 47(1): 35-42.

A recent nonrandomized pilot trial showed that hepatitis C virus (HCV) patients with genotype 2/3 and rapid virological response (RVR) had a 90% sustained virological response (SVR) rate after 14 weeks of treatment. We aimed to assess this concept in a randomized controlled trial. In the trial, 428 treatment-naive HCV RNA-positive patients with genotype 2 or 3 were enrolled. Patients with RVR were randomized to 14 (group A) or 24 (group B) weeks of treatment. Patients were treated with pegylated interferon alpha-2b (1.5 microg/kg) subcutaneously weekly and ribavirin (800-1400 mg) orally daily. The noninferiority margin was set to be 10% between the two groups with a one-sided 2.5% significance level. RVR was obtained in 302 of 428 (71%), and 298 of these were randomized to group A (n = 148) or group B (n = 150). In the intention-to-treat analysis, SVR rates were 120 of 148 (81.1%) in group A and 136 of 150 (90.7%) in group B (difference, 9.6%; 95% confidence interval, 1.7-17.7). Among patients with an HCV RNA test 24 weeks after the end of treatment, 120 of 139 (86.3%) patients in group A achieved SVR compared with 136 of 146 (93.2%) in group B (difference, 6.9%; 95% confidence interval, -0.1 to +13.9). CONCLUSION: We cannot formally claim that 14 weeks of treatment is noninferior to 24 weeks of treatment. However, the SVR rate after 14 weeks of treatment is high, and although longer treatment may give slightly better SVR, we believe economical savings and fewer side effects make it rational to treat patients with genotype 2 or 3 and RVR for only 14 weeks.

4. Diago, M., J. Crespo, et al. (2007). "Clinical trial: pharmacodynamics and pharmacokinetics of re-treatment with fixed-dose induction of peginterferon alpha-2a in hepatitis C virus genotype 1 true non-responder patients." *Alimentary Pharmacology & Therapeutics* 26(8): 1131-8.

BACKGROUND: Patients infected with hepatitis C virus genotype 1 who are true non-responders to previous therapy suffer from a very difficult-to-cure disease. New approaches to treatment are necessary. AIM: To explore the efficacy, pharmacokinetics and safety of fixed-dose induction with peginterferon alpha-2a and ribavirin in this difficult-to-cure population. METHODS: Seventy-five hepatitis C virus genotype 1 true non-responder patients to a previous interferon-based combination regimen were

randomised to receive peginterferon alpha-2a 360, 270 or 180 microg/week for 12 weeks, followed by 180 microg/week for 36 weeks, in combination with ribavirin (1000/1200 mg/day). Peginterferon alpha-2a concentration was measured throughout the study. RESULTS: Sustained virological response rates were 38%, 30% and 18%, in the 360, 270 and 180 microg/week groups, respectively (relapse rates: 25%, 50% and 64%, respectively). The area under the serum concentration-time curve of peginterferon alpha-2a from 0-12 weeks increased in a dose-dependent manner ($P < 0.0001$) and was associated with the sustained virological response (odds ratio: 1.35; 95% CI: 0.89, 2.06). The three regimens were equally well tolerated. CONCLUSION: Fixed-dose induction of peginterferon alpha-2a resulted in increased drug exposure and improved the likelihood of achieving a cure, without compromising safety in hepatitis C virus genotype 1 true non-responder patients.

5. Fontana, R. J., L. A. Bieliauskas, et al. (2007). "Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C." *Hepatology* **45**(5): 1154-63.

Treatment of chronic hepatitis C with pegylated interferon (peginterferon) and ribavirin can cause or exacerbate depression but its effects on cognitive function are largely unknown. The aim of this study was to determine whether treatment with peginterferon and ribavirin adversely impacts cognitive function in patients with chronic hepatitis C. Prior nonresponders to interferon were retreated with peginterferon alfa-2a and ribavirin for 24 (n=177) or 48 weeks (n=57) in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis trial. Cognitive function was prospectively assessed using a battery of 10 standardized neuropsychological tests at weeks 0, 24, 48, and 72. Cognitive impairment was defined based upon a global deficit score. The Beck Depression Inventory and Brief Symptom Inventory were used to assess mood status. The 57 subjects who completed 48 weeks of antiviral therapy reported significant increases in difficulty concentrating, emotional distress, and symptoms of depression, all of which improved after cessation of therapy [$P < 0.0001$, analysis of variance (ANOVA)]. Nonetheless, the frequency of cognitive impairment did not increase during the first 24 weeks of treatment in 177 patients (34% versus 32%, $P = 0.64$) nor in the 57 patients completing 48 weeks of treatment ($P = 0.48$, ANOVA). CONCLUSION: Retreatment of prior non-responders with peginterferon and ribavirin was not associated with objective evidence of cognitive impairment as measured by a comprehensive battery of neuropsychological tests. The lack of cognitive impairment is reassuring and suggests that self-reported symptoms of cognitive dysfunction are more likely related to the systemic and psychiatric side effects of antiviral treatment rather than measurable changes in cognition.

6. Fuster, D., R. Planas, et al. (2006). "Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV-coinfected patients with no early virological response.[erratum appears in Antivir Ther. 2006;11(5):667]." *Antiviral Therapy* **11**(4): 473-82.

OBJECTIVE: To assess the efficacy and safety of an extended treatment period in HIV/hepatitis C virus (HCV)-coinfected patients without early virological response (EVR). METHODS: Patients received pegylated interferon (peg-INF)-alpha2a 180 microg/week plus ribavirin 800 mg/d for 12 weeks. Patients achieving EVR at week 12 continued under therapy for an additional 12 or 36 weeks depending on genotype. Patients without EVR were randomized to complete the standard treatment or treatment

lasting 72 weeks (extension arm). RESULTS: One hundred and ten patients were included (mean age 38.7 years, mean weight 68 kg, 74% males, 74% on highly active antiretroviral therapy, mean CD4+ T-cell count 564 cells/mm³). Fifty-one patients harboured genotype 1, 44 genotype 2/3, and 15 genotype 4. Fifty-three had an HCV load >800,000 IU/ml. Premature interruptions occurred in 32.7%. EVR was achieved in 63.6% (51% in genotype 1, 88.6% in genotype 2/3, 33.3% in genotype 4). End-of-treatment response was 52.7% (47.2% in genotype 1, 68.2% in genotype 2/3, 26.7% in genotype 4). Sustained virological response (SVR) was achieved in 41.8% (37.3% in genotype 1, 54.6% in genotype 2/3, 20% in genotype 4). Only one patient allocated to the extended arm achieved SVR. The rate of drop-outs in the extension arm was 68%. The negative predictive value of EVR was 97.5%. CONCLUSIONS: This study shows no benefit of extending therapy in patients without EVR at week 12. Measures to improve adherence to HCV antiviral therapy should be considered when new approaches based on extended periods of treatment are investigated.

7. Kamal, S. M., S. S. El Kamary, et al. (2007). "Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response." *Hepatology* 46(6): 1732-40.

In patients chronically infected with hepatitis C virus (HCV) genotype 4, the optimum duration of therapy and the predictors of sustained virologic response (SVR) have not been adequately determined. In this study, 358 patients with chronic hepatitis C genotype 4 were randomly assigned to pegylated interferon (PEG-IFN) alpha-2b (1.5 mg/kg/week) plus oral ribavirin (10.6 mg/kg/day) for a fixed duration of 48 weeks (control group, n = 50) or for a variable duration (n = 318). In the variable-duration group, patients with undetectable HCV RNA at week 4 were treated for 24 weeks (group A, n = 69), patients with undetectable HCV RNA at week 12 were treated for 36 weeks (group B, n = 79), and the rest of the patients were treated for 48 weeks (group C, n = 160). The primary endpoint was SVR (undetectable HCV RNA 24 weeks after treatment cessation). Groups A-C and the control group had SVR rates of 86%, 76%, 56%, and 58%, respectively. After the study was controlled for predictors, a low baseline histologic grade and stage were associated with SVR (P < 0.029) in all groups. In addition, among patients in group C, older age (P = 0.04), a higher baseline body mass index (P = 0.013), and low baseline HCV RNA (P < 0.001) were also associated with SVR attainment. The incidence of adverse events and the rate of discontinuation were higher in patients in the variable-duration and fixed-duration groups treated for 48 weeks. Conclusion: In patients with chronic hepatitis C genotype 4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN alpha-2b and ribavirin for 24 weeks and 36 weeks, respectively, is sufficient.

8. Mangia, A., N. Minerva, et al. (2008). "Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial." *Hepatology* 47(1): 43-50.

It was hypothesized that in hepatitis C virus (HCV) genotype 1 patients, variable treatment duration individualized by first undetectable HCV RNA is as effective as standard 48-week treatment. Patients (n = 696) received peginterferon alfa-2a, 180 mg/week, or peginterferon alfa-2b, 1.5 mg/kg/week, plus ribavirin, 1000-1200 mg/day, for 48 weeks (standard, n = 237) or for 24, 48, or 72 weeks if HCV-RNA-negative at weeks 4, 8, or 12, respectively (variable, n = 459). Sustained virologic response (SVR)

was achieved in 45.1% [95% confidence interval (CI) 38.8-51.4] of the patients in the standard group and in 48.8% (CI 44.2-53.3) of the patients in the variable group ($P = 0.37$). The percentages of patients who first achieved undetectable HCV RNA at weeks 4, 8, or 12 were 26.7%, 27.8%, and 11.3%, respectively. In the standard treatment group, 87.1%, 70.3%, and 38.1% of patients who first achieved undetectable HCV RNA at 4, 8, or 12 weeks attained SVRs, respectively. In the variable group, corresponding SVR rates were 77.2%, 71.9%, and 63.5%. Low viremia levels and young age were independent predictors of response at week 4 [rapid virologic response (RVR)]. RVR patients with baseline viremia $\geq 400,000$ IU/mL achieved higher SVR rates when treated for 48 weeks rather than 24 weeks (86.8% versus 73.1%, $P = 0.14$). The only predictive factor of SVR in RVR patients was advanced fibrosis. Conclusion: Variable treatment duration ensures SVR rates similar to those of standard treatment duration, sparing unnecessary side effects and costs.

9. Mimidis, K., V. P. Papadopoulos, et al. (2006). "Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data." *Journal of Gastrointestinal & Liver Diseases* **15**(3): 213-9.

AIM: To evaluate the significance of induction with high doses of pegylated interferon -2b (Peg-IFNalpha-2b) and the predictability of sustained virologic response (SVR) in naive patients with chronic hepatitis C. METHODS: 188 consecutive naive patients with chronic hepatitis C were enrolled in a randomised controlled clinical trial. Patients were randomised to receive either Peg-IFN -2b 3.0 mcg/kg QW x 12 weeks followed by 1.5 mcg/kg QW x 36 weeks plus 800-1200 mg ribavirin (Arm A) or Peg-IFNalpha-2b 1.5 mcg/kg QW x 48 weeks plus 800-1200 mg ribavirin (Arm B). HCV-RNA was obtained at 0, 4, 8, 12, 16, 24, 48 and 72 weeks. Differences between schemes were evaluated by Kaplan-Meier curves. Predictability of SVR was assessed by two-way contingency table analysis and ROC curve analysis. RESULTS: From 176 patients, 75 had genotype 1, 15 genotype 2, 75 genotype 3 and 11 genotype 4. No statistical significance emerged in HCV-RNA positivity, side effects and withdrawals between schemes. Patients with genotype 1 achieved lower SVR (46.6%) in comparison to patients with genotypes 2/3 (94.1%, $p < 0.001$) and 4 (90.9%, $p = 0.002$). The most appropriate time for estimation of SVR for genotype 1 is week 8 (accuracy = 0.84, AUC = 0.90) while predictability increases with time in genotypes 2/3, reaching maximum accuracy = 0.93 and AUC = 0.76 at week 16. CONCLUSION: Induction with high doses of Peg-IFNalpha-2b does not preclude better outcome and rapid virologic response at 4 weeks of treatment sufficiently predicts SVR. These findings might be useful in an attempt to gain supportive evidence for decision making in difficult-to-treat patients.

10. Napoli, N., G. Giannelli, et al. (2008). "The use of different Peg-interferon alpha-2b regimens plus ribavirin in HCV-1b-infected patients after rapid virological response does not affect the achievement of sustained virological response." *Journal of Viral Hepatitis* **15**(4): 300-4.

In patients with chronic hepatitis C, rapid virological response (RVR) at week 4 of treatment seems to be strongly associated with a high probability of achieving a sustained virological response (SVR). The aim of this study was to investigate the outcome of different pegylated interferon-alpha2b (Peg-IFN-alpha2b) dosages plus ribavirin (RBV)

in patients with RVR. Forty-five naive patients chronically infected with hepatitis C virus (HCV)-1b started Peg-IFN-alpha2b (1.5 microg/kg/week) in combination with weight-based RBV doses (800-1200 mg/day). Thirty-one patients (68.9%) attained RVR at week 4 of therapy, while four further patients showed negative HCV-RNA values for the first time at week 12 and were considered early virological responders (EVR). The 31 RVR patients were randomized to receive either RBV plus 1.5 microg/kg/week (17 pts) or 1.0 microg/kg/week (14 pts) of Peg-IFN-alpha2b for the remaining 44 weeks. The two groups were matched for age, sex, baseline alanine aminotransferase levels, viral load and fibrosis score. After 6 months of post-treatment follow-up, the prevalence of SVR was 94.1% (16/17) among RVR patients treated with 1.5 microg/kg/week and 92.8% (13/14) in RVR patients treated with 1.0 microg/kg/week (P = not significant). A high-baseline viral load (P = 0.01) and bridging fibrosis/cirrhosis (P = 0.02) negatively influenced the likelihood of achieving RVR. On the contrary, the ability of RVR patients to achieve SVR did not correlate with these baseline characteristics in either of the treatment group. Finally, the SVR rate among EVR patients who responded after more than 4 weeks of treatment was significantly lower than among RVR patients (1/4 = 25% vs 29/31 = 93.5%; P = 0.0058), because of a high prevalence of post-treatment relapse among patients with EVR.

- 11.** Pearlman, B. L., C. Ehleben, et al. (2007). "Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders.[see comment]." Hepatology **46**(6): 1688-94.

In hepatitis C virus (HCV) genotype 1 infection, the duration of interferon-based therapy is a critical determinant in achieving sustained virologic response (SVR). Slow or late responders to peginterferon and ribavirin may benefit from an extended treatment course. We sought to determine if therapy extension could improve response rates in a United States population of slow responders. Slow response was defined by achieving at least a 2-log decrement in HCV RNA from baseline, yet having detectable HCV RNA at 12 weeks and undetectable HCV RNA at 24 weeks (polymerase chain reaction, TaqMan, Roche; detection limit 10 IU/mL). Patients were treatment-naive, chronically infected genotype 1-infected slow responders to 1.5 mug/kg/week of peginterferon-alpha2b and 800-1400 mg/day of ribavirin and were randomly assigned 1:1 to complete a total of 48 or 72 weeks of therapy. Dose reductions and treatment discontinuations for adverse events or laboratory abnormalities were similar between the 2 treatment arms. End-of-treatment response rates were similar in the 72-week group compared with those in the 48-week group (48% versus 45%; P value not significant). Overall, the rate of SVR was superior in patients treated for 72 weeks versus 48 weeks (38% versus 18%, respectively; P = 0.026). Conclusion: Extending the treatment duration from 48 weeks to 72 weeks in genotype 1-infected patients with slow virologic response to peginterferon-alpha2b and weight-based ribavirin significantly improves SVR rates. Treatment extension does not seem to increase the rate of dose reduction or therapy discontinuation.

- 12.** Shiffman, M. L., F. Suter, et al. (2007). "Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3.[see comment]." New England Journal of Medicine **357**(2): 124-34.

BACKGROUND: Patients infected with hepatitis C virus (HCV) genotype 2 or 3 have sustained virologic response rates of approximately 80% after receiving treatment with

peginterferon and ribavirin for 24 weeks. We conducted a large, randomized, multinational, noninferiority trial to determine whether similar efficacy could be achieved with only 16 weeks of treatment with peginterferon alfa-2a and ribavirin. **METHODS:** We randomly assigned 1469 patients with HCV genotype 2 or 3 to receive 180 mug of peginterferon alfa-2a weekly, plus 800 mg of ribavirin daily, for either 16 or 24 weeks. A sustained virologic response was defined as an undetectable serum HCV RNA level (<50 IU per milliliter) 24 weeks after the end of treatment. **RESULTS:** The study failed to demonstrate that the 16-week regimen was noninferior to the 24-week regimen. The sustained virologic response rate was significantly lower in patients treated for 16 weeks than in patients treated for 24 weeks (62% vs. 70%; odds ratio for 16 weeks vs. 24 weeks, 0.67; 95% confidence interval, 0.54 to 0.84; $P < 0.001$). In addition, the rate of relapse (a detectable HCV RNA level during follow-up in patients who had undetectable HCV RNA at the end of treatment) was significantly greater in the 16-week group (31%, vs. 18% in the 24-week group; $P < 0.001$). The sustained virologic response rates in patients with a pretreatment serum HCV RNA level of 400,000 IU per milliliter or less was 82% with the 16-week regimen and 81% with the 24-week regimen. Among patients with a rapid virologic response (an undetectable HCV RNA level by week 4), sustained virologic response rates were 79% in the 16-week group and 85% in the 24-week group ($P = 0.02$). **CONCLUSIONS:** Treatment with peginterferon and ribavirin for 16 weeks in patients infected with HCV genotype 2 or 3 results in a lower overall sustained virologic response rate than treatment with the standard 24-week regimen. (ClinicalTrials.gov number, NCT00077636 [ClinicalTrials.gov]). Copyright 2007 Massachusetts Medical Society.

13. Sood, A., V. Midha, et al. (2008). "Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience." Journal of Gastroenterology & Hepatology 23(2): 203-7.

BACKGROUND AND AIMS: In chronic hepatitis C virus (HCV) infection with genotype 3, therapy with pegylated interferon (peg-IFN) alfa-2b in a dose of 1.5 mug/kg/week and ribavirin (800-1000 mg/day) is recommended for 24 weeks. Reduced doses of peg-IFN may increase compliance and decrease cost and adverse events. This study aimed to assess the safety and efficacy of two different regimens of peg-IFN alfa-2b, in combination with ribavirin, in genotype 3 patients. **METHODS:** A total of 103 liver biopsy-proven chronic HCV patients with genotype 3, having alanine aminotransferase levels $> 1.2 \times \text{ULN}$ and positive HCV-RNA were randomized into two groups: group I ($n = 76$; age, 43.1 \pm 11.4 years; male/female, 67/9) received peg-IFN 1.0 mug/kg/week + ribavirin 10.6 mg/kg/day, while group II ($n = 27$; age, 37.3 \pm 11.6 years; male/female, 21/6) received peg-IFN 1.5 microg/kg/week + ribavirin 10.6 mg/kg/day. Patients in both groups were treated for 24 weeks. End of treatment viral response (ETVR) and sustained viral response (SVR) after a 6-month follow-up period were assessed. **RESULTS:** In both groups I and II, one patient was lost to follow-up, while one patient in group II withdrew due to side-effects. ETVR was seen in 72/76 (94.7%) of patients in the low dose group and 24/27 (88.9%) of patients in the high dose group ($P = 0.375$). SVR was seen in 60/76 (78.9%) of patients in the low dose group and 25/27 (92.6%) of patients in the high dose group ($P = 0.145$). Age (Pearson correlation coefficient = 0.263; $P = 0.008$) and fibrosis (correlation coefficient, 0.263; $P = 0.008$)

showed a significant correlation with the SVR. **CONCLUSION:** In patients with genotype 3, peg-IFN at 1.0 microg/kg/week with ribavirin is as effective as peg-IFN at 1.5 mug/kg/week with ribavirin.

- 14.** Yu, M.-L., C.-Y. Dai, et al. (2007). "A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C." *Gut* **56**(4): 553-9.

BACKGROUND: The recommended treatment for patients infected with hepatitis C virus genotype 2 (HCV2) is pegylated interferon (peginterferon) and ribavirin for 24 weeks. **AIM:** To assess whether a shorter 16-week treatment is as effective as a standard 24-week treatment. **METHODS:** Patients with HCV2 infection were randomised in a 1:2 ratio to either 16 weeks (n = 50) or 24 weeks (n = 100) of treatment with peginterferon alpha-2a (180 mug/week) and weight-based ribavirin 1000-1200 mg/day, with a 24-week follow-up period. A rapid virological response (RVR) was defined as seronegative for HCV RNA at 4 weeks of treatment, and the primary end point, sustained virological response (SVR), as seronegative for HCV RNA at the 24-week follow-up. **RESULTS:** The rate of RVR and SVR was 86% (43/50, 95% confidence interval (CI) 76% to 96%) and 94% (47/50, CI 87% to 100%), respectively, in the 16-week group, which was comparable to 87% (87/100, CI 80% to 94%) and 95% (95/100, CI 91% to 99%) in the 24-week group. Patients with RVR had a significantly higher SVR rate than patients without RVR in both 16-week (100% vs 57%, p = 0.015) and 24-week groups (98% vs 77%, p = 0.002). Multivariate analysis showed that RVR and age were independent factors associated with SVR. Both treatment arms were equally well tolerated. The incidence of alopecia was significantly higher in the 24-week group (49%) than in the 16-week group (20%, p = 0.001). **CONCLUSION:** 16 weeks and 24 weeks of peginterferon treatment with weight-based ribavirin at a dose of 1000-1200 mg/day provided equal efficacy in patients with HCV2 who achieved RVR at 4 weeks.