

Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection

Update #1: Preliminary Scan Report

June 2009

**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.

Date of Last Update Scans:

Preliminary Update Scan #1: May 2008

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
<ul style="list-style-type: none"> • Non-pregnant adult outpatients with chronic Hepatitis C infection
<i>Subgroups include:</i>
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Pegylated interferon alfa-2a plus ribavirin • Pegylated interferon alfa-2b plus ribavirin
Effectiveness outcomes
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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 (April 2008 to June 2009) 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 X2[®]) 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 90 citations. Of those, there are 19 new potentially relevant controlled clinical trials, including 5 head-to-head trials, 1 trial of pegylated interferon compared with non-pegylated interferon, and 13 trials of different doses or durations of the same pegylated interferon (Appendix A). Regarding the scope of the head-to-head trials, whereas the Original Report and the previous Preliminary Update Scan only found short-term (eight to twelve weeks) efficacy trials that only assessed end-of-treatment virologic responses, 3 of the 5 head-to-head trials identified in the current scan assessed sustained virologic response (SVR) over 24 to 48 weeks (Escudero 2008, Laguno 2009, Yenice 2006). Also, one head-to-head trial evaluated quality of life outcomes over 48 weeks (Nayman 2008).

Taken together with the 20 trials identified in the previous preliminary update scan, now there is a total of 39 trials that would potentially be added in the event of a full update of this topic.

New Drugs

PegIntron[™]/REBETOL[®] Combo Pack, containing PegIntron[™] REDIPEN[®] Single-dose Delivery System (peginterferon alfa-2b) and REBETOL[®] (ribavirin, USP) capsules was approved on June 13, 2008.

New Indications

In December 2008, the indication for peginterferon alfa-2b, given in combination with ribavirin, was expanded to include the treatment of pediatric patients 3-17 years of age with chronic hepatitis C. To clarify, the DERP review has been limited to the adult population and search results to-date have not included studies in the pediatric population. However, considering that the DERP Participating Organizations may contemplate expanding the scope of this review to include pediatric populations, we assessed titles and abstracts of citations from our existing library from the Original Review, as well as those from the current update scan, to obtain an estimation of the potential size of the body of relevant evidence from controlled clinical trials (Appendix B). We only found one publication that described the design of one placebo-controlled trial of dual therapy with pegylated interferon alpha-2a plus ribavirin in children, referred to as the PEDS-C trial (Murray 2007) and another uncontrolled, open-label study of pegylated interferon alpha-2b plus ribavirin (Wirth 2005).

New Safety Alerts

Peginterferon alfa-2b in combination with ribavirin:

In May 2009, the following information was added to the 'Postmarketing Experience' subsection of the 'Adverse Reactions' section of the Product Label:

“The following adverse reactions have been identified during post-approval use of PegIntron therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Blood and Lymphatic System Disorders- pure red cell aplasia, thrombotic thrombocytopenic purpura

Cardiac Disorders- palpitations

Ear and Labyrinth Disorders- hearing loss, vertigo, hearing impairment

Eye Disorders- Vogt-Koyanagi-Harada syndrome

Gastrointestinal Disorders- aphthous stomatitis

General Disorders and Administration Site Conditions- asthenic conditions (including asthenia, malaise, fatigue)

Immune System Disorders- cases of acute hypersensitivity reactions (including anaphylaxis, angioedema, urticaria); Stevens Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, erythema multiforme

Infections and Infestations- bacterial infection including sepsis

Metabolism and Nutrition Disorders- dehydration

Musculoskeletal and Connective Tissue Disorders- rhabdomyolysis, myositis

Nervous System Disorders- seizures, memory loss, peripheral neuropathy, paraesthesia, migraine headache

Psychiatric Disorders- homicidal ideation

Renal and Urinary Disorders- renal failure, renal insufficiency

Skin and Subcutaneous Tissue Disorders- psoriasis

Vascular Disorders- hypertension, hypotension

Peginterferon alfa-2a in combination with ribavirin:

In December 2008, the Patient Package Insert/Medication Guide was revised to include the risk of cerebrovascular complications due to stroke.

In April 2009, the Adverse Reaction section of the Product Label was modified based on postmarketing experience to include information about the risk of serious retinal detachment.

APPENDIX A: Abstracts of potentially relevant trials of pegylated interferons for chronic hepatitis C infection

Head-to-head trials

Escudero, A., F. Rodriguez, et al. (2008). "Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study." Journal of Gastroenterology & Hepatology **23**(6): 861-6.

BACKGROUND AND AIM: We assessed whether the two regimens of pegylated alpha-interferon-2b (PEG-IFN-alpha2b) plus ribavirin and pegylated alpha-interferon-2a (PEG-IFN-alpha2a) plus ribavirin showed differences in terms of sustained virological response, withdrawal due to side-effects and dose adjustment requirements in the treatment of naive chronic hepatitis C virus (HCV) patients. **METHODS:** A prospective non-randomized, open-label comparison was made of naive HCV-infected patients undergoing standard 24- or 48-week treatment with two PEG-IFN combined with weight-based dosing regimen of ribavirin (PEG-IFN-alpha2a/ribavirin, n = 91; PEG-IFN-alpha2b/ribavirin, n = 92). **RESULTS:** Sustained virological response was similar in PEG-IFN-alpha2a and PEG-IFN-alpha2b (65.9% vs 62%, P = 0.64), without differences according to genotype. In 117 patients with HCV genotype 1, the corresponding rates were 50.8% versus 46.6% (P = 0.713). Rapid virological response at 4 weeks, early virological response at 12 weeks and transient virological response were also similar. In the multivariate analysis, HCV genotype (odds ratio [OR] = 0.076, 95% confidence interval [CI] 0.029-0.198, P = 0.000) and presence of steatosis in the liver biopsy (OR = 2.799, 95% CI 1.362-5.755, P = 0.005) were significantly associated with response to antiviral therapy. The rate of withdrawals due to treatment-related adverse events was 13.2% in the group of PEG-IFN-alpha2a and 10.9% in the group of PEG-IFN-alpha2b. Dose modification of PEG-IFN was necessary in eight patients given PEG-IFN-alpha2a and in seven given PEG-IFN-alpha2b. **CONCLUSION:** The two PEG-IFN plus ribavirin have comparable anti-HCV activity as shown by similar percentages of patients with sustained virological response.

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." 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 through 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 through 4, SVRs were 28% versus 32% ($P = 0.67$) and 62% versus 71% ($P = 0.6$) in genotypes 2 through 3 for PEG 2b and PEG 2a, respectively. Early virological response (EVR; ≥ 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.

Nayman Alpat, S., G. Usluer, et al. (2008). "Effect of pegylated interferon treatments for chronic active hepatitis C on quality of life." *Journal of Chemotherapy* **20**(1): 101-5.

Health-related quality of life (HRQoL) during therapy was found to be improved in patients treated with peginterferon alpha-2a compared to patients receiving interferon alpha-2a. This study aimed to assess the effect of different pegylated interferon therapies used in the treatment of patients with chronic hepatitis C on HRQoL. Forty chronic hepatitis C patients were enrolled. 22 patients were given a combination of peginterferon alpha-2a plus ribavirin and 18 patients received a combination of peginterferon alpha-2b plus ribavirin for 48 weeks. Patients completed a Short Form-36 (SF-36) questionnaire at the start of treatment and at week 12, week 24 and week 48 of treatment and week 24 posttreatment to evaluate HRQoL. In conclusion, the effect of both combination treatments on quality of life was similar.

Scotto, G., V. Fazio, et al. (2008). "Early and sustained virological response in non-responders with chronic hepatitis C: a randomized open-label study of pegylated interferon-alpha-2a versus pegylated interferon-alpha-2b." *Drugs* **68**(6): 791-801.

OBJECTIVES: The purpose of this randomized open-label study was to assess the efficacy of treatment with pegylated interferon-alpha-2a versus pegylated interferon-alpha-2b, both plus ribavirin, in inducing early and sustained virological response (EVR and SVR) in chronic hepatitis C non-responders. **PATIENTS AND METHODS:** A total of 108 patients with chronic hepatitis C who were non-responders to previous combined therapy (standard interferon-alpha plus ribavirin for ≥ 3 months) were enrolled and equally randomized into two groups in this intention-to-treat analysis. The patients exhibited similar baseline features. One group received subcutaneous pegylated interferon-alpha-2a 180 microg once weekly, while the other was treated with subcutaneous pegylated interferon-alpha-2b 1.5 microg/kg once weekly. Ribavirin 15 mg/kg/day was included in both protocols. Treatment duration for EVR was 12 weeks. Patients who demonstrated non-detectable hepatitis C virus (HCV) RNA or a ≥ 2 log₁₀ reduction in viral load at week 12 continued therapy up to 48 weeks, with assessments every 3 months during a follow-up of 24 weeks. **RESULTS:** All patients in both groups completed the EVR study, then seven patients receiving pegylated interferon-alpha-2a and seven patients receiving pegylated interferon-alpha-2b discontinued treatment as a result of severe

adverse effects. After 12 weeks of treatment, viral load reduction was $>2 \log(10)$ with both pegylated interferon-alpha-2a (-2.53) and pegylated interferon-alpha-2b (-2.48) with no significant difference. At the end of week 48, HCV RNA was undetectable in 14 of 54 patients (25.9%) receiving pegylated interferon-alpha-2a and in 15 of 54 patients (27.7%) receiving pegylated interferon-alpha-2b. When terminating follow-up, an SVR was observed in 11 of 54 patients (20.4%) who received pegylated interferon-alpha-2a and 10 of 54 patients (18.4%) receiving pegylated interferon-alpha-2b. The incidence and severity of adverse events was similar in both groups. CONCLUSIONS: Our results seem to show that in chronic hepatitis C patients who are non-responsive to previous therapy, EVR to the two pegylated interferons did not significantly differ with a similar therapeutic efficacy defined as SVR.

Yenice, N., O. Mehtap, et al. (2006). "The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients." Turkish Journal of Gastroenterology **17**(2): 94-8.

BACKGROUND/AIMS: We aimed to compare viral responses to pegylated interferon 2a plus ribavirin with pegylated interferon alpha 2b plus ribavirin. METHODS: Patients with the following characteristics were included: anti HCV(+); normal and/or elevated serum transaminase levels; positive HCV RNA by quantitative PCR; and at least stage 1 fibrosis according to Knodell Scoring System on liver biopsy. Patients were assigned into two groups. Group 1 consisted of 37 patients (24 female, 13 male) who received pegylated interferon alpha 2a 180 microg s.c. weekly plus ribavirin adjusted for patient's weight. All patients were genotype 1. Group 2 consisted of 37 patients (27 female, 10 male) who received pegylated interferon alpha 2b 1.5 microg/kg s.c. weekly plus ribavirin adjusted for patient's weight. At week 24, the treatment was discontinued in patients positive for HCV RNA by PCR, while patients negative for HCV RNA continued treatment up to 48 weeks. The end of treatment and sustained virologic responses of the patients were ascertained by assessing HCV RNA levels at the end of the treatment and after 24 weeks follow-up after the cessation of treatment. Results: At week 48, the proportion of patients with negative HCV RNA (end of treatment viral response) was 28/37 (75.7%) in Group 1 and 27/37 (73%) in Group 2. The group sustained virologic response rates were 48.6% and 35.1% for Group 1 and Group 2, respectively. No significant differences were noted between the two groups. Conclusion: The two pegylated interferon molecules were similar in terms of sustained virologic response rate.

Trials of pegylated interferon compared with non-pegylated interferon

Roffi, L., G. Colloredo, et al. (2008). "Pegylated interferon-alpha2b plus ribavirin: an efficacious and well-tolerated treatment regimen for patients with hepatitis C virus related histologically proven cirrhosis." Antiviral Therapy **13**(5): 663-73.

BACKGROUND: Little is known about the efficacy, safety and tolerability of pegylated interferon plus ribavirin treatment in patients with chronic hepatitis C virus (HCV) infection and histologically proven fully established cirrhosis. We aimed here to evaluate the safety of this regimen in such patients and to identify baseline and on-treatment predictors of a sustained virological response (SVR). **METHODS:** Patients with histologically proven, HCV-induced cirrhosis were randomized to receive pegylated interferon-alpha2b (PEG-IFN-alpha2b; 1.0 microg/kg/week, n=56; group A) or recombinant interferon-alpha2b (IFN-alpha2b; 3 million IU three times/week, n=36; group B), each in combination with a weight-based dose of ribavirin (800-1,200 mg/day) for up to 48 weeks. The primary endpoint of the study was the assessment of SVR, defined as undetectable HCV RNA 24 weeks after treatment cessation. **RESULTS:** Overall, 40% (37/93) of patients attained SVR: 44% (25/57) in group A and 33% (12/36) in group B (P=0.31). SVR rates were significantly higher in genotype 2/3 patients than in genotype 1 patients (69% versus 25%; P<0.0001). Platelet count at baseline, rapid virological response, and early virological response were predictors of SVR. Twelve patients discontinued treatment because of an adverse event and 20 patients required ribavirin dose reduction for the management of anaemia. **CONCLUSIONS:** PEG-IFN-alpha2b plus ribavirin for 48 weeks is an efficacious and well-tolerated treatment regimen for patients with HCV-induced cirrhosis. Although SVR rates were more satisfactory in genotype 2/3 than in genotype 1 patients, our study identified additional predictors of response that could allow physicians to better manage treatment in this 'difficult-to-cure' subset of patients.

Trials of different doses or durations of the same pegylated interferon

Bonkovsky, H. L., A. D. Tice, et al. (2008). "Efficacy and safety of peginterferon alfa-2a/ribavirin in methadone maintenance patients: randomized comparison of direct observed therapy and self-administration." *American Journal of Gastroenterology* **103**(11): 2757-65.

BACKGROUND: Adherence to chronic hepatitis C (CHC) treatment may be particularly challenging in methadone maintenance patients. We assessed the safety, tolerability, and efficacy of peginterferon alfa-2a/ribavirin treatment in methadone maintenance patients previously untreated for CHC. METHODS: Patients were randomized 1:1 to direct observed therapy (DOT) or self-administration (SA) of peginterferon alfa-2a. DOT patients were seen weekly at methadone clinics; SA patients were seen less frequently, only at investigative sites. Genotype 1-infected patients were treated for 48 wk with peginterferon alfa-2a (180 microg/wk)/ribavirin (1,000/1,200 mg/day); genotypes 2- and 3-infected patients were treated for 24 wk with peginterferon alfa-2a (180 microg/wk)/ribavirin (800 mg/day). RESULTS: Based on defined efficacy stopping rules, 77% (37/48) completed their targeted length of treatment, and 44% (21/48) achieved sustained virologic response (SVR). Two DOT and 3 SA patients were withdrawn for safety reasons and 6 and 9, respectively, for nonsafety reasons. Over 60% and 50% of each group were >80% compliant with the planned cumulative doses of peginterferon alfa-2a and ribavirin, respectively, and over 60% with overall treatment duration. SVR rates were 54% (13/24) for DOT and 33% (8/24) for SA; 23% (3/13) and 38% (6/16), respectively, for genotype 1 and 91% (10/11) and 25% (2/8), respectively, for genotypes 2 and 3. Stepwise logistic regression analysis, showed that DOT (vs SA; OR 3.27, 95% CI 0.90-11.91, P = 0.073) and Caucasian race (vs Other; OR 13.31, 95% CI 1.42-124.71, P = 0.023) were predictors of SVR. CONCLUSION: Peginterferon alfa-2a/ribavirin can be used safely and successfully in CHC patients receiving methadone maintenance.

Ferenci, P., H. Brunner, et al. (2008). "A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3." *Hepatology* **47**(6): 1816-23.

We compared the efficacy and tolerability of 24 weeks of treatment with ribavirin 800 mg/day (group A) or 400 mg/day (group B) plus peginterferon alfa-2a 180 mug/week in treatment-naive patients infected with hepatitis C virus (HCV) genotype 2 or 3. A total of 97 of 141 patients randomized to group A (68.8%, 95% confidence interval [CI] 60.5%-76.3%) and 90 of 141 patients randomized to group B (63.8; 95% CI 55.3%-71.7%) achieved a sustained virological response, defined as undetectable serum HCV RNA at the end of untreated follow-up (week 48). Among patients infected with genotype 3, the rate of sustained virological response was 67.5% (95% CI 58.4%-75.6%) in group A and 63.9% (95% CI 54.7%-72.4%) in group B, and among patients infected with genotype 2, the rate of sustained virological response was 77.8% (95% CI 54.2%-93.6%) in group A and 55.6% (95% CI 38.4%-83.7%) in group B. Relapse rates in the 2 treatment groups were similar (17% in group A and 20% in group B). The incidence of adverse events, laboratory abnormalities, and dose reductions was similar in the 2 treatment groups. CONCLUSION: The results suggest that when administered for 24 weeks with

peginterferon alfa-2a, ribavirin doses of 400 and 800 mg/day produce equivalent outcomes in patients infected with HCV genotype 3.

Fried, M. W., D. M. Jensen, et al. (2008). "Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin." *Hepatology* **48**(4): 1033-43.

Treatment response remains suboptimal for many patients with chronic hepatitis C, particularly those with genotype 1 and high levels of viremia. The efficacy of high-dose regimens of peginterferon alfa-2a and ribavirin was compared with conventional dose regimens in patients with features predicting poor treatment responses. Eligible treatment-naive adults with genotype 1 infection, hepatitis C virus (HCV) RNA >800,000 IU/mL and body weight >85 kg were randomized to double-blind treatment with peginterferon alfa-2a at 180 or 270 microg/week plus ribavirin at 1200 or 1600 mg/day for 48 weeks (four regimens were evaluated). The primary endpoint was viral kinetics during the first 24 weeks of therapy. Among patients receiving peginterferon alfa-2a (270 microg/week) the magnitude of HCV RNA reduction was significantly greater than for patients randomized to the conventional dose of peginterferon alfa-2a (180 microg/week) for the pairwise comparison for ribavirin at 1600 mg/day ($P = 0.036$) and numerically greater for the pairwise comparison for ribavirin at 1200 mg/day ($P = 0.060$). Patients randomized to the highest doses of peginterferon alfa-2a (270 microg/week) and ribavirin (1600 mg/day) experienced the numerically highest rates of sustained virologic response (HCV RNA < 50 IU/mL) and the lowest relapse rate (47% and 19%, respectively). The arm with the higher doses of both drugs was less well-tolerated than the other regimens. CONCLUSION: Higher fixed doses of peginterferon alfa-2a (270 microg/week) and ribavirin (1600 mg/day) may increase sustained virologic response rates compared with lower doses of both drugs in patients with a cluster of difficult-to-treat characteristics.

Gelderblom, H. C., H. L. Zaaijer, et al. (2008). "Prediction of virologic response in difficult-to-treat chronic hepatitis C patients during high-dose interferon induction therapy." *Scandinavian Journal of Gastroenterology* **43**(7): 857-69.

OBJECTIVE: To determine (i) whether early viral kinetics or other markers during a modified treatment regimen are predictors of treatment outcome and (ii) whether fast responders can be treated for 24 weeks, without compromising the sustained virologic response (SVR) rate. MATERIAL AND METHODS: One hundred "difficult-to-treat" chronic hepatitis C patients (46 previous non-responders/relapsers (any genotype), 54 treatment-naive patients genotypes 1 and 4) were treated with triple antiviral induction therapy: amantadine hydrochloride and ribavirin, combined with 6 weeks interferon alfa-2b induction (weeks 1-2: 18 MU/day, weeks 3-4: 9 MU/day, weeks 5-6: 6 MU/day), thereafter combined with weekly peginterferon alfa-2b. Fast responders ($\geq 3 \log_{10}$ HCV RNA decline at week 4) were randomized to 24 or 48 weeks. Slow responders ($< 3 \log_{10}$ HCV RNA decline at week 4) were treated for 48 weeks. Treatment was stopped in patients with detectable HCV RNA at week 24. RESULTS: Thirty-six patients achieved SVR: 28 of 60 fast responders (47%) versus 8 of 32 slow responders (25%, $p < 0.05$).

Relapse rates among fast responders treated for 24 or 48 weeks were 27% and 20%, respectively (p=NS). SVR in fast responders was independent of baseline HCV RNA \geq or $<$ 600,000 IU/mL. All treatment-naïve patients with HCV RNA $<$ 5 IU/mL at week 1 or 2 achieved SVR; all treatment-naïve patients with HCV RNA \geq 5 IU/mL at week 16 became non-SVR. In previous non-responders/relapsers, the predictive value for SVR was 83% if HCV RNA was $<$ 5 IU/mL at week 2; all previous non-responders/relapsers with HCV RNA \geq 5 IU/mL at week 8 became non-SVR. CONCLUSIONS: With high-dose interferon induction, SVR and non-SVR can be predicted reliably within 16 weeks. Fast responders can be treated for 24 weeks, and SVR is independent of baseline viral load in fast responders.

Horsmans, Y., I. Collez, et al. (2008). "Weekly pegylated interferon alpha-2b vs daily interferon a-2b versus standard regimen of interferon a-2b in the treatment of patients with chronic hepatitis C virus infection." *Acta Gastroenterologica Belgica* **71**(3): 293-7.

BACKGROUND AND STUDY AIMS: The combination of Pegylated (PEG)interferon alpha-2b and ribavirin is considered to be the standard treatment for naïve chronic hepatitis C patients. Study aims are to evaluate the differences between standard interferon and PEG-interferon by conducting a multi-centre, controlled randomized trial comparing 3 groups. Group A : daily interferon alfa-2b at a dose of 4 MIU + ribavirin, Group B : PEG-interferon alfa-2b at a dose of 100 mcg/week + ribavirin; Group C: interferon alfa-2b at a dose of 3 MIU TIW + ribavirin **PATIENTS AND METHODS:** Multicentred, open label study including naïve chronic Hepatitis C Virus patients randomised in three groups with a ratio of 2:2:1. Group A: daily interferon alpha-2b (4 MIU s.c. for patients $>$ 65 kg or 0.06 MIU/kg $<$ 65 kg) and ribavirin, group B: PEG-interferon alpha-2b (100 microg s.c. weekly for patients $>$ 65 kg or 1.5 microg/kg weekly for patients $<$ 65 kg) and ribavirin and group C (reference arm) : interferon alpha-2b (3MIU s.c. TWI) and ribavirin. The duration of the treatment was 48 weeks for all 3 groups, with a 6 month follow-up period. 336 patients were enrolled in the study and included in the intention-to-treat analysis; 78 never started treatment (35 in group A, 28 in group B and 15 in group C): 101 in group A, 98 in group B and 59 in group C. **RESULTS:** Demographic data, PCR results and reasons for early withdrawal have been statistically analysed. At baseline, the 3 groups did not show any statistical difference regarding age, gender, race, genotypes and METAVIR score. At week 24 on treatment, HCV ribonucleic acid RNA was undetectable in 87% in group A, in 79% in group B and in 69% in group C. At the end of treatment, 73% 74% and 58% respectively, had a negative PCR result. At week 24 of follow-up, these results were 71%, 64% and 48%, respectively. When comparing the efficacy of the daily interferon (+ ribavirin) and the PEG-interferon (+ ribavirin) regimen, no statistical difference was found (p = 0.32). In group A, 38% of drop-outs were due to adverse events compared to 37% in group B and 58% in group C. No statistical differences were observed regarding safety. **CONCLUSION:** Daily weight based interferon alpha-2b dosing and PEG interferon alpha-2b weighed based dosing once weekly both in combination with Ribavirin offer the same efficacy and safety rates.

Ide, T., T. Hino, et al. (2009). "A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C." American Journal of Gastroenterology **104**(1): 70-5.

OBJECTIVES: The treatment of patients with hepatitis C virus (HCV) genotype 1 with peginterferon plus ribavirin treatment for more than 48 weeks demonstrated high sustained virological response (SVR) rates. Although many studies extended the duration of therapy from 48 weeks to 72 weeks, the optimal duration has not yet been determined. **METHODS:** A total of 113 genotype 1b patients with high viral load were randomized at baseline to the standard (n=56) or extended (n=57) treatment group. The standard group patients received 48 weeks of peginterferon plus ribavirin treatment. In the extended group, the treatment was performed for 44 weeks after patients became negative for HCV RNA (total duration 48-68 weeks). **RESULTS:** The SVR rate of the standard and extended group was 36% (20 of 56) and 53% (30 of 57; P=0.07). However, the extended group patients who became negative for HCV RNA between weeks 16 and 24 had a significantly higher SVR rate (78%; 7 of 9) than that of standard group (9%, 1 of 11; P=0.005). The predictive factors for the SVR were the treatment regimen (the standard vs. extended treatment) and the time to HCV RNA negative-status. **CONCLUSIONS:** The extended treatment significantly increased the SVR rate in patients who were HCV RNA negative at 16-24 weeks.

Jensen, D. M., P. Marcellin, et al. (2009). "Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial.[summary for patients in Ann Intern Med. 2009 Apr 21;150(8):l-34; PMID: 19380849]." Annals of Internal Medicine **150**(8): 528-40.

BACKGROUND: Many patients with chronic hepatitis C have not responded to therapy with pegylated interferon plus ribavirin. **OBJECTIVE:** To evaluate use of peginterferon-alpha2a plus ribavirin to re-treat nonresponders to peginterferon-alpha2b plus ribavirin. **DESIGN:** Randomized, parallel-group trial conducted between September 2003 and February 2007. Patients and researchers were not blinded to intervention assignment. Random assignment was centralized, computer-generated, and stratified by geographic region, hepatitis C virus (HCV) genotype, and histologic diagnosis. **SETTING:** 106 international centers. **PATIENTS:** 950 nonresponders to 12 or more weeks of therapy with peginterferon-alpha2b plus ribavirin. **INTERVENTION:** Peginterferon-alpha2a, 360 microg/wk, for 12 weeks, then 180 microg/wk to complete 72 weeks (group A) or 48 weeks (group B), or peginterferon-alpha2a, 180 microg/wk for 72 weeks (group C) or 48 weeks (group D). All patients received ribavirin, 1000 or 1200 mg/d. **MEASUREMENTS:** Sustained virologic response (SVR), defined as undetectable (<50 IU/mL) HCV RNA levels 24 weeks after the end of treatment. **RESULTS:** The SVR rates in groups A (n = 317), B (n = 156), C (n = 156), and D (n = 313) were 16%, 7%, 14%, and 9%, respectively (relative risk [RR] for group A vs. group D [the primary comparison], 1.80 [95% CI, 1.17 to 2.77]; P = 0.006). Extended treatment duration increased SVR rates (16% for 72 weeks [groups A and C] vs. 8% for 48 weeks [groups B and D]; RR, 2.00 [CI, 1.32 to 3.02]; P < 0.001). Complete viral suppression (HCV RNA level <50 IU/mL) at week 12 was achieved in 21% of patients in groups A and B and 13% of those in groups C and D. Rates of SVR were

49% (77 of 157 patients) and 4% (32 of 719 patients) among those with and without complete viral suppression at week 12, respectively. LIMITATION: Nonresponders to peginterferon-alpha2a plus ribavirin were not evaluated. CONCLUSION: Re-treating nonresponders to therapy with peginterferon-alpha2b plus ribavirin for 72 weeks significantly increases SVR rates compared with re-treating them for 48 weeks. The overall SVR rate was low, but patients who are most likely to respond to re-treatment can be identified at week 12. PRIMARY FUNDING SOURCE: Roche.

Lagging, M., N. Langeland, et al. (2008). "Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection.[see comment]." Hepatology **47**(6): 1837-45.

Previous trials investigating the efficacy of treatment durations shorter than the standard of 24 weeks for chronic hepatitis C virus (HCV) genotype 2/3 infections have yielded discordant results. The aims of this investigator-initiated phase III study were to compare the efficacy of 12 or 24 weeks of treatment and to identify patients suitable for short-term therapy. Three hundred eighty-two genotype 2/3-infected patients [intention-to-treat (ITT) population] at 31 centers in Denmark, Finland, Norway, and Sweden were randomized to 12 or 24 weeks of peginterferon alpha-2a (180 microg/week) plus ribavirin (800 mg/day). Twelve weeks of therapy was inferior to 24 weeks in the ITT population (sustained viral response [SVR] rates: 59% versus 78%, $P < 0.0001$) and in the subgroups of patients infected with genotype 2 (56% versus 82%, $P = 0.006$) or 3 (58% versus 78%, $P = 0.0015$). These differences were observed regardless of the fibrosis stage. Age and HCV-RNA levels on days 7 and 29 were independent predictors of SVR. Short-term treatment was useful in patients < 40 years old, especially if HCV-RNA was undetectable on day 29, and also in patients ≥ 40 years old, provided that HCV-RNA was below 1000 IU/mL on day 7 in addition to being undetectable on day 29. If neither of these two criteria were met for patients ≥ 40 years old, 24 weeks of therapy was superior ($P < 0.0001$). CONCLUSION: Peginterferon/ribavirin treatment for 12 weeks in HCV genotype 2/3 infection is overall inferior to 24 weeks of treatment but may be useful in some patients with a rapid initial clearance of virus.

Liu, C.-H., C.-J. Liu, et al. (2008). "Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial." Clinical Infectious Diseases **47**(10): 1260-9.

BACKGROUND: Comparable sustained virologic response (SVR) rates have been documented between Asian patients who received 24 weeks of pegylated interferon (IFN) plus ribavirin and white patients who received 48 weeks of combination therapy for hepatitis C virus genotype 1 (HCV-1) infection. Whether a 48-week course of combination therapy shows a better SVR rate than a 24-week course of such therapy among Asian patients with HCV-1 infection has not been confirmed in multicenter, randomized studies. METHODS: In this multicenter, randomized trial, 308 treatment-naive HCV-1-infected Asian patients were randomly assigned to receive either 24 or 48 weeks of pegylated IFN-alpha-2a (180 microg per week) plus ribavirin (1000-1200

mg/day) therapy. The primary end point was SVR, defined as an undetectable serum HCV RNA level 24 weeks after discontinuation of therapy. In addition, rapid virologic response (RVR) was defined as an undetectable serum HCV RNA level at week 4 of therapy, and complete early virologic response was defined as an undetectable serum HCV RNA level at 12 weeks of therapy in the absence of RVR. RESULTS: By intention-to-treat analysis, patients who received 48 weeks of therapy had a significantly higher SVR rate than did those who received 24 weeks of therapy (76% vs. 56%; $P < .001$). Among patients with a baseline serum HCV RNA level $<800,000$ IU/mL and RVR, SVR rates were comparable between 24- and 48-week courses of therapy (94% vs. 100%; $P = .13$). In contrast, 48 weeks of therapy was associated with a significantly higher SVR rate than was 24 weeks of therapy among patients without RVR (39% vs. 16%; $P = .01$) and among those who achieved a complete early virologic response (44% vs. 20%; $P = .02$). CONCLUSIONS: In treatment-naïve Asian patients with HCV-1 infection, 48 weeks of pegylated IFN-alpha-2a plus ribavirin therapy is associated with a higher SVR rate, compared with 24 weeks of such therapy. Patients with a baseline serum HCV RNA level $<800,000$ IU/mL and who have achieved an RVR can receive a 24-week course of therapy without compromising the SVR rates; however, those who have not achieved an RVR but who have achieved a complete early virologic response should receive a 48-week course of therapy.

Pugnale, P., E. Herrmann, et al. (2008). "Hepatitis C viral kinetics in plasma and peripheral blood mononuclear cells during pegylated interferon-alpha2a/ribavirin therapy." Journal of Hepatology **48**(6): 932-8.

BACKGROUND/AIMS: Analysis of hepatitis C virus (HCV) RNA kinetics in compartments other than plasma may help in understanding HCV replication and identifying clinically significant patterns of treatment response. METHODS: After 6 weeks of pegylated interferon-alpha2a/ribavirin therapy, 74 chronic hepatitis C patients were randomized to individualized or standard treatments for another 42 weeks. HCV RNA was quantified in peripheral blood mononuclear cells (PBMCs) by TaqMan-based real-time PCR and compared to plasma HCV RNA. RESULTS: HCV RNA declines in PBMCs and plasma were comparable during the initial 12 weeks of therapy (Spearman's rank correlation range over different time points, 0.73-0.97). However, a delay of HCV RNA decay in PBMCs, expected if kinetics in PBMCs only reflected kinetics in plasma, was rarely observed. For many patients, HCV RNA decline in PBMCs started as early as in plasma and for some of them the kinetics strongly differed in the two compartments, hinting at a compartment-specific HCV replication and treatment effect. Fast viral decay in PBMCs was associated with sustained virological response, but viral kinetics in PBMCs added only minor predictive information compared with kinetics in plasma. CONCLUSIONS: Future kinetics studies of HCV RNA during therapy with new antivirals should take into account their compartment-specific effect.

Tang, K. H., E. Herrmann, et al. (2008). "Clinical trial: individualized treatment duration for hepatitis C virus genotype 1 with peginterferon-alpha 2a plus ribavirin." Alimentary Pharmacology & Therapeutics **27**(9): 810-9.

BACKGROUND: Individualized treatment regimens, taking into account the heterogeneity of patients with chronic hepatitis C, are needed to improve treatment outcomes. **AIM:** To investigate prospectively the period of undetectable viraemia required for a high rate of sustained virological response in patients with chronic hepatitis C genotype 1 and the relationship to early viral kinetics. **METHODS:** Forty-five chronic hepatitis C genotype 1 patients were given peginterferon-alpha 2a plus ribavirin. Viraemia and hepatocyte HCV-RNA levels were quantified using a TaqMan assay. Beyond the first time point of undetectable viraemia (<20 IU/mL) between baseline and treatment week 12, 32 of 45 (71%) patients were randomized to additional 12 weeks (G12); 24 weeks (G24) or 36 weeks therapy (G36). The remaining 13 patients received 48 weeks' treatment (G48). **RESULTS:** The sustained virological response rates were: G12--five of 11 (45%); G2 --eight of 10 (80%); G36--eight of 11 (73%); G48--four of 13 (31%). The anti-viral efficacy (epsilon) and treatment-induced loss of infected hepatocytes (Mdelta), were significantly higher in patients with early viral clearance. In G12, patients with sustained virological response had lower baseline viraemia than those who relapsed. **CONCLUSIONS:** Early viraemia clearance is a better marker than baseline viral load and differentiates chronic hepatitis C genotype 1 with high or low probability of sustained virological response. In patients with viraemia clearance within 12 weeks of starting peg-interferon/ribavirin therapy, an additional period of undetectable viraemia of minimum 24 weeks is required for high sustained virological response.

Toyoda, H., T. Kumada, et al. (2009). "Eight-week regimen of antiviral combination therapy with peginterferon and ribavirin for patients with chronic hepatitis C with hepatitis C virus genotype 2 and a rapid virological response." Liver International **29**(1): 120-5.

BACKGROUND: It remains unclear how we can shorten the treatment duration of antiviral combination therapy with peginterferon and ribavirin for patients with chronic hepatitis C virus (HCV) genotype 2 infection who achieved a rapid virological response (RVR). **AIM:** We compared the efficacy of antiviral combination therapy with peginterferon and ribavirin for 8 vs. 24 weeks for the treatment of patients with HCV genotype 2 infection and with RVR. **METHODS:** Sixty-one patients were enrolled. Serum HCV RNA was not detected at 4 weeks after the start of treatment in 32 patients with an RVR. These 32 patients were randomly assigned to 8-week (n=15) or 24-week (n=17) treatment regimens. Patients in the 8-week group who relapsed underwent a 24-week retreatment. **RESULTS:** No significant difference in patient characteristics was observed between the 8- and the 24-week treatment groups. A sustained virological response (SVR) was seen in five of 15 patients (33.3%) in the 8-week treatment group and 14 of 17 (82.4%) in the 24-week treatment group; the rate was significantly higher in the 24-week treatment group (P=0.0140). Nine of 10 relapsed patients in the 8-week treatment group underwent a 24-week retreatment, and seven achieved an SVR. **CONCLUSION:** An 8-week regimen of combination antiviral therapy with peginterferon and ribavirin

yielded an increase in the relapse rate, indicating the limitation of a reduction of treatment below 12 weeks in patients with genotype 2, after RVR.

Yu, M.-L., C.-Y. Dai, et al. (2008). "Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial." *Hepatology* **47**(6): 1884-93.

Recommended treatment for hepatitis C virus genotype 1 (HCV-1) patients is peginterferon plus ribavirin for 48 weeks. We assessed whether treatment duration of 24 weeks is as effective as standard treatment in HCV-1 patients with a rapid virological response (RVR; seronegative for hepatitis C virus [HCV] RNA at 4 weeks). Two hundred HCV-1 patients were randomized (1:1) to either 24 or 48 weeks of peginterferon-alpha-2a (180 microg/week) and ribavirin (1000-1200 mg/day) with a 24-week follow-up. The primary endpoint was a sustained virological response (SVR; seronegative for HCV RNA at 24-week follow-up). Overall, the 48-week arm had a significantly higher SVR rate (79%) than the 24-week arm (59%, $P = 0.002$). For 87 (43.5%) patients with an RVR, the 24-week arm had a lower SVR rate [88.9%; 95% confidence interval (CI): 80%-98%] than the 48-week arm (100%, $P = 0.056$). For 52 patients with low baseline viremia (<400,000 IU/mL) and an RVR, the 24-week arm had rates (CI) of relapse and SVR of 3.6% (-3%-11%) and 96.4% (89%-103%), respectively, which were comparable to those of the 48-week arm (0% and 100%) with difference (CI) of 3.6% (-7.2%-6.6%) and -3.6% (-14.3% to -0.6%), respectively. Multivariate analysis in all patients showed that RVR was the strongest independent factor associated with an SVR, followed by treatment duration, mean weight-based exposure of ribavirin, and baseline viral load. CONCLUSION: HCV-1 patients derive a significantly better SVR from 48 weeks versus 24 weeks of peginterferon/ribavirin even if they attain an RVR. Both 24 and 48 weeks of therapy can achieve high SVR rates (>96%) in HCV-1 patients with low viral loads and an RVR.

Appendix B. Studies of pegylated interferons in children with Hepatitis C

Murray, K. F., J. R. Rodrigue, et al. (2007). "Design of the PEDS-C trial: pegylated interferon +/- ribavirin for children with chronic hepatitis C viral infection." *Clinical Trials* **4**(6): 661-73.

BACKGROUND: PEDS-C is the first multicenter placebo-controlled trial for the treatment of chronic hepatitis C (HCV) in childhood that has ever been conducted in the United States (USA). Establishment of the research team, protocol, administrative infrastructure, and ancillary contributors for the pediatric trial took years of planning. **PURPOSE:** To study the safety and efficacy of pegylated-interferon alpha (PEG-2a) plus ribavirin (RV) with PEG-2a monotherapy in children aged 5 years through 18 years. To assess the health-related quality of life and growth and body composition in children with chronic hepatitis C infection, before, during, and after treatment. **METHODS:** Eleven centers of pediatric hepatobiliary clinical research were united in a National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) funded grant with financial support from the Food and Drug Administration (FDA) and a corporate sponsor to conduct the treatment trial. **LIMITATIONS:** The most important initial limitation in the design of this complex study was securing the financial support and infrastructural organization, a process that took several years. Challenges faced by the study group included identifying the optimal study design given the limited study population, and determining what ancillary studies could be incorporated into the treatment trial. **CONCLUSIONS:** In this article the process taken to design the study and administrative infrastructure, the lessons learned, and the controversial issues deliberated during the planning process are discussed. The evolution of the study and the considerations taken in the development of the protocol are valuable tools which can be applied to pediatric clinical trials in general.

Wirth, S., H. Pieper-Boustani, et al. (2005). "Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C." *Hepatology* **41**(5): 1013-8.

Peginterferon plus ribavirin is standard therapy for adults with chronic hepatitis C. As no data are available for children, the aim of the study was to evaluate the efficacy and tolerability of peginterferon alfa-2b in combination with ribavirin in chronically infected children. Genotypes, alanine aminotransferase levels, and different routes of viral transmission were considered. In an open-labeled, uncontrolled pilot study, 62 children and adolescents (range, 2-17 years) were treated with subcutaneous peginterferon alfa-2b at a dose of 1.5 microg/kg body weight once per week plus oral ribavirin (15 mg/kg x day) for 48 weeks. Sixty-one patients completed the study. Twenty-three children discontinued therapy after 6 months according to study protocol. Sustained viral response was documented in 22 (47.8%) of 46 patients with genotype 1, in 13 (100%) of 13 with genotype 2 or 3, in 1 of 2 with genotype 4, in 19 (70.4%) of 27 children with parenteral, in 12 (48%) of 25 with vertical, and in 5 of 9 with unknown route of infection. Overall, treatment was well tolerated. Nevertheless, some side effects were present in all treated patients. Eighty-three percent had leucopenia, but only 3 individuals required dose reduction and 10.3% developed thyroid autoantibodies and

thyroid dysfunction. In conclusion, combination treatment of peginterferon alfa-2b with ribavirin showed encouraging results and was well tolerated in children and adolescents with chronic hepatitis C. Weekly dosing of peginterferon alfa-2b is a considerable advance for this age group. The treatment is not approved for children. Further controlled trials are needed.