Advances in Treatment of Hepatitis C: Making Clinical Sense of New and Emerging Data

A CME Satellite Symposium presented during the 53rd AASLD Annual Meeting.
This activity is not affiliated with AASLD.

Syllabus

Monday, November 4, 2002
Boston, Massachusetts
Dear Colleague:

Pegylated interferon plus ribavirin combination therapy is the standard of care for the treatment of hepatitis C virus (HCV) infection. The efficacy and safety data from the use of pegylated interferon plus ribavirin was shown in pivotal clinical trials and was recently affirmed in the NIH Consensus Development Conference Statement: Management of Hepatitis C: 2002. Accordingly, the majority of HCV-infected patients can achieve a sustained virologic response with the therapy available today. Many are also experiencing favorable histologic responses.

Our panel of experts will show you how to take advantage of today’s effective therapy and strategies to optimize response in your patients and to manage side effects. Through didactic lecture and panel discussion of case presentations, these experts will explain how the already superior efficacy of pegylated interferon plus ribavirin can be boosted further by refinement of treatment protocols, such as the use of adherence strategies and weight-based dosing. They will show you how to tailor treatment to achieve virologic response in patients with multiple challenges. These experts also will describe how determination of quantitative HCV RNA can be used to reliably predict response to therapy as early as 12 weeks, and why early prediction can be beneficial for your patients. In addition, they will discuss the clinical implications of pegylation, thereby giving you a fuller understanding of pegylated interferon itself.

By attending Advances in Treatment of Hepatitis C: Making Clinical Sense of New and Emerging Data, you will get the critical information you need to carry out defensible treatment regimens for all of your HCV-infected patients.

Sincerely,

Willis C. Maddrey, MD
Chair
Advances in Treatment of Hepatitis C: Making Clinical Sense of New and Emerging Data

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8:00 PM  Dinner
Learning Objectives

This activity is designed for hepatologists and hepatology health professionals who treat patients with hepatitis C. After participating in this activity, the participant should be able to:

• Describe the efficacy and safety implications of the pharmacodynamic and pharmacokinetic properties of pegylated interferons
• Discuss new data regarding the effect of weight-based dosing of ribavirin and treatment duration on treatment safety and efficacy
• Evaluate the potential of early HCV RNA levels to predict response or nonresponse and the usefulness of such predictions in making early treatment stopping decisions
• Prescribe peginterferon/ribavirin combination therapy for all patient demographic groups, including patients with multiple challenges
• Relate the histologic benefit of peginterferon/ribavirin combination therapy to the need of patients with fibrosis, including those with cirrhosis

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Introduction

Willis C. Maddrey, MD

Peginterferon alfa-2b/ribavirin has now been in use for over a year, having replaced interferon/ribavirin as the standard of care. During this time, we have seen a considerable increase in sustained response rates with more than half of our hepatitis C patients achieving sustained virologic response. As we have gained experience with peginterferon alfa-2b/ribavirin, we have also learned that we can further improve outcomes by promoting adherence and by basing drug doses on body weight. The 2002 National Institutes of Health (NIH) Consensus Statement on the Management of Hepatitis C further supports use of peginterferon/ribavirin, noting that it is more effective than standard interferon/ribavirin combination therapy or peginterferon monotherapy.

With the high level of efficacy associated with peginterferon/ribavirin, the risk:benefit ratio has shifted further in favor of treatment for more patients. Arguably one of the most noteworthy accomplishments of the NIH Consensus Statement was to broaden the range of patients who should be considered for treatment of hepatitis C. In fact, according to the statement, “All patients with chronic hepatitis C are potential candidates for antiviral therapy.” The increased efficacy of these new regimens also provides a rationale for re-treating patients who have previously failed to achieve sustained response with the older, less effective regimens.

In October, the US Food and Drug Administration approved a new pegylated interferon, peginterferon alfa-2a, for use as monotherapy. Recently published investigations of this drug in combination with ribavirin (presently off-label use) also indicate sustained response rates >50%.

With new therapies and treatment approaches, and a more complete understanding of HCV, management of chronic hepatitis C is becoming more successful and more challenging. New guidelines are emerging; however, individualized management decisions are becoming increasingly necessary, especially for subgroups of patients with hard-to-treat disease—for example, those with advanced fibrosis, obese patients, and patients who do not achieve early or sustained virologic response. Moreover, use of newer diagnostic modalities (eg, quantitative HCV RNA evaluated before therapy and after 12 weeks of therapy) allows for earlier determination of virologic response, requiring physicians to again carefully weigh individual patient factors in making management decisions at new decision points. We hope this activity, *Advances in Treatment of Hepatitis C: Making Clinical Sense of New and Emerging Data*, will help you review the newest data and treatment options, and explore the nuances of care through a series of case studies designed to address common clinical challenges and maximize treatment outcomes for your hepatitis C patients.

Suggested Readings


Revisiting Critical Decision Points: Clinical Implications of 12-Week Data

Gary L. Davis, MD

Interferon-based regimens are highly effective for treatment of chronic hepatitis C virus (HCV), with the current standard regimen of pegylated interferon and oral ribavirin eradicating virus in more than half of cases. There are challenges associated with this regimen, however, in that the regimen is complicated, uses two drugs administered by different routes, lasts 6 to 12 months, requires frequent monitoring, usually causes side effects, and is expensive. Thus, determination of response early during the treatment course is desirable, thereby providing the option of discontinuing treatment in patients who would not respond.

HCV Kinetics Following Interferon

HCV replication generates $10^{10}$ to $10^{12}$ viral particles per day that have a half-life of only a few hours. Pegylated interferon inhibits HCV replication by about 90%, resulting in a rapid decline in HCV RNA. This first phase of viral decline, however, is not associated with treatment response. In contrast, the slow, prolonged, and more variable second phase of viral decay correlates very closely with sustained virologic response (SVR) to interferon-based treatment regimens. This close association suggests that measurement of HCV RNA during the first several weeks of therapy might predict eradication of HCV.

Early Virologic Response

Early studies of standard interferon monotherapy showed that failure to lose HCV RNA after 12 weeks of treatment, as measured by qualitative PCR testing, was strongly associated with treatment failure in both 6- and 12-month regimens. Davis et al studied the association between early response and treatment failure in data from the 511 subjects treated with pegylated interferon alfa-2b 1.5 µg/kg QW plus ribavirin 800 mg/day in the phase 3 clinical trial by Manns et al. The definition of early virologic response (EVR) that optimized capture of potential responders (highest sensitivity), while excluding the largest proportion of nonresponders (highest negative predictive value) was sought. Quantitative HCV RNA levels were measured at 4, 12, and 24 weeks of treatment and compared with the baseline level. The best definition of EVR was a drop of at least 2 logs in HCV RNA from baseline or undetectable HCV RNA after 12 weeks of treatment. Seventy-four percent (379/511) of patients achieved this. If treatment had been discontinued in the remaining 26% (132/511) of patients, only 0.8% (1/132) of all sustained viral responders would have been lost by premature termination of treatment. Furthermore, more than 99% (131/132) of those who failed to reach EVR were nonresponders 24 weeks after completing a full course of treatment. Looked at another way, among those who did not achieve EVR after 12 weeks, the chance of reaching SVR following completion of the full course of treatment was less than 1%

Of those patients who did reach an EVR, 72% went on to achieve SVR. Response rates were lower among patients who remained PCR positive at 12 weeks despite a 2-log drop (21% versus 84%; $P<0.001$) and those who were unable to remain adherent to the prescribed dose (61% to 63% versus 75% to 77%) or duration of therapy (50% versus 78%).

Subgroup Analysis

A ≥2-log decrease in HCV RNA level or undetectable HCV RNA at week 12 was the optimal definition of EVR regardless of viral genotype, although almost all patients with genotypes 2 and 3 infection achieved EVR (95% versus 66% for genotype 1 infection). Patients who had genotype 1 infection, high HCV RNA levels, low serum ALT levels, and poor adherence in the first 3 months were less likely to achieve EVR.

The ≥2-log drop in HCV RNA or undetectable HCV RNA at week 12 of treatment was also the optimal definition of EVR for patients who received ribavirin doses >10.6 mg/kg/day (the equivalent of an 800-mg dose in a 75-kg individual) and patients who received standard interferon and ribavirin.

Recommendations

Based on these data, patients who do not achieve EVR are not likely to achieve SVR, and therefore should discontinue therapy. Patients with EVR who are still virus positive should be retested at 24 weeks. If virus is still present at that time, treatment should be stopped. EVR is so common in patients infected with genotypes 2 and 3 that for these patients, HCV RNA testing during therapy may not be cost effective. Consideration of these recommendations, however, requires recognition of the limitation of viral quantitation and the potential, yet unproven, benefits of treatment in nonresponders.

Conclusion

Measuring EVR is helpful in the management of chronic hepatitis C in patients who receive treatment with standard or pegylated interferon plus ribavirin. It can provide patients and treating physicians with an early goal and motivate them to adhere to treatment.
recommendations. Discontinuation of therapy in the minority who fail to achieve EVR reduces treatment costs and avoids the morbidity of therapy in those with no chance of viral clearance. Utilization of quantitative HCV RNA testing to assess EVR has recently been recommended by the National Institutes of Health Consensus Development Conference Statement, “Management of Hepatitis C: 2002.”

**Suggested Readings**


What Is Pegylation and What Are Its Clinical Implications?

Ira M. Jacobson, MD

With pegylated interferon alfa-2b available for nearly 2 years for the treatment of chronic hepatitis C, and pegylated interferon alfa-2a introduced more recently, it is timely to review the pharmacologic aspects of pegylation and their implications for clinical use. Pegylation represents the binding of inert ethylene oxide polymers to drug products, including protein pharmaceuticals. The goals of pegylating a protein molecule include:

- prolongation of drug clearance, with more sustained blood concentrations,
- the potential for decreased proteolysis of the drug, and
- reduced immunogenicity.

The pegylation process may be carried out to create a polyethylene glycol (PEG) polymer of any desired size, and the polymer may be either linear or branched when bound to amino acid residues on the target protein.

Pegylated drug products have been the focus of much interest in the pharmaceutical industry. Other pegylated proteins in clinical use include pegaspargase (pegylated L-asparaginase) for acute lymphoblastic leukemia, pegademase (pegylated adenosine deaminase) for severe combined immunodeficiency disease, and pegfilgrastim (pegylated granulocyte colony-stimulating factor [G-CSF]). In addition, a pegylated growth hormone receptor antagonist (pegvisomant) has been developed for acromegaly.

Pegylation of interferon alfa-2a and alfa-2b for use in hepatitis C is attractive because the standard interferons have plasma half-lives of only 3 to 8 hours and are virtually undetectable after 24 hours. Viral kinetic studies have demonstrated that maximum suppression of HCV replication is not maintained during the traditional 48- to 72-hour dosing cycle when standard interferons are used. Both peginterferons result in marked prolongation of interferon clearance and have kinetics suitable for once-weekly administration. The PEG molecule in peginterferon alfa-2b is a linear 12-kD molecule, and that in peginterferon alfa-2a is 40 kD and has two 20-kD PEG branches bound to an amino acid residue on the interferon molecule.

An inverse correlation between treatment efficacy and body weight, or body surface area, has been observed with standard, fixed dosing of interferons as monotherapy or in combination with ribavirin. To equalize efficacy across all patients regardless of body weight, peginterferon alfa-2b was designed to be dosed by body weight, currently at 1.5 µg/kg when used in combination with ribavirin. In contrast, peginterferon alfa-2a has been developed as a fixed-dose product, with 180 µg emerging from early dosering trials as the favored dose.

The larger 40-kD PEG molecule has been associated with a volume of distribution about one fourth that of standard interferon or the 12-kD peginterferon product. This is potentially relevant to the issue of fixed versus weight-based dosing of interferon. Presuming this difference in volume of distribution does exist, body surface area remained inversely associated with efficacy of peginterferon alfa-2a monotherapy, and body weight was inversely associated with efficacy of treatment in the recently published trial of peginterferon alfa-2a 180 µg combined with ribavirin 1000/1200 mg, with an odds ratio of 1.91 for sustained response with body weight ≤75 kg. This issue will be of ongoing interest as additional data and experience accrue.

The theoretical benefits of both peginterferons have been substantiated repeatedly in clinical trials. Studies of the pegylated interferons given as monotherapy demonstrated a twofold increase in the rate of sustained response compared with the respective standard interferons, thereby confirming the translation of theoretical pharmacokinetic considerations into greater efficacy as well as the convenience to the patient of once- versus thrice-weekly parenteral drug administration. The recent trials of Manns et al and Fried et al further confirmed the anticipated superiority of pegylated interferons combined with ribavirin versus standard interferon plus ribavirin.

Both peginterferons are metabolized primarily in the liver, but approximately 30% of peginterferon alfa-2b undergoes renal excretion compared with virtually no peginterferon alfa-2a because of a limitation in the size of molecules that can be cleared by the kidneys. Peginterferon alfa-2b has sustained maximal serum concentrations for 48 to 72 hours after drug administration, and elimination half-life is about 10-fold greater, with mean apparent clearance about one tenth, that of nonpegylated interferon alfa-2b. The absorption half-life is much longer, and elimination half-life somewhat longer, with peginterferon alfa-2a, which achieves maximum concentrations at 72 to 96 hours and has more sustained blood levels as a result of the larger PEG molecule.

Peginterferon alfa-2a has a peak to trough ratio of 1.5–2:1, while that for peginterferon alfa-2b is 6:1. Despite this difference, trough blood levels at steady state for peginterferon alfa-2b still are similar to drug levels near
peak values obtained when nonpegylated interferon alfa-2b is used. Whether the different rates of clearance of the two peginterferons might be clinically significant under certain circumstances of drug toxicity remains to be evaluated as experience accumulates.

In considering the pharmacokinetic differences between the two peginterferons, it must be borne in mind that an important implication of PEG size, other than its effect on clearance, is on specific activity of the resultant peginterferon product. A larger PEG molecule is expected to result in greater steric hindrance by affecting the ability of the active site of the interferon molecule to bind with its receptor, or by altering the conformation of the molecule. Substantial differences in specific activity of the two peginterferons have, in fact, been demonstrated using in vitro assays in several model systems. In a model involving infection of fibroblasts by encephalomyocarditis virus, the specific activity (as measured by protein concentration needed to provide 50% antiviral protection) was 30% for peginterferon alfa-2b and 1% for peginterferon alfa-2a compared with interferon alfa-2b as the standard.\textsuperscript{12} In a model of bovine kidney cells challenged with vesicular stomatitis virus, peginterferon alfa-2a had an antiviral specific activity of 7% compared with interferon alfa-2a.\textsuperscript{13} Studies on antiproliferative and downstream intracellular signaling events activated by interferon further demonstrated decreased activity of peginterferon alfa-2a in comparison to peginterferon alfa-2b when analyzed at equivalent weight dosing.\textsuperscript{14,15}

Pegylation in general is expected to result in loss of specific activity, and a lesser degree of in vitro specific activity associated with a larger PEG molecule may not result in a less clinically effective drug. The prolonged half-life of a larger PEG is expected to be more of a factor determining biological effects in vivo than in vitro. Experimental data support this contention by demonstrating that there is a direct relationship between PEG mass and in vivo activity, unlike the inverse correlation of PEG size and specific activity observed in vitro.\textsuperscript{3} Moreover, the use of a pegylated interferon with less specific activity may warrant the administration of a greater amount of the protein, and in fact a larger amount of interferon protein is given with peginterferon alfa-2a in the fixed dose of 180 µg than with peginterferon alfa-2b 1.5 µg/kg. Thus, the higher and more prolonged drug concentrations achieved with peginterferon alfa-2a by using a larger PEG molecule and a greater amount of drug can be regarded as compensatory for the reduction in its specific activity.

In addition to PEG molecular weight and structure, other determinants of specific activity of the peginterferons are the number of attached polymer side chains and the conjugation sites.\textsuperscript{7} Studies with pegylated G-CSF, for example, have demonstrated an adverse effect of bi- or tripegylation on specific activity. However, both peginterferon alfa-2a and pegylated interferon alfa-2b are almost exclusively monopegylated. A more substantive difference between the two peginterferons is that peginterferon alfa-2b has a large proportion (50%) of its PEG molecules bound to histidine,\textsuperscript{16} with the remainder bound to lysine, while peginterferon alfa-2a contains binding almost exclusively to lysine residues.\textsuperscript{17} Binding to histidine has been associated with approximately fourfold greater preservation of specific activity in comparison to lysine.\textsuperscript{18} However, histidine binding is more susceptible to hydrolysis, which explains why peginterferon alfa-2b is prepared as a lyophilized product requiring reconstitution.

In summary, pegylating a protein with known clinical activity does not change the basic mechanism of action, and is a well-established method of decreasing clearance rates and proteolysis of the drug. In the case of peginterferons, the underlying interferon remains the active antiviral agent. Both peginterferon alfa-2b and peginterferon alfa-2a have been shown to be more effective in achieving sustained viral response compared with their nonpegylated counterparts, and allow for a weekly dosing schedule, thereby improving convenience.

However, the two peginterferons differ in several important structural and biochemical aspects. Compared with peginterferon alfa-2b with its single 12-kD PEG molecule, peginterferon alfa-2a, with its two 20-kD PEG branches, has more prolonged absorption, a longer half-life, smaller volume of distribution, less specific activity, and more restricted clearance via liver only (versus clearance via both liver and kidney for peginterferon alfa-2b).

The slower clearance rates, higher dose, and higher, more prolonged drug concentrations associated with the larger PEG molecule must be balanced against the lesser degree of specific activity. Whether the differences in clearance rates and specific activity of these two peginterferon products result in clinically significant differences in toxicity and outcome remains to be seen as experience accumulates.
References

**Rationale for Pegylation of Interferons**

What Is Pegylation and Why Do We Do It?
- Polymers of ethylene oxide bound to drug molecules
  - Decreases clearance: prolongation of half-life, maximum concentration
  - Decreases proteolysis of drug
  - Decreases immunogenicity


**Factors Influencing Biological Characteristics of Pegylated Proteins**

- PEG molecular weight/structure
- Number of attached polymer chains
- Conjugation site


**Concentration Time Profiles**

![Graph showing concentration-time profiles for PEG-IFN-2a and PEG-IFN-2b](image)

- (PEG-IFN-2a) 190 µg SC once weekly
- (PEG-IFN-2b) SC once weekly
- Standard Interferon alfa 3 MIU TIW


**Specific Activity of Pegylated Interferon**

- Pegylation involves loss of specific activity
  - Steric hindrance with receptor binding site
  - Conformational change in protein
- Larger PEG leads to greater loss of activity
- Specific activity can be measured in vitro
  - Assays of antiviral protection in tissue culture
- Specific activity more highly preserved in pegylated interferon alfa-2b than in pegylated interferon alfa-2a

*Cox et al. Hepatology. 2002;36:547A.

**Histidine Pegylation**

- Main component (positional isomer) of PEG IFN-2b involves pegylation of a histidine residue (His34) of IFN-2b
- His34 PEG IFN has a higher specific activity

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<tr>
<td>IFN</td>
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<td>(Lys121) PEG IFN</td>
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<tr>
<td>(N-terminal) PEG IFN</td>
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**Pegylation of Interferons: Summary**

- The underlying interferon is still the active antiviral agent
- Size, number, and attachment position can have significant impact on function of the protein
- Considerations of clearance must be balanced against issues of specific activity
John G. McHutchison, MD

Case Presentation

A motivated, middle-aged, obese gentleman presented for evaluation of incidentally detected hepatitis C virus (HCV) infection. His evaluation included elevated liver enzymes, normal complete blood count (CBC) and hepatic synthetic function, HCV genotype 1 infection, and high viral load (1.1 million IU/mL). Liver biopsy revealed moderate inflammation and steatosis, and cirrhosis.

The patient had no contraindications to therapy. Therefore, after discussing his situation and the results of his liver biopsy, it was decided that he begin therapy with a weight-based dosing regimen of peginterferon alfa-2b and ribavirin. At 12 weeks, he had a significant reduction in viral load (to 15,000 IU/mL), some reduction in his liver enzymes, and expected, but tolerable, side effects, including rash, insomnia, and weight loss. He continued on therapy, and repeat testing at week 24 revealed no detectable serum HCV RNA. He successfully completed 48 weeks of therapy (with the addition of antidepressants) and was virus free at that time, as well as at 3-months posttreatment. Currently, he awaits his 6-month follow-up visit to determine that he has achieved a sustained virologic response (SVR).

Adherence and its importance were discussed and recorded at each monthly visit during therapy. He received 90% of the prescribed medication dosages.

Adherence to Therapy

Adherence or compliance to therapy is associated with enhanced sustained response rates in a number of diseases, including hepatitis C. Thus, promoting adherence to therapy is an important component of care for patients with hepatitis C.

In the peginterferon alfa-2b/ribavirin phase 3 clinical trial, 63% of patients who received ≥80% of expected doses of both peginterferon alfa-2b 1.5 µg/kg and ribavirin 800 mg/d for ≥80% of the recommended duration of therapy (80+80+80 adherence) achieved an SVR, compared with 54% of patients, overall. Patients who received peginterferon 1.5 µg/kg and ribavirin >10.6 mg/kg, patients with 80+80+80 adherence achieved higher response rates than nonadherent patients: 72% versus 61%.

As seen in this patient, the impact of adherence to therapy was particularly significant in genotype-1–infected patients. Among genotype-1–infected patients who received peginterferon alfa-2b 1.5 µg/kg and ribavirin 800 mg/d, 51% of adherent patients achieved SVR compared with 34% of nonadherent patients. Similarly, in those receiving peginterferon 1.5 µg/kg and ribavirin >10.6 mg/kg, 63% of adherent patients achieved SVR compared with 34% of nonadherent patients. Both these differences were statistically significant and indicate the importance of adherence to achieving SVR, particularly in these most difficult to treat patients.

Viral Load Testing

Patients with chronic HCV infection usually have detectable serum HCV RNA. Reliable assays to detect viremia and quantify circulating viral RNA concentrations have become an integral part of the management of HCV in infected patients before, during, and after therapy. Pretreatment viral load provides some estimate as to the likelihood of response to therapy, and viral load reductions during therapy provide an accurate picture of whether a patient will be an eventual sustained responder or non-responder.

For HCV RNA assays to be used in a meaningful manner, the clinician must be cognizant of certain factors: the precision of most assays is 0.5 log, the individual patient variability is 0.5 to 1.0 log, and results with different assays are not interchangeable. To this end, the introduction and acceptance of a WHO standard (now reported in International Units per mL or IU/mL) has allowed some degree of uniformity, as most assays are now reported with these units.

Conclusions

In this case, the patient achieved a near 2-log viral load reduction at week 12. In view of his early response, the limitations of these assays, his advanced disease (cirrhosis), and his overall poor patient profile in terms of factors predicting nonresponse (genotype 1 infection, high viral load, age, gender, significant fibrosis and body weight), a decision to continue him on therapy was appropriate. Fortunately, despite his severe disease and unfavorable profile, his management plan, which took into account the issues outlined above, and his weight-based drug dosing regimen have provided him with the potential long-term benefits of an SVR.
**Suggested Readings**


Nezam H. Afshal, MD

Case Presentation

A Caucasian male, 42 years old and weighing 205 pounds, was seen in the Liver Center. He had been diagnosed with hepatitis C virus (HCV) infection, genotype 1a, in 1993 when he presented with an abnormal ALT level during an evaluation for life insurance. He likely acquired the infection when he used intravenous drugs 22 years earlier while in college. A heavy drinker from age 22 to 33 years, he has had no alcohol for the last 8 years.

A liver biopsy at the time of diagnosis showed grade 2 inflammation and stage 2/3 disease. He was treated elsewhere with interferon alfa-2b 3 MIU TIW and ribavirin 1200 mg/day. He failed to respond and so therapy was stopped after 6 months. He reported that he had taken the full doses throughout treatment. In 1999, he presented with fatigue and occasional right upper quadrant pain.

At this presentation, he was found to have hepatosplenomegaly and the following laboratory results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<td>ALT</td>
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<td>AST</td>
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<td>Normal</td>
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<td>WBC</td>
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<td>Hemoglobin</td>
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<tr>
<td>Platelets</td>
<td>68.000/mm³</td>
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<tr>
<td>HCV RNA</td>
<td>4.32 million copies/mL (NGI assay)</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>23 ng/mL (normal &lt;7 ng/mL)</td>
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An ultrasound confirmed hepatosplenomegaly without any focal mass or ascites. A liver biopsy showed well-established cirrhosis, stage 4, grade 2. An upper-GI endoscopy showed small esophageal varices.

The risks and benefits of therapy were discussed with the patient and the decision was made to start the patient on a weight-based treatment regimen of peginterferon alfa-2b 1.5 µg/kg QW and ribavirin 1200 mg/day. The patient tolerated treatment well with no dose reductions.

At week 12, his viral load had dropped to 1.3 million copies/mL and at week 24, to 810,000 copies/mL. This less than 2-log response by week 24 predicted that the patient would not achieve sustained virologic response with a full course of therapy. After further discussion, the patient elected to enter the COPiLOT clinical trial and was randomized to a maintenance therapy program with peginterferon alfa-2b 0.5 µg/kg. He tolerated this well with occasional thrombocytopenia down to 30,000/mm³, which resolved after cessation of peginterferon for a week. After 18 months of maintenance therapy, a repeat liver biopsy and endoscopy showed stage 3 disease and no visible varices. The patient remains on maintenance therapy with peginterferon alfa-2b.

Retreatment Decision Point

At the time this patient presented to the Liver Center, the decision point was whether to re-treat with weight-based peginterferon plus ribavirin. The current approach to the patient who has failed standard interferon/ribavirin therapy is complex and requires both individualization and an understanding of the secondary goals of therapy, which are to prevent disease progression and decrease the risk of hepatocellular cancer.

The patient's stated adherence to his initial treatment regimen was good and his classification at 6 months as a nonresponder appears appropriate. These factors are important when one considers retreatment with peginterferon/ribavirin therapy. Despite the initial treatment regimen, however, he had clinical progression of disease to cirrhosis. Results of the index liver biopsy are often the best predictor of risk of progression and even though he was only stage 2/3 on initial biopsy, up to 50% of these patients will progress to cirrhosis in less than 10 years.

The patient had several factors predictive of a poor response to therapy, including genotype 1a infection, high viral load, advanced fibrosis with bridging, and a large body surface area. Yet negative predictive factors may potentially be counter-balanced by the higher efficacy offered by weight-based dosing of pegylated interferon and, therefore, should not be used to limit a patient's treatment options.

The presence of compensated cirrhosis is a strong indication for retreatment and the patient elected to try another course. The potential for a secondary histologic benefit has been demonstrated in the large interferon-based treatment studies, as outlined by Poynard et al.

Maintenance Therapy Decision Point

Unfortunately, upon retreatment, the patient again had not achieved a virologic response and the clinician and
patient faced the difficult decision of whether to stop all treatment or to consider maintenance therapy. The lack of significant viral load reduction at 12 and 24 weeks certainly indicated a lack of early viral response (EVR). Treatment could potentially have been stopped at week 12, but due to his individual factors and cirrhosis, treatment was continued through week 24.

The decision to switch to and continue with a maintenance therapy regimen is based on the rationale that continuing low-dose peginterferon can prevent disease progression. Histologic regression has been seen with as little as 0.5 µg peginterferon per kg body weight, the commonly used maintenance dose. The resolution of cirrhosis after 2 years of continuous treatment has been reported and is the goal of maintenance therapy. Interestingly, recent data from the COPILOT study have begun to show an initial trend in reduction of complications of liver disease in cirrhotic patients treated with peginterferon 0.5 µg/kg weekly compared with those randomized to colchicine 0.6 mg BID. The COPILOT study is ongoing and histologic and outcomes data are expected in the next few years.

**Suggested Readings**

Afdhal NH, Freilich B, Black M, Levine R, Brass C and the National COPILOT Investigators. Comparison of therapy with PEG-INTRON 0.5 µg/kg versus colchicines 0.6 mg bid in 250 patients with cirrhosis and HCV: interim data from COPILOT. *Hepatology*. 2002;36:312A.


Re-treating with Peginterferon/Ribavirin: Hope for the Nonresponder

Ira M. Jacobson, MD

Case Presentation

A 49-year-old Caucasian male, weighing 79.1 kg, was referred for evaluation. He had been diagnosed with hepatitis C virus (HCV) infection, genotype 1b, in 1998. A biopsy done at that time showed stage 3, grade 3 liver disease, with moderate to severe steatohepatitis, perivenular and pericellular fibrosis, and mild neuro-inflammatory activity consisting of aggregates of neutrophils.

At the time of his diagnosis, his HCV RNA level by PCR was >1 million copies/mL and AST and ALT levels were 70 U/L and 164 U/L, respectively. He was started on interferon/ribavirin combination therapy shortly after diagnosis. Three months into treatment, his ALT level was normal. Six months into treatment, his ALT level was 100 U/L with HCV RNA 62,000 copies/mL. At the end of 12 months of treatment, his ALT level was 37 U/L with HCV RNA 20,000 copies/ml by PCR. Six months posttreatment, his HCV RNA level was 530,000 copies/mL and ALT level was 112 U/L.

At the time of the patient's current evaluation, he and his physician discussed the possibility of achieving sustained response by retreatment with a regimen of peginterferon/ribavirin. The patient agreed to enroll in a study and was randomized to receive peginterferon alfa 2b 1.0 µg/kg and ribavirin 1200 mg/day. Starting treatment with a viral load of >1 million copies/mL, his HCV viral load was <1000 copies/mL, by week 12. By week 24, HCV RNA was undetectable and remained so at 48 weeks of treatment. His treatment was stopped, and his PCR assay remained negative at followup 24 and 72 weeks posttreatment.

During treatment, the patient experienced common side effects of combination therapy, including fatigue, depression, anemia, and rash. Nevertheless, the patient completed therapy with only a transient reduction of ribavirin dose due to anemia. The patient reported relief from side effects within days of completing therapy and felt well throughout the posttreatment follow-up period.

Rationale for Retreatment

Even with the “quantum leap” forward in therapeutic efficacy with the advent of standard interferon/ribavirin combination therapy in the late 1990s, sustained response rates in HCV-infected patients were only 40%. Thus, over half of patients either failed to clear HCV in response to therapy or did so, but subsequently relapsed. With the recent demonstration from two landmark trials that pegylated interferon is superior to standard interferon when combined with ribavirin, the question arises as to whether standard combination therapy failures might benefit from a course of peginterferon and ribavirin.

Clinical Trials

To this end, a number of investigator-initiated trials were started, some of which are now well along in their course and provide substantial information on treatment response, and, more preliminarily, sustained response. Large numbers of patients with either relapse or nonresponse to a prior course of combination therapy have been included in these trials. Since many interferon monotherapy failures were treated with combination therapy after the introduction of ribavirin in 1998, a smaller number of such patients have been available for the new trials with peginterferon.

The investigator-initiated trials reported thus far feature significant heterogeneity in terms of study design, particularly with regard to doses. It is already abundantly clear, however, that peginterferon and ribavirin can clear HCV RNA, as measured by PCR, in a substantial number of patients (25% to 40%) with prior nonresponse to combination therapy. Sustained response data are less plentiful, but data thus far indicate a substantially lower rate of sustained response than end-of-treatment response, eg, 10%. This appears to be related to a higher rate of relapse after 12 months of treatment in these patients than the relapse rates noted in the large trials on treatment-naive patients. This is not surprising since these patients have been defined a priori as relatively resistant to therapy. It is not difficult to conceive that their intrahepatic clearance of virus may be relatively slow. Relapsers after a prior course of combination therapy have better results with peginterferon and ribavirin, eg, 40%–60% thus far.

In the New York metropolitan area, a multicenter study enrolled 330 patients with nonresponse or relapse after prior combination therapy, as well as a smaller number of nonresponders to interferon monotherapy. The patients were randomized to PEG IFN alfa-2b 1.5 µg/kg plus RBV 800 mg (group 1), or PEG IFN alfa-2b 1.0 µg/kg plus RBV 1000–1200 mg (group 2) for 48 weeks and 24 weeks followup.

Nearly all of the patients have reached 72 weeks (n = 306). By intention to treat analysis, 5% of the prior nonresponders in group 1 and 9% of the prior nonresponders in group 2 achieved SVR. In the overall group, SVR was achieved only in those patients who were PCR negative after 3 months of therapy. When all the groups were pooled, the patients with normal ALT had a higher SVR (23%) than patients with high ALT (13%) at entry. Low viral load was associated with higher response than high viral load.
Other investigators have reported similar or somewhat higher rates of treatment response in prior nonresponders to combination therapy. There are several trials reported with preliminary results at AASLD 2002 as indicated below:

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>PEG α-2b (µg/kg)</th>
<th>RBV (mg)</th>
<th>24 wk</th>
<th>48 wk</th>
<th>72 wk</th>
<th>SVR</th>
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<tr>
<td>Gross (RENEW)</td>
<td>195</td>
<td>1.5</td>
<td>1000–1200</td>
<td>39%</td>
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<td></td>
<td></td>
<td>3.0</td>
<td>1000–1200</td>
<td>53%</td>
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<tr>
<td>Krawitt</td>
<td>137</td>
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<tr>
<td>Chosusterman</td>
<td>135</td>
<td>1.0 µg/kg (or 2.0 µg/kg x 8 weeks)</td>
<td>800</td>
<td>33%</td>
<td>18%</td>
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Should the final results of these trials confirm the impression that nonresponders to prior combination therapy have higher relapse rates than seen in treatment-naive populations, it may be speculated that a course of therapy longer than 48 weeks might benefit patients who become PCR negative by that time point.

### Conclusions

What conclusions can be drawn thus far for the practicing hepatologist? First, the occasional interferon monotherapy nonresponder who has never received ribavirin should be offered peginterferon rather than standard interferon despite the absence of comparative data. Second, the results in combination therapy relapers are good enough to warrant strong consideration of a course of peginterferon and ribavirin. Of course, liver histology, tolerability of prior therapy, and patient motivation must be taken into consideration. Finally, and most importantly, nonresponders to prior combination therapy can be offered a course of peginterferon and ribavirin, with more advanced fibrosis and a major drop in viral load with prior therapy bolstering the argument to do so. Patients must be advised, however, that data thus far suggest a low probability of sustained response, and individualized decisions are required regarding duration of therapy. Higher doses of peginterferon may prove to be more effective, but additional data from the RENEW trial are required.

### Suggested Readings


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**Figure 1:** Viral Response in Previous Combination Therapy Nonresponders

**Table:** SVR

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Conclusion

Willis C. Maddrey, MD

Over the past year, peginterferon alfa-2b/ribavirin replaced interferon/ribavirin as the standard of care for the treatment of chronic hepatitis C. Virologic and histologic benefits of this treatment have been confirmed in large clinical trials. In a randomized, phase III study, 54% of patients achieved sustained virologic response (SVR) when given the Food and Drug Administration (FDA)-approved regimen of peginterferon alfa-2b 1.5 µg/kg plus ribavirin 800 mg/d. Moreover, 61% of those who received peginterferon alfa-2b 1.5 µg/kg plus ribavirin >10.6 mg/kg (off-label use) achieved SVR. Patients who maintain the highest levels of adherence to treatment with peginterferon alfa-2b/ribavirin experience even higher response rates. In a study of patients with paired liver biopsies, 24% of those who received optimal weight-based doses of both peginterferon alfa-2b and ribavirin showed improvements in fibrosis, and fibrosis stabilized in another 68%.

Physicians have accumulated considerable knowledge and experience in the nuances of treatment using peginterferon alfa-2b/ribavirin during the past year. We now know that treatment can be tailored to give each patient the best chance at SVR, taking into account factors like genotype, body weight, and degree of fibrosis. Experience with peginterferon alfa-2b/ribavirin has also taught us the importance of treatment adherence in achieving successful outcomes. Thus, comprehensive case management of hepatitis C must include strategies to promote adherence, including patient education and use of an ever-expanding range of adjunctive therapies to manage side effects.

The increased efficacy of pegylated interferon over standard interferon also provides new hope for patients who previously failed interferon/ribavirin therapy. Clinical trials to date indicate that a substantial number of these patients (25% to 40%) clear HCV RNA during retreatment with peginterferon/ribavirin; however, the rate of SVR appears to be quite a bit lower. Further studies are needed to determine whether longer treatment or higher peginterferon doses can reduce the risk of relapse among these initial responders. Nonresponders to peginterferon/ribavirin, particularly those with advanced fibrosis, may be considered for maintenance therapy with low-dose peginterferon monotherapy based on potential histologic benefits. The potential benefits of long-term maintenance therapy are being evaluated in two large-scale national trials.

Quantitative HCV RNA testing allows determination of early virologic response at week 12, defined as undetectable HCV RNA or a >2-log decrease in HCV RNA level. Early virologic response has been shown to correlate well with long-term response. The use of the 12-week evaluation potentially reduces the duration of exposure to treatment and its potential toxicities for those patients not destined to achieve SVR. However, management decisions based on early virologic response must take into account other predictors of treatment response, the limitations of HCV RNA assays, the tolerability of treatment, level of adherence, and the potential histologic benefits of continuing treatment even in the absence of virologic response.

Peginterferon alfa-2a, approved in October for use as monotherapy, provides a new option for treatment, with response rates of 23% to 31% as monotherapy and 56% when used in combination with ribavirin. With multiple options now available, choice of treatment should be based on considerations of pharmacokinetic profiles, efficacy, safety, and record of success.

Pegylation of interferons decreases drug clearance rates and proteolysis of the drug, and also results in less immunogenicity. Pegylation has been successful in improving the efficacy of interferon treatment at least in part because the prolonged half-lives and increased serum
concentrations compared with standard interferons allow for sustained viral suppression. The longer half-lives also allow for the convenience of once-weekly dosing. Compared with peginterferon alfa-2b, the newer peginterferon alfa-2a has a longer duration of absorption and half-life, a smaller volume of distribution, less specific activity, and more restricted route of clearance (via the liver only, versus liver and kidney for peginterferon alfa-2b). The extent to which these differences are clinically relevant remains to be determined as experience with peginterferon alfa-2a accumulates. Since the introduction of other new drug therapies is still a considerable way off for the time being, optimizing treatment outcomes depends on further refining management approaches.

Over the past decade, considerable strides have been made in the treatment of hepatitis C. Management requires individualized approaches, multiple decision points, and an intensive hands-on approach throughout the long course of treatment. The increased efficacy of newer treatments and approaches has also resulted in a broadening of the criteria for treatment candidacy and has increased the demand for treatment by HCV-infected patients. Thus, physicians who treat HCV infection are facing new challenges, but also greater success with improved outcomes for more patients.

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Suggested Readings

Notes:
* (Additional notes can be added here.)
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