Achieving Optimum Outcomes: Customizing Treatment for Patients With HCV Infection

Dear Colleague:

Treating hepatitis C virus (HCV) infection is more important than ever. The incidences of decompensated cirrhosis and hepatocellular carcinoma are increasing, as are the demand for liver transplants and liver-related mortality. Treatment, however, can alter the natural history of HCV infection, slowing, halting, and possibly even reversing progression to these serious complications. Even in patients with mild disease, there is now evidence that immediate treatment reduces future risk of cirrhosis, prolongs survival, and is cost-effective. Moreover, with each new advance in treatment that brings higher rates of sustained virologic response (SVR), more patients benefit.

Pegylated formulations represent the latest advance in the treatment of HCV infection. Peginterferon offers expanded efficacy and convenience compared with standard interferon, and in combination with ribavirin is expected to be the next standard of care. Peginterferon alfa-2b/ribavirin produces an SVR in 54% overall. Another exciting new discovery is that tailoring treatment by body weight will further improve response, allowing up to 61% of patients to achieve an SVR when doses of both peginterferon alfa-2b and ribavirin are optimized.

Physicians have developed a strong level of comfort in using standard antiviral therapies for HCV infection, including managing adverse events and providing necessary patient education and counseling. These improvements in clinical expertise have led to higher rates of treatment completion and therefore higher SVR rates. By applying and building on what we already know to promote adherence to new treatment regimens with pegylated interferons, we can expect even better treatment outcomes.

In this issue of the Tx Reporter, Achieving Optimum Outcomes: Customizing Treatment for Patients With HCV Infection, our distinguished faculty will share with you the latest data on pegylated formulations of interferon, in combination with ribavirin and as monotherapy, and will provide you with practical strategies for individualizing patient care. Thus, you will be able to immediately apply these latest advances to your own clinical practices. I am sure you will find this newsletter both informative and useful.

Sincerely,

Eugene R. Schiff, MD
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State of the Art: Where We Are Today

Nezam H. Afzhal, MD

For the past few years, interferon/ribavirin has been the standard of care for treatment-naive patients, interferon relapsers, and nonresponders to monotherapy. This standard was based on data from numerous trials showing higher SVR rates with interferon/ribavirin combination therapy than interferon monotherapy in these populations. For example, in trials of treatment-naive patients, 41% of patients achieved an SVR to 48 weeks of interferon alfa-2b/ribavirin versus 16% with a similar duration of interferon monotherapy.

Important Lessons Learned With Interferon/Ribavirin

A number of important lessons have been learned from the pivotal trials on interferon alfa-2b/ribavirin, including the nature of the therapeutic contributions of ribavirin, how to use predictors of response to treatment to tailor therapy, the effects of body weight on the likelihood of treatment response, and the great importance of treatment adherence.

Lesson 1: Ribavirin increases end-of-treatment virologic response (ETVR) and enhances durability of response. ETVR rates increased from 29% with 48 weeks of interferon monotherapy to 51% with interferon/ribavirin. Moreover, relapse rates among patients with an ETVR were reduced.

(continued on page 3)
Learning Objectives

This activity is designed for clinical specialists with a fundamental clinical understanding of assessment, diagnosis, treatment, and ongoing management of patients with hepatitis C infection.

After participating in this activity, the physician should be able to:

- Describe the current standard of care for treatment of HCV infection using combination therapy
- Discuss emerging improvements in treatment of HCV infection based on study results and their implications from clinical trials using pegylated interferon/ribavirin combination therapy and pegylated interferon monotherapy
- Describe potential approaches to treatment, including dosing strategies and duration of treatment, that incorporate pegylated interferon into established standards of care

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This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

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by more than half, from 45% to 20%, respectively.10

Lesson 2: Genotype is the most important predictor of response. Patients with genotype 2 or 3 infection have significantly higher SVR rates than those with genotype 1 infection. In addition, genotype 1-infected patients derive additional benefit when therapy is continued for a total of 48 weeks. In contrast, response rates are equivalent at 24 and 48 weeks for patients with genotype 2 or 3 infection, allowing early treatment completion in this group.10 (See Table 1.)

In addition to genotype, other independent predictors of response include low viral load (<3.5 million copies/mL), no or portal fibrosis, female gender, and age <40 years.11 Poynard et al11 recommend discontinuing treatment after 24 weeks for patients with 4 or 5 predictors (including genotype non-1) who have cleared HCV RNA at week 24. Patients with <4 predictors and/or genotype 1 should receive 48 weeks of therapy. These recommendations are controversial, however, and many physicians tailor treatment according to genotype alone or genotype and/or degree of fibrosis.

Lesson 3: Body weight is another key predictor of response to standard doses of interferon. In a recent retrospective analysis of treatment-naive patients randomized to treatment with interferon alfa-2b monotherapy in the control arms of the 2 large interferon/ribavirin trials, SVR to interferon 3 MU TIW for 48 weeks occurred in only 9% of patients >95 kg versus 32% of those <55 kg (Fig. 1). (J.G. McHutchison, unpublished data, 2000.)

Lesson 4: Treatment adherence is critical. In another retrospective analysis of data from the interferon/ribavirin study in treatment-naive patients, McHutchison12 reported that patients who received at least 80% of their total interferon dose and at least 80% of their ribavirin dose for at least 80% of the recommended duration of therapy achieved an SVR rate of 48% versus only 15% among those who received lower doses for a shorter duration. Increased physician comfort and competency in individualizing therapy, managing adverse effects, educating and counseling patients, and maintaining patients on treatment are now leading to increased treatment completion rates, and as a result, higher rates of response.

Conclusion

Although the introduction of interferon/ribavirin combination therapy was a tremendous advance, almost 60% of patients nonetheless fail to reach an SVR. Thus, additional therapeutic strategies that enhance treatment outcomes are necessary. Yesterday’s treatment insights must inform today’s decisions in order to further improve treatment outcomes. Treatment today must account for differences in body weight and other response predictors (eg, genotype). Combination regimens offer additional value over single therapy, and every effort to keep patients on treatment at maximum tolerated doses must be made.
Pharmacokinetics and Pharmacodynamics of Pegylated Interferons

Bruce A. Luxon, MD, PhD

Pegylated interferons represent the next advance in the treatment of chronic HCV infection. These formulations were developed to improve upon the high rate of initial response seen with standard interferons by reducing the subsequent high rates of breakthrough or relapse. Standard interferons have short half-lives (2-3 hours for interferon alfa-2b and 3.7-8.5 hours for interferon alfa-2a), which result in low or undetectable levels of drug between doses when given thrice weekly. These troughs in drug concentration and activity allow the virus to replicate and may allow a resurgence of resistance.

Pegylation, the process by which a large inert molecule (polyethylene glycol [PEG]) is attached to a protein, is a well-established method for decreasing drug clearance. When interferon is pegylated, its half-life is increased. Prolonged concentrations of interferon may increase the extent/duration of its therapeutic activity and allow for the convenience of once-weekly dosing (versus thrice-weekly dosing with standard interferons). In addition, steadier concentration levels throughout the week are assumed to prevent viral rebound between doses. (See Fig. 2.) Pegylation also decreases the antigenicity of the protein to which it is bonded. Advantages of PEG as a protein-modifying agent are that it is inert, water soluble, and nontoxic. Therefore, it is not believed to contribute adversely to the safety profile of the active drug.

PEG can be made any size by varying the number of oxyethylene groups.

The size of the PEG molecule influences its pharmacokinetic and pharmacodynamic effects. As PEG size increases, half-life increases and antiviral activity and clearance by the kidneys decrease.

Currently, there are 2 pegylated formulations of interferon: peginterferon alfa-2b and peginterferon alfa-2a (Table 2).

Peginterferon alfa-2b

Interferon alfa-2b remains the active component of peginterferon alfa-2b, which consists of a conjugate of straight-chain 12 kd PEG and interferon alfa-2b in a 1:1 ratio. It has a 2° and 3° protein structure comparable with interferon alfa-2b. PEG is usually attached to lysine residues, but in a unique proprietary process used in producing peginterferon alfa-2b, 45% of PEG molecules are attached primarily to histidine residues (His34), which allows for maintenance of 35% of native activity of interferon alfa-2b (more than double what would occur if PEG were attached to lysine residues alone) (Schering-Plough Research Institute, data on file).

Table 2. Comparison of Pegylated Interferons

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Peginterferon alfa-2b</th>
<th>Peginterferon alfa-2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of PEG</td>
<td>Straight chain, 12 kd</td>
<td>Branched chain, 40 kd</td>
</tr>
<tr>
<td></td>
<td>- Previously approved</td>
<td>- Not previously approved</td>
</tr>
<tr>
<td>Antiviral activity</td>
<td>35% of IFN α-2b</td>
<td>7% of IFN α-2a</td>
</tr>
<tr>
<td>PK characteristics</td>
<td>Absorption</td>
<td>Unchanged</td>
</tr>
<tr>
<td></td>
<td>Vd</td>
<td>Unchanged</td>
</tr>
<tr>
<td></td>
<td>CL</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>PEG clearance</td>
<td>Eliminated by kidneys</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not cleared by kidneys</td>
</tr>
</tbody>
</table>

*The second and third curves represent superimpositions of the 0-36 hour concentration-time curve rather than actual measurements.

Figure 2. Week 4 Concentration-Time Profile for Peginterferon alfa-2b Versus Interferon alfa-2b.
The addition of PEG to interferon alfa-2b results in decreased clearance (elimination half-life about 54 hours; $C_{max}$ duration 48-72 hours) consistent with once-weekly dosing without altering the dose-responsive, pharmacodynamic effects of interferon.\textsuperscript{14,15}

Peginterferon alfa-2b has good antiviral activity extending throughout the week, even though concentrations begin to decline toward the end of the dosing interval. If half-life were longer and concentrations remained higher for a longer period, safety would be an important issue since it would be more difficult to ameliorate adverse effects in patients requiring dose reduction or treatment discontinuation.

**Peginterferon alfa-2a**

The peginterferon alfa-2a molecule consists of an ester derivative of a branched-chain 40 kd PEG moiety covalently bonded to a free amino group of interferon alfa-2a. In this molecule, PEG is attached predominately to lysine sites. With a single 180 µg dose, 61% is absorbed, half-life is 77 hours, and peak concentration is reached after 80 hours. Renal clearance is reduced 100-fold. Plasma levels are sustained for >168 hours, consistent with once-weekly dosing.

Steady-state concentrations are reached in 5 to 8 weeks. Thereafter, serum concentrations remain stable after each dose throughout treatment (steady-state peak:trough ratio 1.5-2.0).\textsuperscript{16-18} (Roche Pharmaceuticals, data on file.)

**Clearance of Pegylated Interferons**

Although PEG is considered inert, safety of PEG accumulation and long-term circulation has not been confirmed. Thus, clearance of PEG is desirable. Thirty percent of peginterferon alfa-2b is cleared by the kidneys, and 70% is cleared by hepatic catabolism and degradation after binding to cellular interferon receptors (Schering-Plough Research Institute, data on file). Peginterferon alfa-2a is cleared primarily by the liver.\textsuperscript{19} No dose reduction of either peginterferon alfa-2b or peginterferon alfa-2a is necessary when interferon is pegylated, its half-life is increased. Prolonged concentrations of interferon may increase the extent/duration of its therapeutic activity and allow for the convenience of once-weekly dosing.

**Pegylated Interferon Monotherapy**

**Karen L. Lindsay, MD**

Recent clinical trials have demonstrated that pegylated interferon formulations are approximately twice as effective as standard interferons but have similar safety profiles. In addition, once-weekly administration improves ease of administration.

**Peginterferon alfa-2b**

In a US and international multicenter trial presented at the 2000 annual meeting of the European Association for the Study of the Liver (EASL),\textsuperscript{22} 1219 treatment-naive patients with chronic HCV infection were randomized to either interferon alfa-2b 3 MU TIW or 1 of 3 weight-based doses (0.5, 1.0, or 1.5 µg/kg) of peginterferon alfa-2b for 48 weeks. At all doses, peginterferon alfa-2b was significantly more effective than standard interferon alfa-2b, and there was a clear dose-related effect on ETVR (Fig. 3). At the end of treatment, the highest response (49%) was achieved by those treated with 1.5 µg/kg peginterferon alfa-2b. Following treatment discontinuation, relapse rates were high in all 4 treatment groups. Ultimately, patients treated with 1.0 µg/kg peginterferon alfa-2b had the highest SVR rate (25%), but response was similar among those treated with 1.5 µg/kg (23%).\textsuperscript{22}

By multivariate analysis, both HCV genotype and baseline HCV RNA level were found to be independently associated with SVR. Patients with HCV genotype 2 or 3 infection had an SVR rate more than triple that of patients with HCV genotype 1.
(35%-49% in genotype 2 or 3 versus 11%-14% in genotype 1 with peginterferon). Individuals with both genotype 1 infection and high viral level had the lowest SVR to therapy with either peginterferon alfa-2b (7%) or standard interferon alfa-2b (2%). In contrast, individuals with genotype 2 or 3 infection and low viral level had the highest SVR: 68% with 1.5 µg/kg peginterferon alfa-2b compared with 36% with standard interferon alfa-2b. Although SVR rates were lowest in patients infected with HCV genotype 1, rates of ETVR in genotype 1-infected patients were 2 to 3 times greater with peginterferon than with standard interferon, particularly in patients who experienced the lowest response rate to standard interferon, those with genotype 1 infections and high viral levels (>2 million copies/mL) (Table 3).

The safety and tolerability profiles of peginterferon alfa-2b were qualitatively similar to those of interferon alfa-2b. Typical adverse events of interferon (eg, flulike symptoms, asthenia, hematologic changes) were observed at expected incidences. Injection-site inflammation was more frequent with peginterferon alfa-2b, but otherwise, no new adverse events emerged.

**Peginterferon alfa-2a**

An open-label, multinational, phase 3 trial comparing peginterferon alfa-2a (180 µg x 48 weeks) with interferon alfa-2a (6 MU x 12 weeks + 3 MU x 36 weeks) was recently published. The study included 531 treatment-naive patients. Although the baseline characteristics of the study population were different than in the peginterferon alfa-2b trial, the SVR rate also doubled with pegylated interferon in this trial (39% versus 19% with standard interferon alfa-2a) (Fig. 4).

Types/frequencies of adverse events were similar in both groups and typical of interferon alfa-2a. Rates of dose modification and treatment discontinuation were also similar between the 2 groups.

As in other interferon trials, HCV genotype, viral level, age, and fibrosis stage are important predictors of response to peginterferon alfa-2a.23,24 Gender is apparently not an independent predictor, at least according to 1 assessment.24 As with both pegylated and nonpegylated interferon alfa-2b, body weight or body surface area has also been identified as a predictor of response to treatment.22,24 In addition, several novel predictors of response to

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**Table 3. Peginterferon alfa-2b Versus Interferon alfa-2b: ETVR by Genotype/HCV RNA Level**

<table>
<thead>
<tr>
<th>Genotype, Viral Level (Copies/mL)</th>
<th>PEG IFN α-2b 1.5 µg/kg (n = 304)</th>
<th>PEG IFN α-2b 1.0 µg/kg (n = 297)</th>
<th>IFN α-2b 3 MU (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC 1, ≤2 M</td>
<td>50%</td>
<td>43%</td>
<td>35%</td>
</tr>
<tr>
<td>HCV 2/3, ≤2 M</td>
<td>77%</td>
<td>76%</td>
<td>48%</td>
</tr>
<tr>
<td>HCV 1, &gt;2 M</td>
<td>35%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>HCV 2/3, &gt;2 M</td>
<td>76%</td>
<td>76%</td>
<td>52%</td>
</tr>
</tbody>
</table>

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**Figure 3.** Peginterferon alfa-2b Versus Interferon alfa-2b: ETVR by Genotype/HCV RNA Level.

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Peginterferon alfa-2a have been identified, including:

- Rapid viral response (≥2-log decrease in viral titer by week 4 of treatment followed by a ≥2-log decline by week 8)\textsuperscript{25}
- Baseline necroinflammatory markers such as hepatic activity index >10 or alanine aminotransferase (ALT) level >3 times the upper limit of normal\textsuperscript{23,24}

**Conclusions**

Pegylated interferons are significantly more effective than standard interferons, roughly doubling response rates in monotherapy trials. Differences in patient population between the peginterferon alfa-2a and peginterferon alfa-2b trials may account for the difference in response rates in these studies. No direct comparative trials have yet been performed. Genotype and level of HCV RNA continue to be important predictors of response, as is body weight in the absence of weight-based dosing. Although genotype 1-infected patients, especially those with high viral levels, have lower ETVR rates than patients with genotype 2 or 3 infections and/or low viral levels, higher-dose (1.5 µg/kg) peginterferon alfa-2b improves response in genotype 1 patients. Safety of pegylated interferons is similar to that of nonpegylated interferons.

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**Defining the Next Standard of Care**

**JOHN G. McHUTCHISON, MD**

Since peginterferon is more effective than standard interferon, and ribavirin is known to further enhance response rates and the durability of response, it is logical that peginterferon would replace standard interferon in combination regimens with ribavirin. In fact, recent investigations have confirmed that this results in the highest response rates seen to date without significant increases in toxicity. Additional evaluations have demonstrated even greater improvements in efficacy when doses of both interferon and ribavirin are optimized according to body weight.

**Peginterferon alfa-2b/Ribavirin**

In a phase 3, open-label trial presented at the 2000 annual meeting of the American Association for the Study of Liver Diseases (AASLD),\textsuperscript{4} 1530 treatment-naive patients with chronic HCV infection were randomized to 1 of the following regimens:

- Peginterferon alfa-2b 1.5 µg/kg QW plus ribavirin 800 mg/d for 48 weeks
- Interferon 3 MU TIW plus ribavirin 1000 mg/d for patients ≤75 kg or 1200 mg/d for patients >75 kg for 48 weeks

**Efficacy**

The group that received the higher dose of peginterferon alfa-2b (1.5 µg/kg) in combination with ribavirin had the highest ETVR (62%) and SVR (54%) rates observed to date. The lower dose (0.5 µg/kg) of peginterferon alfa-2b plus ribavirin produced response rates similar to those seen with standard combination therapy. (See Fig. 5.) Genotype 1-infected patients had a 42% SVR rate when given 1.5 µg/kg peginterferon alfa-2b plus 800 mg/d ribavirin—also the highest observed to date. Moreover, SVR was nearly universal (82%) among those with genotype 2 or 3 infection.

Data from previous trials have demonstrated the need for weight-based dosing of interferon. (J.G. McHutchison, unpublished data, 2000.) The current trial took this concept a step further,
exploring whether the ribavirin dose could be further optimized according to body weight to achieve even higher response rates. Indeed, logistic regression analysis showed an increased probability of response to peginterferon/ribavirin with increasing dose per kilogram of ribavirin. The optimal dose of ribavirin was identified as 13 ± 2 mg/kg. Moreover, patients who received 1.5 µg/kg peginterferon alfa-2b in combination with at least 10.6 mg/kg of ribavirin had an SVR rate of 61% (Fig. 6). Forty-eight percent of patients with genotype 1 and 88% of those with genotype 2 achieved SVR with 1.5 µg/kg of peginterferon alfa-2b and >10.6 mg/kg of ribavirin.

As in previous trials, adherence to therapy enhanced treatment outcomes. Patients who received ≥80% of the optimized, weight-based doses of both drugs for at least 80% of the recommended duration (“80+80+80 adherence”) had an SVR of up to 72%. (J.G. McHutchison, unpublished data, 2000.)

Safety

Fever, nausea, and injection-site reactions were the only adverse events with a ≥10% difference in incidence between peginterferon/ribavirin- and interferon/ribavirin-treated patients (Table 4). Other adverse events were typical of interferon/ribavirin combination therapy (eg, flulike symptoms, fatigue, anemia, psychiatric effects). The incidence of anemia (hemoglobin <10 g/dL) was 14% with peginterferon/ribavirin versus 12% with interferon/ribavirin.

Rates of treatment discontinuation were about 13% to 14% in all 3 arms (M.P. Manns, unpublished data, 2000), which is notably lower than the 19% to 21% treatment discontinuation rates seen in previous trials of interferon/ribavirin. This suggests that physicians are now more comfortable managing adverse events with dose reduction, allowing patients to continue therapy. Peginterferon at the higher dose, in combination with 800 mg/d of ribavirin, was associated with an increased need for dose reduction (42%) compared with either lower-dose peginterferon/ribavirin (36%) or standard combination therapy (34%).

Peginterferon alfa-2a/Ribavirin

Phase 3 trials of peginterferon alfa-2a/ribavirin have not yet been reported. Preliminary results from a small (N = 20), open-label, phase 2 trial of peginterferon alfa-2a 180 µg QW plus standard doses of ribavirin were presented at the 2000 annual meeting of Digestive Disease Week. ETVR was 65% and SVR was 50%. In genotype 1-infected patients, ETVR was 56% and SVR was 38%, and in genotype non-1-infected patients, both ETVR and SVR rates were 100%. The final results of this trial have not yet been published. Adverse events were typical of those seen with interferon alfa-2a and included fatigue, pyrexia, myalgia, headache, insomnia, irritability, rigors, arthralgia, dermatitis, and nausea/vomiting. There were no treatment discontinuations due to hematologic effects.

Conclusions

Peginterferon alfa-2b 1.5 µg/kg in combination with ribavirin is significantly more effective than standard interferon alfa-2b plus ribavirin, resulting in an SVR rate of 54%. When the ribavirin dose in this combination is optimized by body weight (>10.6 mg/kg), the SVR rate is further increased to 61%. Peginterferon alfa-2b/ribavirin has a safety/tolerability profile similar to that of interferon/ribavirin, with no new adverse events specific to this combination. The incidence of common adverse events of ribavirin (eg, rash, insomnia, dyspnea) was not increased. Preliminary results of peginterferon alfa-2a/ribavirin are promising but require confirmation in larger phase 3 studies.

| Table 4. Adverse Events: ≥10% Difference in Incidence Between Treatment Groups |
|------------------|------------------|------------------|
|                   | Interferon/ Ribavirin (n = 505) | Peginterferon 1.5 µg/kg + Ribavirin (n = 511) |
| Fever             | 33%               | 46%               |
| Nausea            | 33%               | 43%               |
| Injection-site reactions (all) | 36% | 58% |
| Inflammation      | 18%               | 25%               |
Pegylated interferons have demonstrated efficacy over standard interferons, both as monotherapy and in combination with ribavirin, without adding toxicity. Pegylated interferons also offer the convenience of once-weekly dosing. Peginterferon alfa-2b/ribavirin has demonstrated the highest rates of SVR seen to date and may become the next standard of care for eligible treatment-naive patients. The improved efficacy of treatment also lowers the threshold for treatment of patients with chronic HCV infection, including those with mild disease.

Other candidates for peginterferon/ribavirin include monotherapy nonresponders, and relapers and nonresponders to standard interferon/ribavirin combination therapy. Although benefits in these populations remain to be confirmed, peginterferon/ribavirin may induce additional remissions and help to prevent relapse in those who achieve an ETVR. When re-treating these populations with peginterferon/ribavirin, physicians may consider discontinuing therapy at 3 months if a ≥1 log decline in HCV RNA is not observed. Otherwise, treatment should be discontinued at 6 months if HCV RNA remains detectable, and maintenance therapy should be considered if the patient has stage 3 or 4 fibrosis.

Patients currently receiving interferon/ribavirin may derive additional benefit (greater likelihood of remission and reduced likelihood of breakthrough or relapse) and convenience from switching to peginterferon/ribavirin. In light of these considerations, patients currently receiving therapy should be switched to peginterferon/ribavirin without reason for delay, especially if ≥3 months of therapy remain to be completed.

Peginterferon monotherapy is likely to be reserved for patients who are not eligible for ribavirin but for use as maintenance therapy. Two 4-year studies of pegylated interferons as maintenance therapy are currently under way. The HALT-C trial, which is sponsored by the National Institutes of Health, is randomizing peginterferon alfa-2a/ribavirin nonresponders to long-term peginterferon alfa-2a 90 µg QW or placebo. COPiLOT, which is sponsored by Schering Hepatitis Innovations, is randomizing interferon alfa-2b/ribavirin nonresponders to either colchicine or peginterferon alfa-2b 0.5 µg/kg QW.

**Weight-Based Dosing of Peginterferon/Ribavirin**

Weight-based dosing with peginterferon alfa-2b may reduce the effects of weight on the efficacy of interferon.

The optimal dose of peginterferon alfa-2b is 1.5 µg/kg QW when used in combination with ribavirin or 1.0 µg/kg QW when used as monotherapy. Moreover, optimizing the dose of ribavirin to 13 ± 2 mg/kg/d has been suggested to improve rates of SVR to peginterferon alfa-2b/ribavirin. Thus, weight-based dosing of both peginterferon and ribavirin makes sense and is also likely to be part of the next standard of care. Table 5 provides guidelines for selecting appropriate doses of peginterferon alfa-2b and ribavirin according to individual patient body weights. Peginterferon alfa-2a is not dosed according to weight; the recommended dose is 180 µg QW.

**Management Guidelines**

Practical applications of peginterferon/ribavirin are not substantially different from the current applications of interferon/ribavirin. Liver biopsy remains important, as does assessment of viral level at 6 months.
Final Thoughts and Conclusions

**WILLIS C. MADDREY, MD**

Opportunities to improve outcomes in treatment of chronic hepatitis C are clearly expanding. Pegylated interferons offer better efficacy and convenience, and therefore are likely to replace standard interferons in the treatment of chronic HCV infection. More than half of all patients (54%) with chronic HCV infection can now achieve an SVR to therapy when treated with peginterferon alfa-2b/ribavirin. With weight-based dosing of peginterferon alfa-2b and ribavirin, higher response rates are possible (61%). When monotherapy is required, pegylated interferons offer benefits over standard interferons. The availability of these more effective therapies without accompanying increases in adverse events lowers the threshold for treating patients with chronic HCV infection.

Genotype remains the primary predictor of response. Expected outcomes in patients infected with genotypes 2 or 3 are now excellent (SVR 82% overall with peginterferon alfa-2b/ribavirin and 88% with optimized weight-based dosing of both drugs), and are clearly improving in patients with genotype 1 (SVRs of 42% and 48%, respectively). New predictors of response to peginterferon alfa-2a have been identified, including rapid viral response and baseline necroinflammatory markers.

When using new pegylated formulations of interferon, physicians should build on the knowledge and expertise that they have already developed regarding use of standard interferons alone and in combination with ribavirin. Individualizing doses and durations of therapy, managing adverse events, and helping patients to stay on therapy are skills that most physicians who treat HCV infection have already developed, which will serve patients well when applied to new treatment regimens using pegylated interferons.

**Future Studies of Pegylated Interferons**

Promising data are now available to help inform current management decisions, thereby allowing for improved outcomes; however, definitive answers to a number of questions are still needed. Are 6 months of peginterferon/ribavirin sufficient for patients with genotype 2 or 3 infection? Should all cirrhotics be treated for 1 year? Should late responders receive >1 year of therapy? Do all patients with genotype 2 or 3 infections require a liver biopsy since treatment results are so favorable in this group? What effect should viral load have in treatment decisions in patients with genotype 1 infection? To answer these questions, a number of studies are planned or already in progress.

Confirmation of enhanced efficacy with optimized weight-based ribavirin dosing is necessary, as is investigation of >1.5 µg/kg of peginterferon alfa-2b. Prospective studies of pegylated interferons in combination with novel therapies, such as amantadine, interleukin-2, or various antioxidants, may be of interest. Studies are also needed of peginterferon/ribavirin combination therapy in special populations, such as nonresponders, HIV-coinfected patients, and patients with normal ALT levels, and of peginterferon monotherapy in patients undergoing dialysis.

Practical Approaches to Care: Enhancing Outcomes (continued from page 9)
References


17. Algranati NE, Sy S, Modi M. A branched methoxy 40 kDa polyethylene glycol (PEG) moiety optimizes the pharmacokinetics (PK) of peginterferon α-2a (PEG-IFN) and may explain its enhanced efficacy in chronic hepatitis C (CHC) [abstract 120]. Hepatology. 1999;30:190A.


19. Modi MW, Fulton JS, Buckmann DK, Wright TL, Moore DJ. Clearance of pegylated (40 kDa) interferon alfa-2a (PEGASYS®) is primarily hepatic [poster presentation]. Presented at: 51st annual meeting of AASLD; October 27-31, 2000; Dallas, Tex.


21. Martin P, Mitra S, Farrington K, Martin NE, Modi MW. The pharmacokinetics of pegylated (40 kDa) interferon alfa-2a (PEGASYS®) are unaffected by renal impairment [poster presentation]. Presented at: 51st annual meeting of AASLD; October 27-31, 2000; Dallas, Tex.


25. Neumann AU, Zeuzem S, Brunda MJ. Rapid viral response to treatment with pegylated (40kDa) interferon alfa-2a (PEGASYS™) is strongly predictive of a sustained virologic response in patients with chronic hepatitis C (CHC) [abstract 633]. Presented at: 51st annual meeting of AASLD; October 27-31, 2000; Dallas, Tex.

CME Posttest

Achieving Optimum Outcomes: Customizing Treatment for Patients With HCV Infection


Documentation of Participation for CME

To receive documentation of your participation for CME credit, complete the following steps:

1. Read this newsletter carefully.
2. Complete this Posttest, selecting the most appropriate choice for each statement.
3. Complete the Evaluation.
4. Mail or fax your CME Posttest and Evaluation to Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: 1-201-617-7333.

Projects In Knowledge will mail you an acknowledgment of your participation in this activity. Please note: You must score 70% or better on the posttest. If you score lower than 70%, you will be given another chance to take the posttest.

Name __________________________________________________________ Degree ________________
Mailing Address __________________________________________________________________________________________
City __________________________ State ___________ ZIP __________________
Phone __________________________ Fax __________________________
E-mail __________________________________________________________

Please indicate your answers below:

1. The rates of advanced liver disease secondary to HCV infection and its complications are expected to dramatically increase between 1998 and 2008.
   - True    - False

2. Heavier patients are less likely than lighter patients to achieve an SVR to interferon when doses are not adjusted for body weight.
   - True    - False

3. Pegylation of a therapeutic protein increases its half-life, resulting in longer serum concentration times.
   - True    - False

4. The 40 kd PEG molecule in peginterferon alfa-2a is attached predominantly to histidine sites.
   - True    - False

5. Larger PEG molecules are more readily cleared by the kidney.
   - True    - False
6. In monotherapy trials of both peginterferon alfa-2b and peginterferon alfa-2a, SVR rates were approximately doubled relative to standard, nonpegylated interferon alfa-2b and interferon alfa-2a, respectively.
   - True   - False

7. Pegylated interferons are associated with significantly higher incidences of psychiatric and hematologic effects than are standard, nonpegylated interferons.
   - True   - False

8. In a large, phase 3 trial, peginterferon alfa-2b 1.5 µg/kg QW plus 800 mg/d ribavirin produced SVR in 54% of patients overall.
   - True   - False

9. A retrospective analysis of data from patients in the peginterferon alfa-2b/ribavirin trial showed that SVR is increased to 61% when 1.5 µg/kg peginterferon is combined with ribavirin doses of at least 8.0 mg/kg.
   - True   - False

10. Preliminary reports from a small phase 2 study of peginterferon alfa-2a/ribavirin suggest that SVR is about 50%.
    - True   - False

11. Trials of interferon/ribavirin and peginterferon/ribavirin have shown that adherence to ≥80% of expected doses of both drugs for ≥80% of the recommended duration improves SVR rates.
    - True   - False

12. Treatment discontinuation rates were lower in the control (interferon/ribavirin) arm of the phase 3 trial of peginterferon alfa-2b/ribavirin than in earlier trials of interferon/ribavirin, suggesting enhanced physician expertise and comfort in using and maintaining patients on these therapies.
    - True   - False

13. Peginterferon monotherapy is recommended for patients who are not candidates for ribavirin or as maintenance therapy.
    - True   - False

14. Trials of peginterferon/ribavirin have confirmed that 24 weeks of treatment is sufficient for patients infected with genotype 2 or 3 who have achieved a virologic response.
    - True   - False

15. Patients currently receiving standard interferon/ribavirin may derive additional benefit (enhanced convenience, increased likelihood of response, decreased likelihood of breakthrough/relapse) from switching to peginterferon/ribavirin, although these benefits remain to be confirmed in clinical trials.
    - True   - False
CM E Evaluation

TREATMENT REPORTER: Achieving Optimum Outcomes: Customizing Treatment for Patients With HCV Infection


Instructions

Please complete this Evaluation Survey, along with the CME Posttest, and either mail or fax back to Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: 1-201-617-7333.

1. Please rate the extent to which you achieved the learning objectives:

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<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Satisfactory</th>
<th>Poor</th>
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<td>• Describe the current standard of care in treatment of HCV infection using combination therapy</td>
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<td>• Discuss emerging improvements in treatment of HCV infection based on study results and their implications from clinical trials using pegylated interferon/ribavirin combination therapy and pegylated interferon monotherapy</td>
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<td>• Describe potential approaches to treatment, including dosing strategies and duration of treatment, that incorporate pegylated interferon into established standards of care</td>
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2. Please rate the overall value of this enduring material:

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3. Course was free of commercial bias:

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4. Please rate the level of the material presented:

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5. Please list any changes in your practice that you would consider making as a result of participating in this activity:

_____________________________________________________________________________________________________________
_____________________________________________________________________________________________________________

6. Please rate your interest in self-directed or distance learning in the following formats:

   a. Audioconference
   b. Videoconference
   c. Enduring materials (audiocassettes, videotapes, monographs)
   d. Internet (online discussions with experts, educational activities)
   e. Multimedia (online, CD-ROM)

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<th>Very Interested</th>
<th>Moderately Interested</th>
<th>Not Interested</th>
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7. Please tell us how long it took you to complete this course: __________________

8. Please list 3 topics and/or experts you would find interesting and professionally relevant for future CME activities:

_____________________________________________________________________________________________________________
_____________________________________________________________________________________________________________

9. Follow-up:

   As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

   ☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I’m not interested.

   Additional comments:

_____________________________________________________________________________________________________________
_____________________________________________________________________________________________________________

Thank you for your participation.
Achieving Optimum Outcomes: Customizing Treatment for Patients With HCV Infection