Dear Colleague:

This newsletter represents the first part of the expanded five-part CME compendium that comprises The Clinician’s Companion VI. The four newsletters, representing Parts 1 through 4, will feature timely reporting of the latest developments in the field, whereas the monograph, Part 5, will provide in-depth coverage of some of the most important issues in hepatitis C today. Content for the series was developed at a meeting that featured expert presentations, panel discussions, case studies, and recommendations gathered via survey from a nationwide panel of leading experts in hepatitis C. This newsletter, representing Part 1 of the series, covers preliminary findings from ongoing studies of peginterferon/ribavirin.

In August 2001, the Food and Drug Administration (FDA) approved combination therapy with peginterferon alfa-2b 1.5 µg/kg QW plus ribavirin 800 mg/d for treatment of chronic hepatitis C. Data from Manns et al,1 published in The Lancet, showed that this regimen produces a sustained virologic response (SVR) in 54% of patients overall, 42% of patients infected with hepatitis C virus (HCV) genotype 1, and 82% of those infected with HCV genotype 2 or 3. Based on these findings, peginterferon/ribavirin has since replaced interferon/ribavirin as the standard of care. Studies of the investigational agent peginterferon alfa-2a, in combination with ribavirin, have been reported at national conferences, with SVR rates of 56% overall, 46% in genotype 1, and 76% in genotype 2/3.2 Later in this newsletter, John B. Gross, MD, looks at the extent to which the increased efficacy of peginterferon/ribavirin over standard interferon/ribavirin provides new hope of SVR to those who failed to respond to prior therapies.

Retrospective analyses have identified additional means of improving treatment outcomes. Analysis of the Manns et al data determined that the highest SVR rates were attained by patients who received weight-based dosing of peginterferon alfa-2b (1.5 µg/kg) and the highest doses of ribavirin per mg/kg of body weight (>10.6 mg/kg). These patients had an SVR rate of 61% compared with 50% for those who received the same dose of peginterferon alfa-2b with <10.6 mg/kg ribavirin. Patients who received >10.6 mg/kg ribavirin also had lower relapse rates. These retrospective observations led to the initiation of a prospective investigation of weight-based dosing in the WIN-R (Weight-Based Dosing of Interferon and Ribavirin) study. In the first section of this newsletter, Ira M. Jacobson, MD, discusses preliminary observations from WIN-R—the largest hepatitis C treatment trial ever conducted. We are pleased to bring you this update on peginterferon/ribavirin, and hope that you find it, and the rest of The Clinician’s Companion VI, informative and relevant to your patient care.

Sincerely,

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The Clinician’s
CME INFORMATION AND INSTRUCTIONS

A. ACCREDITATION
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Projects In Knowledge designates this educational activity for up to 2.5 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that were actually spent on the educational activity.

B. TARGET AUDIENCE
This CME activity is designed for gastroenterologists and hepatologists who diagnose and treat patients with chronic hepatitis C virus (HCV) infection, and who need immediate and practical information to address real-world clinical challenges associated with care of their patients. It is also designed for physicians who may be called upon to provide basic education on hepatitis C to their communities. An intermediate to advanced level of expertise in caring for patients with HCV infection is assumed.

C. LEARNING OBJECTIVES
The learning objectives for The Clinician’s Companion VI include the following:

• Formulate effective, individualized treatment strategies for patients with chronic HCV infection using pegylated interferon/ribavirin combination therapy
• Use diagnostic procedures, including HCV PCR and liver biopsy, in a timely fashion to determine treatment response
• Promote adherence to anti-HCV therapy by managing side effects and by providing appropriate psychosocial support
• Develop appropriate management strategies for different patient groups, including patients with HIV/HCV, mild disease, normal ALT levels, advanced liver disease, and hepatocellular carcinoma

D. ESTIMATED TIME FOR COMPLETION
Estimated time to complete course: 2.5 hours.

E. FOR CME CREDIT
To receive documentation of your participation:
Read Parts 1, 2, 3, 4, and 5 of The Clinician’s Companion VI.
2. Send the forms to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094, or fax to (201) 617-7333, before September 1, 2003.
Projects In Knowledge will mail you a certificate of completion if you score 70% or higher on the posttest. If you score lower than 70%, you will be given another chance to take the posttest.

F. CONTENT DEVELOPMENT INFORMATION
The Clinician’s Companion series is part of Projects In Knowledge’s Education Initiative in Gastroenterology, which was created to advance the knowledge base and clinical skills of practitioners in the field; to facilitate collaboration among thought leaders in research, academia, and clinical practice; and to provide a forum for discussion among representatives from diverse sectors of the healthcare enterprise. Other educational activities in the Education Initiative in Gastroenterology can be found at www.projectsinknowledge.com.

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The Disclosure Policy of Projects In Knowledge requires that faculty participating in a CME activity disclose to the audience any significant relationship they may have with a pharmaceutical or medical equipment company, product, or service that may be mentioned as part of their presentation, as well as any relationship with the commercial supporter of this activity. This independent CME activity is supported by an unrestricted educational grant from

TREATMENT REPORTER  Emerging Advances: Preliminary Findings From Ongoing Studies of Peginterferon/Ribavirin

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

The opinions expressed during this activity are those of the faculty and do not necessarily reflect those of the sponsor or the commercial supporter.

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Gary L. Hills, DO, has received grant/research support from Bristol-Myers Squibb Company, Glaxo Wellcome Inc, InterMune Inc, and Wyeth-Ayerst Pharmaceuticals. Barry P. Kaufman, MD, has received grant/research support from Schering-Plough; is a consultant for Schering-Plough; and is a stockholder in Enzon Inc. Kelly Kesinger, MD, has received grant/research support from Roche Pharmaceuticals and Schering-Plough.

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Gary L. Hills, DO, has received grant/research support from Bristol-Myers Squibb Company, Glaxo Wellcome Inc, InterMune Inc, and Wyeth-Ayerst Pharmaceuticals. Barry P. Kaufman, MD, has received grant/research support from Schering-Plough; is a consultant for Schering-Plough; and is a stockholder in Enzon Inc.
grant/research support from InterMune Inc, Roche Laboratories, and Schering; is a consultant for Gilead Sciences Inc, InterMune Inc, Roche Pharmaceuticals, and Schering; and is on the speakers bureaus of AstraZeneca and the speakers bureau of Schering-Plough.

Paul Pockros, MD, has received grant/research support from Schering-Plough. Gary Polevany, MD, has received grant/research support from Amgen Inc, Roche Pharmaceuticals, and Schering-Plough; and is on the speakers bureau of Schering-Plough. Fred Poordad, MD, has received grant/research support from Gilead Sciences, Roche Pharmaceuticals, and Schering-Plough; and is on the speakers bureau of Schering-Plough. Barry H. McGovern, MD, has received grant/research support and is on the speakers bureau of Schering-Plough. Jonathan McCone, MD, has received grant/research support from Schering, and is on the speakers bureau of Merck Inc, Janssen Pharmaceutica Products, LP, and TAP Pharmaceuticals Inc. Jeffrey Medoff, MD, has received grant/research support and is on the speakers bureau of Schering-Plough. Guy Neff, MD, has not provided disclosure.

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Methodology

The content of The Clinician’s Companion VI was developed during a meeting of a large, distinguished panel of hepatologists, gastroenterologists, and other specialists engaged in research or treatment of hepatitis C. At this meeting, several formats and techniques were used to gather information and establish consensus recommendations on difficult diagnostic and treatment issues.

Presentations were made on a variety of topics pertaining to hepatitis C including HCV virology and effects of treatment; impact of HIV on the natural history of hepatitis C; treatment of mild chronic hepatitis C (F0–F1); weight-based dosing; predictors of response and their treatment implications; strategies to alleviate side effects and promote adherence; assessing response to treatment; management of nonresponders; future drug development; hepatocellular carcinoma; and liver transplantations.

Consensus on these issues was then assessed using a written survey, which included 45 multipart questions regarding clinical practices prepared by the presenters and Projects In Knowledge. Survey questions asking for a preference were scored on a five-point rating scale. A special feature of the survey results is that they report not only the recommended choice but also the relative strength of opinion for each option assessed by a single question. For other questions, respondents were asked to provide an approximate percentage, results of which are reported as means, medians, and ranges. For certain items, respondents provided rounded estimates for these percentages.

Criteria for Inclusion on the Expert Consensus Panel

Selection of members for the expert perspectives panel was based on a number of criteria. First, national and international thought leaders who have made profound contributions to the understanding of hepatitis C through their research and participation in national and international science and public health forums were invited. Many of these distinguished leaders participated as presenters. Second, invitations were made to authors of recently published clinical research and recipients of federal or industry research grants. Third, physicians currently participating in clinical trials and those who had participated in major trials within the last year were invited. Finally, invitations were sent to clinicians who treat many hepatitis C patients and who offer the perspective of broad practical experience.

The expert perspectives panel for The Clinician’s Companion VI consisted of 193 survey respondents with an average of 14.9 years of practice (median, 15 years). Demographic characteristics are presented in Tables I–V.

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<th>Table I. Practice Region</th>
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<tr>
<td>Northeast</td>
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<td>Midwest</td>
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<td>Southwest</td>
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<td>Southeast</td>
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<td>South</td>
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<td>Northwest</td>
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<td>Rocky Mts.</td>
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<th>Table II. Nature of Practice</th>
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<tr>
<td>Specialty group practice</td>
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<tr>
<td>Academic, predominantly clinical</td>
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<tr>
<td>Private solo practice</td>
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<tr>
<td>Academic, administrative, &amp; clinical</td>
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<tr>
<td>Multispecialty group practice</td>
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<tr>
<td>Academic, predominantly research</td>
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<tr>
<td>HMO staff provider</td>
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<tr>
<td>General gastroenterology/ hepatology</td>
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<tr>
<td>Predominantly hepatology</td>
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<td>Infectious disease</td>
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<th>Table III. Patient Population: Race/Ethnicity</th>
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<tr>
<td>White</td>
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<td>Black or African American</td>
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<td>Hispanic or Latino</td>
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<td>Asian</td>
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<tr>
<td>Other</td>
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<td>(Middle Eastern, Pacific Islander)</td>
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<tr>
<td>Native American</td>
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<th>Table IV. HCV Patient Population</th>
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<td>Number with HCV infection in past 6 months:</td>
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<td>Mean</td>
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<td>Median</td>
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<tr>
<td>Number with HIV/HCV coinfection in past 6 months:</td>
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<td>Mean</td>
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<tr>
<td>Median</td>
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<td>Percentage of patients currently being treated who are:</td>
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<td>Treatment-naive</td>
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<td>Nonresponders</td>
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<td>Relapsers</td>
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<th>Table V. HCV Epidemiology in Past Year</th>
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<td>Number of patients seen with HCV infection has:</td>
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<tr>
<td>Increased</td>
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<td>Remained the same</td>
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<tr>
<td>Number of patients seen with HI/HCV coinfection has:</td>
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The WIN-R Trial: Early Observations on Weight-Based Dosing of Peginterferon alfa-2b/Ribavirin

Ira M. Jacobson, MD

In the registration trial of peginterferon/ribavirin for treating chronic HCV infection, Manns et al reported a strikingly linear relationship between the dose of ribavirin in mg/kg and the rate of SVR on retrospective logistic regression analysis, suggesting that weight-based dosing of ribavirin is likely to enhance its efficacy. As a result, weight-based peginterferon alfa-2b and ribavirin combination therapy was approved in Europe in March 2001. However, in the absence of prospective data on weight-based ribavirin dosing, the FDA approved only a fixed ribavirin dose of 800 mg/d in combination with peginterferon alfa-2b 1.5 µg/kg QW in August 2001. The prospective WIN-R Trial was subsequently initiated by investigators to address this issue in the United States.

Design of the WIN-R Trial

The WIN-R Trial is being conducted in 23 regions of the United States, each containing an average of 10 subsites. Participants with chronic HCV infection and elevated alanine aminotransferase levels are assigned by central randomization and stratified by genotype and degree of fibrosis, to either:

- Standard dosing (STD): peginterferon alfa-2b 1.5 µg/kg QW + ribavirin 800 mg/d, or
- Weight-based dosing (WBD): peginterferon alfa-2b 1.5 µg/kg QW + ribavirin dosed according to body weight: 800 mg/d for <65 kg, 1000 mg/d for 65 to 85 kg, 1200 mg/d for 86 to 105 kg, and 1400 mg/d (a dose not previously studied) for >105 kg.

Patients infected with genotype 2/3 are also randomized to either 24 or 48 weeks of therapy; patients with genotype 1 are all treated for 48 weeks. WIN-R enrollment of patients with HCV genotype 1 ended in January, while enrollment of patients with genotype 2/3 is ongoing. Thus far, approximately 4900 patients have been enrolled, including 400 African Americans. The principal investigator and Steering Committee are currently blinded to data on antiviral efficacy; thus, no data regarding virologic response are available yet. However, a large body of demographic, clinical, and hematologic data has begun to accumulate.

Demographic Data

The age distribution of the WIN-R population is typical of the HCV-infected population nationwide, with 63.4% being 45 to 64 years of age and 29% aged 35 to 44 years. Eighty-two percent are Caucasian, 10% African American, 5% Latino, 2% Asian, and 1% other. The majority (68%) are infected with genotype 1. As in other investigations, the prevalence of genotype 1 infection is disproportionately higher among African Americans at 91%, versus 72% among Latinos, 66% among Caucasians, and 55% among Asians. The prevalence of genotype 3 is lower in older age groups than among younger patients, further supporting previous hypotheses that this genotype is the most recently introduced into the United States. Seventy percent of the population has stage F0 to F2 fibrosis, and the rest have more advanced disease. (Jacobson IM, et al, unpublished data, 2002.)

Analysis of the demographic data from the WIN-R population indicates that genotype 1 is associated with about a twofold higher viral level than genotype 2/3. However, neither genotype nor viral level is correlated with the degree of progression of fibrosis. African Americans, who have a higher prevalence of genotype 1, are not more likely than Caucasians to have severe fibrosis. Persons infected with genotype 3 are more likely to have steatosis. In the overall study population, steatosis is associated with a higher prevalence of severe fibrosis. (Jacobson IM, et al, unpublished data, 2002.)

Hematologic Safety Data

In the study by Manns et al., patients receiving the higher dose of peginterferon (1.5 µg/kg QW) were given ribavirin 800 mg/d because of concerns that excess
hematologic toxicity might occur if the then-standard dose of ribavirin (1000–1200 mg/d) were used. Thus, the WIN-R study is carefully assessing hematologic toxicity, particularly among patients receiving higher doses of ribavirin. The WIN-R trial allows the use of erythropoietin for hemoglobin <10 g/dL and granulocyte colony-stimulating factor for absolute neutrophil count (ANC) <750/mm³. Use of these growth factors is not permitted to substitute for the dosage reductions mandated by the protocol, but concurrent dose reductions and use of growth factors are permitted. According to the study protocol, a neutrophil count of <750/mm³ mandates a reduction to peginterferon alfa-2b 1.0 mg/kg, and a hemoglobin level <10 g/dL mandates a decrease of between 200 and 400 mg in ribavirin dose. However, doses of peginterferon or ribavirin can be increased to their original levels if the ANC exceeds 1250/mm³ or the hemoglobin exceeds 11.5 g/dL after growth factors have been started.

At all points evaluated thus far (up to 24 weeks), mean hemoglobin level has been slightly lower (by about 0.5 g/dL) in patients treated with WBD versus patients treated with STD. At week 12, mean hemoglobin level was 11.9 g/dL versus 12.4 g/dL, respectively, and at week 24 was 11.8 g/dL versus 12.3 g/dL, respectively. Within the WBD group, however, there are no significant differences in hemoglobin level by ribavirin dose (Fig. 1). Particularly of note, the degree of anemia is not any greater in patients who received 1400 mg/d than among patients who are receiving lower doses of ribavirin. The discrepancy lessens by week 24, presumably as a result of a combination of dose reduction, use of growth factors, and patient adaptation. There is a lower incidence of anemia among heavier patients treated with fixed doses of ribavirin, whereas the incidence of anemia is somewhat comparable across all weight groups among those treated with WBD (Fig. 2).

Neutrophil counts were similar in both treatment groups at week 12 (1771/mm³ with STD and 1787/mm³ with WBD) and week 24 (1952/mm³ and 1900/mm³, respectively). Mean ANC is lower in African Americans than in Caucasians, but this appears to be associated with lower neutrophil counts at baseline. Platelet counts were not significantly different between treatment groups. Due in large part to the difference in incidence of anemia, there is a greater incidence of dose
modification in the WBD group (33% versus 27% with STD), but rates of drug discontinuation do not differ (9.4% in both groups). The incidence of dose modification decreases with increased patient body weight among patients given a fixed dose of ribavirin, whereas the incidence is fairly equivalent across weight groups in the WBD arm (Fig. 3).  

**Weight-Based Dosing of Ribavirin With Fixed-Dose Peginterferon alfa-2a**

A recent study reported at the 37th annual meeting of the European Association for the Study of the Liver (EASL) supports the concept of superior efficacy of WBD of ribavirin and the need for 48 weeks of treatment among persons with genotype 1 infection (Fig. 4). This study evaluated peginterferon alfa-2a 180 µg plus either a fixed ribavirin dose of 800 mg or weight-based ribavirin doses of 1000 mg/d for patients ≤75 kg or 1200 mg/d for those >75 kg for 24 or 48 weeks. The highest SVR rate (51%) among genotype 1 patients occurred in the subgroup treated with the higher, weight-based ribavirin dose (1000 or 1200 mg) for the longer duration (48 weeks). This study also found that neither duration of treatment nor WBD affected response among persons with genotype 2/3 infection—SVR rates ranged from 73% to 78% irrespective of ribavirin dose or treatment duration.  

**Survey Findings**

A written survey of the full panel of *Clinician’s Companion VI* contributors indicates that most clinicians already believe in the benefits of WBD of ribavirin: 96% said that when treating patients with peginterferon/ribavirin they use a ribavirin dose of >10.6 mg/kg. Even without complete data from WIN-R, survey respondents also believe that a ribavirin dose of 1400 mg/d is appropriate (rating 4.1 on a scale of 1 = highly inappropriate to 5 = highly appropriate) for patients >105 kg. They also rated a dose of 1200 mg/d as appropriate for such patients (rating 3.9). (Please refer to page 6 for more information about the survey methodology and population.)

**Conclusions**

Abundant demographic data have accumulated from this large study, shedding light on the epidemiology of HCV infection and confirming clinical correlations between genotype and viral level. This study also confirms that African Americans have a remarkably high prevalence of genotype 1, but indicates that genotype, race, and viral load are not correlated with fibrosis.  

To date, the WIN-R study shows that WBD does not have a dramatic impact on hematologic toxicity of peginterferon/ribavirin. WBD is associated with a mean hemoglobin level about 0.5 g/dL lower than is observed with STD, and a greater incidence of hemoglobin <10 g/dL; however, the higher incidence of anemia appears manageable with dose reduction rather than drug discontinuation in most cases. As long as ribavirin is dosed by body weight, higher doses are not associated with greater risks of hematologic toxicity. Neutrophil count is not adversely affected by WBD of ribavirin.  

Further analysis of the WIN-R study should yield prospective data on whether WBD translates into greater efficacy among patients treated with peginterferon alfa-2b/ribavirin. A preliminary report using peginterferon alfa-2a/ribavirin seems to support the notion that WBD of ribavirin increases efficacy, at least for patients with HCV genotype 1 infection. However, based on retrospective data from previous investigations, WBD of ribavirin has already become the standard of care.
John B. Gross, Jr, MD

Prior to the introduction of peginterferon/ribavirin, an estimated 400,000 patients were treated with standard interferon/ribavirin. At least 60% (an estimated 240,000–280,000) did not achieve an SVR. Many either have symptoms associated with HCV infection or are at risk for progressive liver disease, and most would consider retreatment with peginterferon/ribavirin if there were a chance of clearing their HCV infection. Therefore, further attempts at viral eradication are often warranted. Several investigator-initiated trials are in progress to assess the effectiveness of retreatment with peginterferon/ribavirin in this group of patients.

Conventional Dosing

Various ongoing studies are assessing conventional doses of peginterferon alfa-2b/ribavirin—ie, 1.5 µg/kg QW peginterferon alfa-2b + 800 mg/d ribavirin or 1.0 µg/kg peginterferon alfa-2b QW + 1000 to 1200 mg/d ribavirin—in patients who failed to achieve an SVR with interferon/ribavirin. In the two largest studies, on-treatment viral clearance at week 24 ranged from 16% to 30%, and SVR rates have been 10% to 11%. Interestingly, one study showed that the rate of clearance at week 24 was 45% among those who had previously had at least a 1-log drop in HCV viremia, while it was only 20% among those who had not. Dose reduction has been required in 15% to 33%, with discontinuation in up to 22%.

At the recent National Institutes of Health consensus conference on hepatitis C, Shiffman reported preliminary findings of the lead-in phase of the HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis) Trial in which nonresponders to interferon monotherapy or interferon/ribavirin were re-treated with 1 year of peginterferon alfa-2a 180 µg QW plus ribavirin 1000 to 1200 mg/d. All participants have advanced fibrosis. Among 212 patients, the 24-week on-treatment response rate was 30%. A preliminary estimate of the SVR is 11%.

High-Dose Therapy

Higher doses of peginterferon/ribavirin may further improve outcomes in interferon/ribavirin nonresponders. The RENEW trial is comparing peginterferon alfa-2b 0.5, 1.5, and 3.0 µg/kg QW, all with ribavirin 12 to 15 mg/kg/d. The low-dose arm was closed when the FDA approved 1.5 µg/kg for treatment-naive patients. Ninety-two percent of participants are infected with HCV genotype 1, 63% have stage 2 to 4 fibrosis, and 17% are African American (Gross JB Jr, et al, unpublished data, 2002).

Among 195 patients for whom 24-week treatment results were recently analyzed, the intent-to-treat rates of HCV RNA clearance have shown a dose-related effect, with 53% of patients in the 3.0 µg/kg peginterferon/ribavirin arm responding (Fig. 5). Among 516 patients who have started therapy, the rates of discontinuation due to an adverse event have been 6%, 5%, and 9% for the 0.5, 1.5, and 3.0 µg/kg doses of peginterferon, suggesting that even 3.0 µg/kg is reasonably well tolerated. Rates of dose reduction have been 22%, 24%, and 33%, respectively. Small numbers of serious adverse events have occurred at equal rates with 1.5 and 3.0 µg/kg (Gross JB Jr, et al, unpublished data, 2002).

Survey Findings

Survey respondents want to see more data on high-dose peginterferon/ribavirin before putting it into clinical practice, and are “on the fence” about re-treating at all, at least in patients with mild disease. Contributors were asked to rate the appropriateness (on a scale of 1 = highly inappropriate to 5 = highly appropriate) of various options for retreatment of a patient with HCV genotype 1a and grade 1, stage 2 histologic findings who tolerated but failed to respond to standard doses of interferon and ribavirin. Their first choice was peginterferon alfa-2b 1.5 µg/kg QW plus ribavirin 12 to 15 mg/kg/d (rating 4.2). Assuming its availability, peginterferon alfa-2a...
180 µg plus ribavirin 1000 to 1200 mg/d was the second choice (rating 3.2). The high-dose (3.0 µg/kg) regimen of peginterferon alfa-2b/ribavirin used in the RENEW study was rated 2.7, and the FDA-approved regimen of peginterferon 1.5 µg/kg QW plus ribavirin 800 mg/d was rated 2.4. Other regimens with even lower doses of peginterferon alfa-2b or alfa-2a and ribavirin received even lower ratings, indicating that they were considered inappropriate.

Given a similar patient with genotype 1b infection of 15-year duration, histologically mild disease (grade 1, stage 1), who drinks two beers per day (20 g/d ETOH), the survey respondents said that two appropriate management options would include no further treatment because of the small chance of SVR (rating 3.1) or retreatment with conventional doses of peginterferon/ribavirin (rating 2.9). Retreatment with high-dose peginterferon/ribavirin and no further treatment due to the slow rate of fibrosis progression were each rated 2.8. Maintenance therapy was also considered fairly inappropriate as a next option for this patient (ratings 1.9–2.1).

Conclusion

In summary, peginterferon/ribavirin in conventional doses produces on-treatment viral clearance rates of 20% to 30%, and SVR in 10% to 11% of nonresponders to prior treatment with interferon/ribavirin. Preliminary data suggest the possibility of higher viral clearance rates with high-dose (3.0 µg/kg) peginterferon and weight-based ribavirin, with approximately half of patients having undetectable HCV RNA levels at 24 weeks thus far.

Relapse and SVR rates with high-dose peginterferon and weight-based ribavirin remain to be determined.

References

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