Dear Colleague:

Side effects of peginterferon/ribavirin are common, but prompt and effective alleviation of these symptoms can prevent them from becoming treatment limiting. Many of the side effects of peginterferon and ribavirin can be managed with adjuvant therapies, thereby making treatment more tolerable and possibly avoiding the need for dose reduction or treatment discontinuation.

The first three parts of this four-part Tx Reporter series, New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy, now available at http://www.projectsinknowledge.com/Init/G/1616/index.html, focused on management of ribavirin-related anemia, primarily with epoetin. In this final issue in the series, we also include information about the management of neutropenia and other side effects associated with peginterferon. As was seen with epoetin in the previous cases, these adjuvant therapies make treatment more tolerable and may allow for maintenance of recommended doses of antiviral therapy.

This Tx Reporter, like the rest of the series, is designed to give you critical information and practical treatment strategies that can be incorporated into your regular management of hepatitis C. I hope that you have enjoyed this series and found it to be interesting, thought-provoking, and educational.

Sincerely,

Robert G. Gish, MD

Chair

Robert G. Gish, MD
CME Activity Chair
Medical Director
Liver Transplant Program
California Pacific Medical Center
San Francisco, California

Patient Description

Jason, a 40-year-old man, presents with blood tests showing a positive result for anti-HCV antibodies. Other lab test results are shown below. His creatinine level is elevated due to a long-standing history of hypertension. The patient reports mild symptoms of fatigue. Workup for cryoglobulins is negative, including negative rheumatoid factor despite ongoing joint pain. Jason undergoes liver biopsy, which shows bridging fibrosis and one early nodule formation. Abdominal ultrasound is negative for cancer but shows a spleen size of 11 cm, the upper limit of normal. Jason weighs 78 kg.

Lab Tests at Baseline

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>68 IU/L</td>
</tr>
<tr>
<td>HCV RNA level</td>
<td>1,200,000 copies/mL</td>
</tr>
<tr>
<td>Genotype</td>
<td>1b</td>
</tr>
<tr>
<td>Liver synthetic function tests</td>
<td>Normal</td>
</tr>
<tr>
<td>White blood cell (WBC) count</td>
<td>4300/mm³</td>
</tr>
<tr>
<td>Platelet count</td>
<td>125,000/mm³</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>40 mL/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5 mg/dL (upper limit of normal = 1.2 mg/dL)</td>
</tr>
</tbody>
</table>

Jason begins treatment of HCV infection with peginterferon alfa-2b 0.5 mL of the 80 µg/0.5 mL vial (dosed at a rate of 1.5 µg/kg QW) and ribavirin 600 mg in AM and 400 mg in PM daily (dosed at the rate of 12 mg/kg/d). During therapy, he develops severe fatigue that prevents him from working.

(continued on page 2)
Learning Objectives
This case-based educational activity is designed to update gastroenterologists on emerging data on the use of growth factors to manage treatment-related anemia in hepatitis C virus (HCV)-infected patients.

After participating in this activity, physicians should be able to:
- Review the prevalence of treatment-induced adverse hematologic events in HCV-infected patients and their impact on treatment outcomes
- Discuss the pharmacology, risks, and benefits of epoetin alfa to treat chemotherapy-associated anemia and extrapolate treatment principles to managing anemia associated with anti-HCV therapy
- Examine new data on the use of epoetin alfa in patients on anti-HCV therapy
- Develop treatment strategies based on new and emerging data on the use of growth factors in treating anemia in HCV-infected patients

CME Information
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This 4-part CME newsletter is planned and produced in accordance with the ACCME Essential Areas and Policies.

Projects In Knowledge designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Successful completion for 1 hour of CME credit requires a passing score of 70% or higher on the posttest. Full instructions for submission are included on the posttest accompanying this newsletter.

Disclosure
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.

Robert G. Gish, MD, has received grant/research support from, is a consultant for, is on the speakers bureau of Gilead Sciences Inc, GlaxoSmithKline, Ortho Biotech Products, L.P., Schering-Plough Corporation, and Triangle Pharmaceuticals.

The opinions expressed during this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge or the commercial supporter. This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

This CME activity is provided by Projects In Knowledge solely as an educational service. Specific patient care decisions are the prerogative of the physician caring for the patient. This independent CME activity is supported by an educational grant from Ortho Biotech.

Patient Description (continued from page 1)

Question 1
How should the patient’s fatigue be managed?
- a. The patient should go on disability insurance
- b. Caffeine equal to 4 cups of coffee daily
- c. Methylphenidate
- d. Modafinil
- e. Stop treatment
- f. Check hemoglobin level

Discussion
(c or d) Anecdotal evidence suggests that modafinil (100–400 mg/d) or methylphenidate (5–20 mg/d) may be of benefit in the treatment of fatigue in patients receiving treatment for HCV infection.

Modafinil is a wakefulness-promoting agent that was developed for Air Force pilots and approved by the US Food and Drug Administration (FDA) for treatment of narcolepsy. It promotes daytime wakefulness without interfering with nighttime sleep architecture or patients’ ability to fall asleep at night.1 In studies of narcolepsy, it improved patients’ ability to participate in daily activities.2,3 Modafinil is generally well tolerated, and adverse events in clinical trials were generally mild to moderate. The most common side effects of modafinil include headache, infection, nausea, nervousness, anxiety, and insomnia. Patients with a history of drug abuse should be followed closely while taking modafinil because of its potential for misuse or abuse.1

Anecdotal evidence suggests that modafinil (100–400 mg/d) or methylphenidate (5–20 mg/d) may be of benefit in the treatment of fatigue in patients receiving treatment for HCV infection.

The FDA-approved dose of modafinil is 200 mg/d given as a single dose in the morning; however, in patients with severe hepatic impairment, the dose should be reduced by half. It should not be used in patients with a history of left ventricular hypertrophy or ischemic electrocardiogram changes, chest pain, arrhythmia, or other clinically significant manifestations of mitral valve prolapse in association with central nervous system (CNS) stimulants, and it should be used with caution in patients with a recent history of myocardial infarction or unstable angina. Caution is equally warranted in patients with a history of psychosis. Modafinil may reduce the effectiveness of steroidal contraceptives, which is important to consider in fertile women receiving treatment for HCV infection, since ribavirin is teratogenic.

Methylphenidate is a mild CNS stimulant that has been used since the 1950s for the treatment of depression. It is FDA-approved for treatment of narcolepsy and attention deficit disorder, for which it is widely used today. The prescribing information indicates that the average dose used for these indications is 20 to 30 mg/d.4 At the Texas Liver Institute, where it is being investigated as an adjunct to interferon in side effect management, methylphenidate is initiated at a dose of 5 mg in the morning and 5 mg at noon, and is increased if needed to 10 mg in the morning and 10 mg at noon. The sustained-release 20-mg tablet can be used instead, once daily in the morning. Researchers there have reported that this regimen results in rapid onset of action, with significant improvement in fatigue and ability to concentrate.5

Methylphenidate is contraindicated in patients with marked anxiety, tension, or agitation, as well as those with glaucoma, motor tics, or family history/diagnosis of Tourette’s syndrome. It should not be used in patients who have taken monoamine oxidase inhibitors within the previous 2 weeks. It should be used with caution in patients with hypertension or a history of seizures. There is a potential for drug interactions with guanethidine, pressor agents, coumarin, anticonvulsants, tricyclic drugs, and clonidine. The most common side effects include nervousness and insomnia, which can usually be controlled by reducing the
dosage and omitting the drug in the afternoon/evening.4

Case Continues

Jason is treated with modafinil, 200 mg/d, since his hematocrit is now 33.5 mL/dL. This results in an immediate profound improvement in his daily activity level and energy without affecting his sleep at night. At week 6, the hematocrit is 30 mL/dL, the hemoglobin level is 10 g/dL, and the creatinine level has risen to 1.9 mg/dL. Due to the patient’s high creatinine level, the dose of ribavirin is decreased to 600 mg/d, which stabilizes the hematocrit at 31.1 mL/dL. Since the patient lives at sea level, has a sedentary lifestyle, is not experiencing shortness of breath, and has a substantial reticulocyte count, epoetin therapy is not initiated.

Jason’s WBC count decreases to 1500/mm3, with an absolute neutrophil count (ANC) of 556/µL. He also has a low-grade fever and his neutrophil count is <500/mm3.5 However, as noted elsewhere in this Tx Reporter series, failure to receive at least 80% of the recommended dose of peginterferon and at least 80% of the recommended dose of ribavirin for at least 80% of the recommended duration of treatment is associated with a significant reduction in the rate of sustained response.

Anecdotal evidence indicates that G-CSF can increase WBC and neutrophil counts while allowing patients to receive peginterferon at doses closer to or at those recommended. For correction of peginterferon-related neutropenia (ANC <1000/mm3), G-CSF is generally given at a dose of 700 µg SQ once to thrice weekly and then titrated to maintain an ANC >750/mm3. The dose usually can be reduced to 150 µg twice weekly, and patients can save the remaining half dose for the next administration. For maximum effect, G-CSF should be given at least 24 hours before peginterferon administration. If peginterferon dose reduction is necessary, the dose can be increased again once ANC is >1000/mm3 while on G-CSF.

Use of adjunctive therapies can relieve side effects, improve quality of life, and allow patients to maintain therapeutic doses of antiviral therapy for HCV infection. In this case study, several adjunctive therapies are used successfully, including modafinil for fatigue, G-CSF for neutropenia, and hydroxychloroquine for joint pain. Although these side effects are associated with use of peginterferon, the patient is able to complete a full course of peginterferon at the recommended dose and achieves sustained response. 

Final Outcome

Filgrastim (G-CSF) is initiated at a dose of 200 µg BIW SQ, and the peginterferon dose is maintained. After two filgrastim injections, Jason’s WBC count increases to 5000/mm3 and his ANC to 2400/µL. The filgrastim dose is then decreased to 100 µg BIW. After 3 weeks, the ANC is 1200/µL.

Anecdotal evidence indicates that G-CSF can increase WBC and neutrophil counts while allowing patients to receive peginterferon at doses closer to those recommended.

Use of adjunctive therapies can relieve side effects, improve quality of life, and allow patients to maintain therapeutic doses of antiviral therapy for HCV infection.

References

Epoetin alfa has been used effectively and safely for more than a decade in treating chemotherapy- and malignancy-induced anemia. In three large, open-label, nonrandomized, community-based studies of more than 7000 chemotherapy patients, epoetin increased hemoglobin level by a mean of 1.8 to 2.0 g/dL, reduced the need for transfusions, and improved quality of life. Epoetin is now showing benefits in patients who develop anemia secondary to use of antiviral therapies for treatment of chronic hepatitis C.

Peginterferon/ribavirin induces anemia through a suppressive effect of interferon on bone marrow erythropoiesis and a dose-dependent, extravascular, hemolytic anemia with reticulocytosis associated with ribavirin. Hemoglobin level decreases to <10 g/dL in 9% to 13% of patients treated with peginterferon/ribavirin or interferon/ribavirin. The incidence of anemia is 3.5 times higher in patients with HIV/HCV coinfection than in patients with HCV monoinfection. Ribavirin-induced anemia occurs most commonly in the first 4 to 6 weeks of treatment. Hemoglobin and reticulocyte counts return to baseline within 4 to 8 weeks after stopping antiviral therapy. With careful monitoring and treatment using the tips provided below, anemia can often be managed successfully with epoetin, without antiviral dose reduction.

- Evaluate for anemia before treating HCV infection. If anemia is present, pretreat with epoetin alfa to correct anemia before starting antiviral therapy and continue it to maintain hemoglobin levels during antiviral therapy.

- Consider and address all possible causes of anemia, including blood loss from gastropathy, vitamin and mineral deficiencies, abnormal iron metabolism, bone marrow suppression secondary to chronic disease, and reduced erythropoietin levels. Useful tests to identify causes of anemia include iron studies; thyroid function tests; ferritin, folate, and vitamin B₁₂ levels; guaiac test of stools; colonoscopy if guaiac is positive; and endoscopy to assess for bleeding esophageal varices if the patient has cirrhosis.

- Recommend high-dose vitamins C (1000 mg) and E (800 mg) to potentially reduce the hemolytic effect of ribavirin.

- Be aware that the labeling for interferon/ribavirin recommends dose reduction of ribavirin when hemoglobin levels are between 8.5 and 10 g/dL and discontinuation of ribavirin for hemoglobin <8.5 g/dL, with even stricter criteria for patients with pre-existing cardiac disease.

- Keep in mind that dose reduction or treatment discontinuation may interfere with the efficacy of treatment: It has been shown that patients who take at least 80% of their peginterferon dose and at least 80% of their ribavirin dose for at least 80% of the recommended duration of treatment have higher sustained response rates than those who receive less of their therapeutic regimen.

- Consider epoetin instead of dose reduction. Compared with dose reduction, epoetin results in greater increases in hemoglobin level and quality of life and allows ribavirin dosing closer to the recommended dose. The only contraindication to epoetin is hypertension.

- Initiate epoetin at 40,000 U SQ QW, and assess response at week 8. Discontinue if hemoglobin increases <1 g/dL at week 8 or whenever hemoglobin reaches >14 g/dL in women or >16 g/dL in men. Resume epoetin at 30,000 U SQ QW if hemoglobin becomes <13 g/dL in women or <15 g/dL in men, and then titrate dose by increments of 5000 to 10,000 U to a maximum of 40,000 U QW.

- Be aware that epoetin alfa enhances stamina and athletic performance but that intensive use can predispose to serious thromboembolic complications.

- Consider other adjunctive therapies (eg, G-CSF for neutropenia, modafinil or methylphenidate for fatigue) as needed to relieve side effects, improve quality of life, and allow patients to maintain a therapeutic dose of peginterferon.
New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series

CME Instructions
To receive documentation of your participation in this four-part CME activity for a total of 1 hour of CME credit, please complete the following steps:

1. Read each newsletter carefully.
2. Complete the CME Posttest included in each of the newsletters.
3. Mail or fax each of the completed CME Posttests to Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: 1-201-617-7333.*
4. After reading the fourth newsletter in this four-part series, complete the CME Evaluation Survey for the overall activity contained in the last issue.
5. Mail or fax your CME Posttest for the fourth newsletter and the CME Evaluation Survey for the overall activity to Projects In Knowledge, One Harmon Plaza, 6th Floor, Secaucus, NJ 07094; fax: 1-201-617-7333. All four posttests and the evaluation survey must be received by October 31, 2003, for you to be eligible to receive CME credit.

*At the end of the series, Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score for all four CME Posttests is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to take a single test covering information from all four of the newsletters.

Name ______________________________________ Degrees/Credentials __________________
Mailing Address _____________________________________________________________________________________________
City _____________________________________________________________________ State ________ ZIP ________________
Phone ________________________________________________ Fax _________________________________________________
E-mail _____________________________________________________________________________________________________

Please indicate your answers below.

1. Ancedotal evidence suggests that modafinil or methylphenidate may be of benefit in the treatment of fatigue in patients receiving treatment for HCV infection.
   ❑ True ❑ False

2. The dose of modafinil does not need to be reduced for patients with hepatic impairment.
   ❑ True ❑ False

3. Patients with a history of drug abuse should be followed closely while taking modafinil because of its potential for misuse or abuse.
   ❑ True ❑ False

4. Methylphenidate is contraindicated in patients with marked anxiety, tension, or agitation.
   ❑ True ❑ False

5. According to the prescribing information, both peginterferon alfa-2b and ribavirin should be permanently discontinued if WBC is <100/mm³ or neutrophil count is <500/mm³.
   ❑ True ❑ False

6. For maximum effect in treating peginterferon-induced neutropenia, G-CSF should be given at the time of peginterferon administration.
   ❑ True ❑ False

7. G-CSF is generally given at a dose of 200 µg SQ once to thrice weekly and then titrated to maintain an ANC >750/mm³.
   ❑ True ❑ False
New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series

Instructions

Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.

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

- Review the prevalence of treatment-induced adverse hematologic events in HCV-infected patients and their impact on treatment outcomes
- Discuss the pharmacology, risks, and benefits of epoetin alfa to treat chemotherapy-associated anemia and extrapolate treatment principles to managing anemia associated with anti-HCV therapy
- Examine new data on the use of epoetin alfa in patients on anti-HCV therapy
- Develop treatment strategies based on new and emerging data on the use of growth factors in treating anemia in HCV-infected patients

2. Please rate the educational value of this material:

3. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why?

4. Please rate the level of the material presented:

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:

<table>
<thead>
<tr>
<th>Very Interested</th>
<th>Moderately Interested</th>
<th>Not Interested</th>
</tr>
</thead>
</table>
   a. Audioconference | ❑ ❑ ❑ | ❑ | ❑ |
   b. Videoconference | ❑ ❑ ❑ | ❑ | ❑ |
   c. Enduring materials (audiocassettes, videotapes, monographs) | ❑ ❑ ❑ | ❑ | ❑ |
   d. Internet (on-line discussions with experts, educational activities) | ❑ ❑ ❑ | ❑ | ❑ |
   e. Multimedia (on-line, CD-ROM) | ❑ ❑ ❑ | ❑ | ❑ |

7. Please tell us how long it took you to complete this course: ........................................................................................................................................................................................................................................................................................................................................................................................................................................

8. Please list 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 in participating in a follow-up survey.

   Additional comments about this activity:
   ........................................................................................................................................................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................................................................................................................................................
   ........................................................................................................................................................................................................................................................................................................................................................................................................................................

Thank you for your participation.