New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series

Dear Colleague:

Dealing with treatment-related anemia and maintaining patients infected with hepatitis C virus (HCV) on a full dose of ribavirin poses a dilemma for physicians. Patients are often dissatisfied because of anemia-related fatigue. They often complain about lack of energy, tiredness, and not being able to do or enjoy their daily activities. Reduced ribavirin doses are recommended when hemoglobin levels are ≤10 g/dL and it is recommended that ribavirin be discontinued when hemoglobin levels are ≤8.5 g/dL. Yet, adherence to a full dose of antiviral medication for the full treatment schedule is more likely to produce a sustained virologic response (SVR).

In this CME newsletter series, New Data on Managing Anemia with Growth Factors for Patients on Anti-HCV Therapy: A Case-Based Series, we provide strategies for managing ribavirin-induced anemia while maintaining adherence to antiviral treatment for HCV infection. Epoetin alfa is the key to solving the problem and it improves patient quality of life as well. The case presented in this newsletter is a surgeon who has an HCV infection, which has largely been asymptomatic and has caused him to lose his operating room privileges. Standard treatment with peginterferon/ribavirin produces anemia and impairs the surgeon’s enjoyment of his hobby — marathon running. This patient needs to have a treatment with a high probability of an SVR to have his operating room privileges restored and to resume his career. The case discussion provides practical strategies for managing treatment-related anemia with epoetin alfa without diminishing the likelihood that the patient will have an SVR. A surprising clinical twist to the case is also managed successfully.

This CME activity, a four-part series of newsletters, is designed to give you critical new information and treatment strategies for the management of HCV patients during antiviral therapy that can be incorporated into your clinical practice. Practical strategies for managing anemia while treating patients with full anti-HCV therapy are discussed. When all four parts of the activity are completed, physicians can receive 1 hour of CME credit.

We hope that you will find this series of newsletters interesting, thought provoking, and educational.

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Patient Description

Harrison, a 52-year-old male cardiovascular surgeon and highly competitive marathon runner, presents for treatment of his HCV infection after being denied operating room privileges. At least six of his patients have been diagnosed with HCV and the Centers for Disease Control have traced the source of the infection to him. Sequence analysis of the virus showed that Harrison and his patients share the same virus. Harrison appears healthy. Prior liver enzyme tests were normal except for an elevated ALT on two to three occasions. His ALT was normal when the tests were repeated. He has one drink of an alcoholic beverage every evening. Laboratory tests ordered to evaluate the status of the patient confirm the diagnosis of HCV. He has an ALT of 56 IU/L and an AST of 45 IU/L. His viral load is 4.5 million IU/mL and his HCV genotype is 1a. Ultrasound testing finds a fatty liver and a liver biopsy reveals stage 3/4 fibrosis. Harrison is started on peginterferon/ribavirin and scheduled for follow-up visits. He is advised that if he continues to enjoy his evening drink, he may reduce the effectiveness of his antiviral treatment because alcohol is an important cofactor in the progression of HCV infection to cirrhosis and hepatocellular carcinoma. Safe levels of alcohol consumption have not been determined.

Harrison returns for his 2-week visit and denies any symptoms or side effects except for a “little fever.” His white blood cell count and hemoglobin level for this visit and subsequent visits are shown in Table 1. Results for liver enzymes and viral load measured at subsequent visits are also listed in Table 1. At his 3-month follow-up visit, he complains that he can only run 2 miles per day. The lab results show that Harrison has become anemic and a course of action is discussed. He has seen recent reviews on the treatment of HCV infection and the results of the Hadziyannis, et al study described in an abstract on the Internet for the 2002 European Association for the
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 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.

Projects In Knowledge designates this educational activity (a four-part series of case-based newsletters) for up to 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours that he/she actually spent in the educational activity.

This independent CME activity is planned and produced in accordance with the ACCME Essential Areas and Policies.

Disclosure Information

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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.

Robert G. Gish, M.D., has received significant grant/research support from, is a consultant for, and is on the speakers bureau of Bayer Corporation, Gilead Sciences, Inc, GlaxoSmithKline, Roche Pharmaceuticals, Schering Corporation, and Triangle Pharmaceuticals.

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Patient Description

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<table>
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<th>Visit</th>
<th>WBC (per µL)</th>
<th>Hemoglobin (g/dL)</th>
<th>Viral Load (IU/mL)</th>
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<td>8.3</td>
<td>&lt;600</td>
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Study of the Liver meeting. He realizes that ribavirin is the likely cause of his anemia. Reducing his dose of ribavirin may help his anemia, but he is less likely to have a sustained virologic response (SVR). Because he would like to increase his chances of an SVR, he suggests that he could arrange for a transfusion for himself and does not want to reduce his dose of ribavirin.

Question 1

Treatment-related hematologic abnormalities occur in many HCV patients given interferon alfa or peginterferon in combination with ribavirin. The most common of these may be:

- a. Anemia with hemoglobin ≥10 g/dL. White blood cell and platelet counts are decreased but are still within the normal range
- b. Anemia with hemoglobin ≥10 g/dL, decreases in white blood cell count (still within normal range), no change in platelet count
- c. Anemia with hemoglobin ≥10 g/dL, neutropenia, and no change in platelet counts
- d. Anemia with hemoglobin ≥10 g/dL, leukopenia, and thrombocytopenia
- e. Severe anemia with hemoglobin <8 g/dL, leukopenia, and thrombocytopenia
- f. Leukopenia and thrombocytopenia
- g. Severe anemia with hemoglobin <8 g/dL

Discussion

(b and c) A retrospective analysis of pooled data from two clinical studies in treatment-naive and treatment-experienced HCV patients, revealed that hemoglobin levels declined ≥3 g/dL in slightly more than one-half of the patients and more than 1/3 of the patients had a >25% decrease in hemoglobin levels from baseline. Hemoglobin levels were decreased to <10 g/dL in 10.3% of all patients treated with interferon alfa/ribavirin.6 Women were five times more likely than men to have hemoglobin levels <10 g/dL. White blood cell counts decreased, but remained within the normal range in two randomized clinical trials with chronic HCV patients treated with interferon alfa/ribavirin.1,3 In a large randomized clinical study comparing interferon alfa or peginterferon in combination with ribavirin for the treatment of chronic HCV, both treatment regimens caused neutropenia resulting in dose reductions.8 Platelet counts were unchanged whether patients were treated with interferon alfa or peginterferon in combination with ribavirin.9,10 Thrombocytopenia is common only in patients with advanced fibrosis.

Question 2

How would you manage treatment-related hematological abnormalities in an HCV-infected patient you are treating with peginterferon/ribavirin who has a hemoglobin of 9.5 g/dL; white blood cell count, 450/µl; neutrophils, 1500/µl; and platelets, 176,000/µl after 4 weeks of treatment?

- a. Stop treatment with peginterferon and ribavirin
- b. Stop ribavirin treatment and continue with the same dose of peginterferon
- c. Order transfusions
- d. Reduce the dose of ribavirin and continue with the same dose of peginterferon
- e. Continue with the same doses of peginterferon and ribavirin and prescribe epoetin alfa
- f. Test for iron if appropriate

Discussion

(e) The labeling for interferon alfa/ribavirin recommends decreasing the dose of ribavirin when hemoglobin levels are between 8.5 and 10 g/dL and stopping ribavirin altogether when hemoglobin levels are <8.5 g/dL.1 Less ribavirin means that the patient is less likely to have an SVR. In a randomized, double-blind study, the combination of interferon alfa and ribavirin produced an SVR in 38% of patients after 48 weeks of treatment versus
an SVR in 13% of patients treated with interferon alfa monotherapy. Patients who adhered to the 80+80+80 rule (more than 80% of their dose of interferon alfa and more than 80% of their dose of ribavirin for more than 80% the time) had higher SVR rates compared with patients who did not, according to the findings of a retrospective analysis of patients in randomized, controlled clinical trials. The best course of action is to treat anemia with epoetin alfa and maintain the patient on the same doses of peginterferon/ribavirin.

Epoetin alfa has been used for 10 years to improve hemoglobin levels and to reduce transfusion requirements in cancer patients on chemotherapy and in HIV patients treated with zidovudine with minimal side effects. Quality of life is improved in these patients as their hemoglobin levels increase and the patients have less fatigue and more energy. The only contraindication to epoetin alfa treatment is hypertension, which can be exacerbated due to increases in vascular resistance and blood viscosity as anemia is corrected. Most patients with HCV infection have high ferritin levels and don’t need iron supplements; however, stores need to be checked.

Case Continues

Epoetin alfa is suggested to Harrison as an alternative to transfusion. He comments that he remembers hearing about cyclists in the Tour de France using epoetin alfa to improve performance. He is told about new clinical data on the treatment of anemia in HCV patients with epoetin alfa that will be presented at the coming 2002 AASLD meeting. The abstract can be viewed on the AASLD Web page. Ninety-six percent of patients treated with epoetin alfa at a dose of 40,000 to 60,000 IU given subcutaneously once per week were able to maintain their dose of ribavirin compared to 63% in the placebo group (Figure 1). Mean hemoglobin levels increased 2.1 g/dL from 11.1 g/dL to 13.2 g/dL in patients treated with epoetin alfa after 8 weeks of treatment whereas hemoglobin levels in the placebo group were essentially unchanged (mean baseline hemoglobin, 10.8 g/dL) (Figure 1). Energy, activity level, and overall quality of life were significantly improved by epoetin alfa (Table 2 and Figure 2). The incidence of adverse events was similar in both groups and attributed to antiviral therapy for HCV.

Harrison is convinced that treatment with epoetin alfa is better than transfusion and he is started on a dose of 40,000 IU of epoetin alfa, weekly. His dose of ribavirin is not reduced. He returns for follow-up visits at 2-week intervals. His hemoglobin levels and comments about his running distance at each of these visits are listed in Table 3.

Four weeks after starting epoetin alfa, Harrison complains that he can only run 2.5 miles per day. He is concerned because he has a race coming up and he is not performing well. Harrison refuses to decrease his dose of ribavirin because he wants his anti-HCV treatment to produce an SVR and he threatens to double his dose of epoetin alfa. His dose of epoetin alfa is then increased to 60,000 IU per week. At his week 6 and 8 visits, Harrison expresses delight that his daily running distance has increased and the patients have less fatigue and more energy. The only contraindication to epoetin alfa treatment is hypertension, which can be exacerbated due to increases in vascular resistance and blood viscosity as anemia is corrected. Most patients with HCV infection have high ferritin levels and don’t need iron supplements; however, stores need to be checked.

Discussion

(e) When epoetin alfa is taken to enhance performance, red blood cell mass is increased without a change in total blood volume and systolic blood pressure is increased during submaximal exercise. The athlete is predisposed to thromboembolic complications because of increased blood viscosity from dehydration during exercise and the ability of erythropoietin to enhance endothelial activation and platelet reactivity. The findings of animal studies suggest that intensive use of epoetin alfa can result in a secondary
anemia when epoetin alfa is discontinued. The bone marrow appears exhausted at the level of erythroid progenitors.22

Case Continues

When Harrison returns 1 month later, he is very pleased with his progress, especially with his running distance and stamina. His hemoglobin level has risen to 16.8 g/dL. When confronted with the laboratory results, Harrison confesses that he did not reduce his dose of epoetin alfa as ordered because he is enjoying his new athletic prowess. He is told that while epoetin alfa can enhance athletic performance, there are significant risks, including thromboembolic complications. Use of epoetin alfa to enhance performance is thought to have contributed to the deaths of professional European cyclists about 10 years ago.23 It is thought that the cyclists may have had hematocrits >60%. Harrison is finally convinced that he needs to reduce his dose of epoetin alfa.

Twelve months after starting treatment for his HCV infection, Harrison is negative for HCV RNA and his hemoglobin level is 12 g/dL. Peginterferon and ribavirin are discontinued. Harrison remains negative for HCV RNA at his 1-month, 3-month, and 6-month follow-up visits. He is delighted to finally have his operating room privileges restored.

Conclusion

Quality of life during treatment for their infection is very important to HCV patients as demonstrated by the case in this newsletter. Successful treatment of HCV infection with interferon/ribavirin can take as long as 24 or 48 weeks depending on viral genotype and other indicators of disease progression.7,8 Ribavirin can produce significant anemia that adversely affects quality of life, impairing the patient’s ability to perform usual activities. Ribavirin-related anemia has been treated by counterproductive dose reductions or discontinuations. Epoetin alfa can increase hemoglobin levels, prevent ribavirin dose reductions, correct anemia, and improve patient quality of life during antiviral therapy.

References

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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 1, 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. Alcohol has no effect on the effectiveness of antiviral treatment for HCV.
   □ True    □ False

2. Hemoglobin levels decline >3 g/dL in more than one-half of patients treated with interferon alfa/ribavirin.
   □ True    □ False

3. Women are five times more likely than men to have hemoglobin levels <10 g/dL when they are treated with interferon alfa/ribavirin for HCV infection.
   □ True    □ False

4. Patients treated with a reduced dose of ribavirin because of treatment-related anemia have the same rates of SVR as patients who are able to remain on a full dose of ribavirin.
   □ True    □ False

5. Transfusions are more effective than epoetin alfa for treating anemia due to ribavirin.
   □ True    □ False

6. Epoetin alfa improves quality of life in HCV patients with treatment-related anemia.
   □ True    □ False

7. Abuse of epoetin alfa to enhance athletic performance can be life threatening.
   □ True    □ False