Dear Colleague:

Anemia is a common side effect of standard hepatitis C treatment with peginterferon and ribavirin and often necessitates dose reductions that can adversely affect treatment efficacy. Historically, anemia has been managed by dose reduction, which has the potential to reduce sustained virologic response rates, particularly during the first 12 weeks of therapy. Thus, managing anemia is a challenge.

Erythropoietin (EPO) has increasingly been used off-label for the management of anemia in hepatitis C patients, since it significantly improves hemoglobin levels and allows for maintenance of ribavirin dose, which may improve response rates. However, this adjunctive therapy is associated with its own potential side effects and significant additional costs to the patient’s treatment regimen.

This Tx Reporter was developed by a faculty of distinguished researchers in hepatitis C. Here you will learn about the clinical importance of anemia and ways to address its sometimes challenging management. This newsletter will also address the unique needs of special populations, such as those with co-morbid conditions and advanced disease. The advantages and disadvantages of using EPO in hepatitis C patients with anemia are described. We also provide information related to the development of an analog of ribavirin that has shown a low prevalence of anemia.

We hope you find this publication insightful and helpful to your patient care.

Sincerely,

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Anemia in HCV Patients

Pegylated interferon/ribavirin (PEG IFN/RBV) is currently the standard of care for treating hepatitis C. Hemolytic anemia is the primary dose-limiting toxicity of RBV.1 To a lesser extent, PEG IFN contributes to anemia by suppressing bone marrow function, limiting production of erythroid progenitor cells and red blood cells.1 Anemia begins to develop immediately after therapy begins and becomes most pronounced after the initial 4 to 6 weeks.1 Hemoglobin (Hgb) level generally decreases by 2.5 g/dL to 3.0 g/dL, although more severe cases of hemolysis can occur.1 In registration trials, 12% to 13% of patients treated with PEG IFN/RBV developed anemia.2,3 Anemia contributes to treatment-related fatigue, shortness of breath, and other symptoms that may significantly impair quality of life (QOL). In the PEG IFN/RBV registration trials, the overall incidence of fatigue was 54% to 64%.2,3 A recent survey was sent to approximately 3000 community gastroenterologists, about 7% (n = 196) of whom responded to the mailing. Approximately 90% of physicians reported that fatigue was the aspect of anemia that had the greatest impact on their patients’ QOL (Projects In Knowledge, data on file, 2005.)

Key Issues in the Management of Anemia

Anemia is a major reason for dose reductions of RBV. The product information for PEG IFN/RBV recommends RBV dose reduction by 200 mg/d (for PEG IFN alfa-2b/RBV) or to 600 mg/d (for PEG IFN alfa-2a/RBV) if Hgb decreases to <10 g/dL in a patient without cardiac risk factors, and discontinuation of RBV if Hgb becomes <8.5 g/dL.4,5 In registration trials, RBV dose reduction due to anemia was observed in 9% of patients treated with PEG IFN alfa-2b/RBV6 and 22% of those treated with PEG IFN alfa-2a/RBV7. A snapshot of the prevalence of dose reductions encountered in the community setting was recently captured in the previously mentioned survey (Fig. 1). (Projects In Knowledge, data on file, 2005.) Clinical trial analyses have also shown that lower doses of IFN, PEG IFN, or RBV significantly diminish sustained virologic response (SVR) rates, particularly in difficult-to-treat genotype-1 patients.4,6,7 In addition, a retrospective analysis of two randomized trials of genotype-1 patients with chronic hepatitis C virus (HCV) found that the highest SVR rates were achieved in patients who were maintained on ≥80% of their total PEG IFN alfa-2b and ≥80% of their total RBV doses for ≥80% of the proposed duration of therapy.3,8 The study noted that adherence would enhance the likelihood of achieving an initial virologic response, and that adherence beyond 12 to 24 weeks would be advantageous only for those patients who achieved an early virologic response (EVR).9 The impact of dose reduction in genotype-1 patients is also supported by pooled data from two trials, presented at the 2005 annual meeting of the European Association for the Study of the Liver (EASL). Of the 427 patients who completed these trials with PEG IFN/RBV, 43% (182 patients) had their RBV reduced to <97% and 27% (114 patients) had their PEG IFN reduced to <97%. Twelve patients (3%) discontinued RBV before week 42 but remained on PEG IFN. Discontinuations of both drugs were made due to lack of response (n = 53), side effects or laboratory abnormalities (n = 65), and other reasons (n = 24). RBV dose was the most influential factor for treatment response, and the results suggested that discontinuing RBV early in treatment had the greatest impact on SVR.10 Furthermore, Shiffman et al4,11 found that reducing the dose of both PEG IFN and RBV from >80% to ≤60% reduced the response rate in genotype 1 treatment-refractory patients from 17% to 6%. When RBV was stopped altogether, the SVR rate

Figure 1. Survey of Community Gastroenterologists (n = 196).

What percentage of your patients requires dose reduction while on PEG IFN/RBV therapy?

<table>
<thead>
<tr>
<th>% of Patients Dose Reduced</th>
<th>Respondents (%)</th>
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<tbody>
<tr>
<td>10%</td>
<td>60%</td>
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<tr>
<td>20%</td>
<td>28%</td>
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<tr>
<td>30%</td>
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Treatment Reporter: Gastroenterology

Known that lower RBV doses lead to lower SVR rates, many physicians are reluctant to reduce RBV. Although EPO is not approved in the United States for HCV-induced anemia, there is a growing perspective that it has a role in maintaining RBV dose, especially when the patient is symptomatic.

A recent trial by Afdhal et al1 in 185 patients who developed anemia (Hgb ≤ 12 g/dL) during combination therapy supports the benefit of EPO in maintaining RBV dose.14 Patients were randomized to receive weekly injections of EPO (40,000 U/SC) versus placebo. At the end of the 8-week double-blind phase of the trial, 88% of the patients receiving supportive therapy versus 60% of patients in the control group maintained their RBV doses (P < .001). Mean QOL scores improved significantly, and the mean Hgb increased by approximately 2.2 g/dL ± 1.3 g/dL in the EPO patients compared with an increase of only 0.1 ± 1.0 g/dL in the placebo group. This study was not designed to compare SVR rates. There is some evidence that use of EPO may improve response rates in genotype 1 patients. In a retrospective review of 215 patients at the UMass Memorial Medical Center, it was determined that for patients with genotypes other than 2/3, SVR rates were higher if they had used EPO (70.8%) for anemia than if they had developed anemia but not used EPO (42.6%) (P = .01). This effect was not apparent in patients with genotypes 2/3.15

Figure 2 depicts HCV RNA and Hgb data in a patient who developed severe anemia within 1 month of combination therapy. The patient initially underwent dose reduction of RBV from 1000 mg/d to 600 mg/d. An EVR was achieved, but the patient later relapsed. Subsequently, the patient was re-treated with combination therapy plus EPO when the Hgb declined to 12 g/dL (25 months). Hgb stabilized within 3 months of reinstating RBV at 1000 mg/dL, and the patient went on to achieve an SVR.1

Darbopepin alfa, a long-acting form of EPO, has also been approved by the FDA for treatment of anemia associated with chronic renal failure and cancer chemotherapy. In an open-label study of 50 hepatitis C patients treated with PEG IFN/RBV, darbopepin (3 μg/kg every 2 weeks, titrated to a target Hgb of 10.5–12 g/dL) was initiated if Hgb dropped ≤10 g/dL. Eighteen patients received darbopepin, which successfully increased Hgb and maintained it in the target range. Ninety-two percent of patients maintained an RBV dose >10.6 mg/kg/d. After 8 weeks, darbopepin was associated with clinically relevant improvements in health-related QOL.16

Transfusions are used rarely for treating anemia associated with combination therapy, but Dr. Manns considers transfusion when the Hgb <8.5 g/dL and it is believed that dose reductions and/or EPO will not cause a rapid enough rise in hemoglobin levels to avoid severe toxicity. According to Dr. Manns, patients at greater risk for needing a transfusion include those with renal insufficiency or failure, hemoglobinopathies, individuals not monitored frequently enough to detect and manage anemia early, and those with a preexisting anemia.

Anemia in Diverse Patient Populations

There are special populations of patients who are either at increased risk for anemia or for whom dose reductions are especially undesirable. These patients may need particularly careful monitoring and aggressive management of anemia in order to obtain the best treatment outcomes. Such populations potentially include the elderly. African Americans, those with advanced disease, liver transplant recipients, and those with co-morbidities, such as HIV infection, cardiovascular disease, renal insufficiency, and hemoglobinopathies (eg, thalassemia) and chronic anemias. Elderly patients may be less tolerant of hemolytic anemia, especially if cardiovascular disease is present. Anemia is associated with significant cardiovascular morbidity and mortality and can exacerbate preexisting cardiovascular disease. Thus, elderly patients may require closer monitoring and more aggressive management of anemia.

African Americans have the highest observed rate of HCV infection among all ethnic groups in the United States (3.2%), nearly twice that reported for non-Hispanic Caucasians.18 To date, rates of anemia and dose reductions for anemia are comparable to those in Caucasian patients.19,20 However, African Americans are more likely to be infected with genotype 1, and therefore adherence becomes particularly important in this population.

A 2003 study reported that obese patients (body mass index > 30 kg/m²) with HCV have an approximately 80% lower chance of responding to IFN monotherapy or IFN/RBV combination therapy.21 Weight-based dosing of PEG IFN and RBV may improve SVR in obese patients.22,23 However, weight-based dosing of RBV is associated with higher rates of anemia overall than flat RBV dosing.24 In the latest update from the WIN-R study, anemia (Hgb < 11 g/dL) occurred in 32% of patients who received flat dosing versus 46% of those given weight-based doses; however, within the weight-based dosing group, rates of anemia were consistent across four subgroups categorized by weight.25 Thus, it is important to treat obese patients with adequate doses, to monitor carefully for anemia, and to manage side effects including anemia to avoid dose reductions.

SVR rates are lower in patients with advanced fibrosis than in those with histologically mild disease, and patients with advanced fibrosis are at the greatest risk of complications with further disease progression. Thus, it is particularly important to maintain the highest tolerable RBV dose to improve the outcome. According to Dr. Brown, there may be an increased rate of anemia in this population, a blunted response to EPO, and a greater likelihood of portal hypertension and splenic sequestration.

The rate of reinfection of the allograft is high among liver transplant recipients with HCV infection. Management strategies include treating with antiviral therapy either preemptively before the development of new histologic injury or after injury occurs. Tolerability of antiviral therapy is poor in this population. Significant anemia is common and may result from both drug-induced bone marrow suppression and the potentiation of RBV-induced hemolysis by renal insufficiency.26 Patients infected with HIV are also at increased risk for anemia, particularly since some antiretroviral agents (eg, zidovudine) are also associated with anemia. The 1-year incidence of anemia (Hgb < 10 g/dL) ranges from 3.2% to 36.9% in patients infected with HIV, with the highest incidence among those with ≥1 AIDS-defining opportunistic illnesses.26 EPO is currently approved for the treatment of anemia related to zidovudine therapy in HIV-infected patients. HIV/HCV-infected patients are also at increased risk for disease progression without successful treatment, since HIV accelerates HCV-related liver damage.

Compromised renal function or cardiovascular disease can affect drug metabolism and can alter the toxicity profile for combination therapy. RBV should not be used in patients with creatinine clearance <50 mL/min due to problems of drug accumulation caused by reduced clearance.27,28 A small study by Bruchfeld et al29 of seven patients

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Figure 2. EPO Corrects HCV Treatment-Related Anemia.8

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with HCV-associated renal disease and renal insufficiency suggested that combination therapy could be used with reasonable safety in HCV-related vasculitis and glomerular nephritis. A full blood count (including Hgb) was performed monthly, renal function was assessed by creatinine clearance, and RBV trough levels were measured an average of three times during the first 2 to 3 months of therapy and occasionally thereafter or whenever indicated by infection or unexpected reduction in Hgb. Virologic response occurred in six of seven patients, with four maintaining both virologic and renal remission and one maintaining virologic and partial renal remission. Anemia was the major side effect, and five of the seven patients required use of EPO and iron.

Thalassemia is a contraindication to treatment with PEG IFN/RBV, and patients undergoing regular transfusions may be at greater risk for anemia if they are treated with anti-HCV therapies. In addition, multiple transfusions lead to iron overload. Nonetheless, investigators of one pilot study investigating combination therapy for these patients, in this study of 11 transfusion-dependent patients, five (46%) achieved SVR with IFN alfa-2b/RBV, despite having failed prior IFN monotherapy. The authors suggested that RBV-related anemia was likely responsible for an increased need for transfusions during therapy. Responders also showed significant decreases in serum ferritin levels. Although EPO was not evaluated in this study, it should be noted that normal iron stores are necessary for EPO to be effective.

How Does Effective Therapy for Anemia Impact Healthcare Costs in HCV?

It was estimated in 1998 that direct healthcare costs associated with hepatitis C had exceeded $1 billion. Future predictions estimate a four-fold increase between 1990 and 2015 in persons at risk of chronic liver disease. However, a recent cost-effectiveness analysis demonstrated that combination therapy increases life expectancy by 1.5 to 1.7 discounted years and by 2.2 to 2.5 discounted quality-adjusted life years, and reduces the lifetime risk of developing decompensated cirrhosis or hepatocellular carcinoma. Moreover, although no comparative study has been done, available data suggest PEG IFN/RBV is at least as cost-effective as colon cancer screening, and more effective than highly active antiretroviral treatment for HIV, intensive glycemic control in non–insulin-dependent diabetes mellitus, hemodialysis for kidney failure, or fundoplication for reflux disease (Fig. 3).

Based on these data, Dr. Wong notes that despite the cost of antiviral therapy, it still appears to be more cost-effective than other well-accepted screening tests or accepted treatments. Although not all hepatitis C patients develop disease progression, when it does occur, it shortens life expectancy and reduces QOL in addition to incurring high healthcare costs, such as those associated with management of decompensated disease or liver transplantation. Thus, the cost of antiviral therapy is offset by future savings through the prevention of liver complications and the extension of life and reduction in future morbidity.

Side effects, such as anemia, not only have the potential to reduce response rates by necessitating dose reductions/treatment discontinuations, but they add costs to the overall management. These costs come in the form of additional office visits and staff time in returning phone calls, as well as the costs of transfusions and adjuvant therapies, such as EPO. Devine et al estimated an average cost of $170 per patient (range, $68–$632) for anemia management and treatment. RBV analogs that reduce the incidence of anemia and other side effects can potentially reduce healthcare costs by reducing the need for EPO.

Looking Ahead in Anemia Management

In the future, the availability of newer antiviral therapies may reduce the impact of anemia on anti-HCV treatment outcomes. Viramidine is a new RBV analog that may eventually be used in place of RBV in combination therapy. It preferentially targets the liver, causing less accumulation of drug in red blood cells and hemolysis; consequently, it may lessen the incidence of anemia.

Preliminary results from an ongoing phase 2 trial of viramidine (400, 600, or 800 mg BID) versus RBV (1000/1200 mg/d) in 180 treatment-naive patients found that efficacy of viramidine was comparable to that of RBV. End-of-treatment response rates were 55%, 63%, and 55% with the three doses of viramidine, respectively, versus 62% with RBV. Similarly, SVR rates were 23%, 37%, and 29% with viramidine, respectively, none of which was significantly different from the 44% SVR with RBV (Gish R, personal communication). However, treatment with PEG IFN plus viramidine resulted in significantly fewer patients with anemia than standard combination therapy (Fig. 4). Two larger international phase 3 studies are now ongoing using the 600-mg dose of viramidine compared with RBV in combination with PEG IFN alfa-2b. Results, expected in early 2006, will clarify the potential benefits of viramidine in anemia management.

Conclusion

Anemia is a common side effect of PEG IFN/RBV therapy that can cause symptoms that negatively impact QOL. In addition, anemia is the most common reason for RBV dose reductions, which can reduce the efficacy of treatment. To avoid dose reductions, some physicians use EPO to raise Hgb levels and maintain full RBV dose. Evidence from clinical trials suggests that this is an effective strategy in HCV-infected patients with anemia, and may improve QOL and possibly SVR rates. However, EPO adds an additional cost to the patient’s treatment regimen, which increases costs, inconvenience, and, potentially, side effects. Moreover, EPO is not FDA approved for use in hepatitis C. A new RBV analog, viramidine, may eventually be substituted for RBV in combination with PEG IFN and is expected to be associated with a lower incidence of anemia and similar SVR rates.

**Figure 3. Cost-Effectiveness of Combination Therapy for HCV Compared with Other Disease States**

Not a comparative study; each bar represents data from a separate cost-effectiveness assessment. Gradations indicate range.

- PegIFN
- Colorectal CA Screen
- HAART
- NIDDM
- Hemodialysis
- Fundoplication

**Figure 4. Incidence of Anemia at End of Treatment in Ongoing Phase II Study of Viramidine Versus Ribavirin (RBV)**

- **0%**
- **2%**
- **11%**
- **27%**

**Viral Load (%)**

**400 mg**

**600 mg**

**800 mg**

**RBV**

**Anemia (%)**

**Conclusion**

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