Managing the hematologic side effects of antiviral therapy for chronic hepatitis C:

Anemia, neutropenia, and thrombocytopenia

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ABSTRACT

Hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia are common during combination therapy with pegylated (or standard) interferon and ribavirin for chronic hepatitis C. Ribavirin-induced hemolytic anemia is a common cause of dose reduction or discontinuation. Bone marrow suppression also contributes to the anemia and is the predominant mechanism for interferon-induced neutropenia and thrombocytopenia. Although dose reduction or discontinuation of combination therapy can reverse these abnormalities, they may reduce virologic response. Hematopoietic growth factors may provide a useful alternative for managing these hematologic side effects without reducing the optimal dose of the combination antiviral regimen. Treatment of anemia also may improve patients' health-related quality of life and their adherence to combination antiviral therapy. The impact of growth factors on sustained virologic response and their cost-effectiveness in patients with chronic hepatitis C need further assessment.

The most effective therapeutic regimen for infection with hepatitis C virus (HCV) today is the combination of pegylated interferon alfa and ribavirin (combination therapy), which yields sustained virologic response (SVR) in up to 56% of patients.[1,2] However, one of the main drawbacks of this combination therapy (and also of regimens combining nonpegylated interferon with ribavirin) is the development of side effects, which can result in suboptimal dosing or discontinuation of therapy. That can limit the likelihood of SVR, since one of the determinants of SVR is adequate dose and duration of therapy, as previously discussed in this supplement. Among the side effects of combination therapy, hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia have been reported to result in dose reduction and discontinuation of therapy in up to 25% and 3% of patients, respectively.[3]

Management of hematologic abnormalities during antiviral therapy for HCV infection can be an important strategy for maximizing treatment outcomes. While information on the use of hematopoietic growth factors during therapy for HCV infection remains preliminary, these agents are important since they can be helpful as adjuncts to antiviral therapy. This review explores the incidence, clinical significance, and management of anemia, neutropenia, and thrombocytopenia associated with combination therapy for HCV infection.

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ANEMIA

A leading cause of dose reduction and discontinuation

Among the hematologic abnormalities associated with combination therapy, anemia is probably the most significant, as it can reduce patients' health-related quality of life and may be the main determinant of fatigue.[4] A pooled analysis of data from three large trials comparing pegylated interferon (peginterferon) with nonpegylated interferon determined that worsening of fatigue scores was a significant predictor of treatment discontinuation.[5] Interruption and premature discontinuation of antiviral therapy decreases the efficacy of antiviral therapy. In large multicenter clinical trials of

combination therapy for HCV infection, dose reduction for anemia occurred in up to 23% of patients.[1,2] Discontinuation was uncommon in these trials, but the rate of discontinuation is higher outside of clinical trials. In one study that evaluated "real world" patients, anemia was the leading cause of premature discontinuation of combination therapy, accounting for 36% of all discontinuations (ie, in 8.8% of all patients).[6]

Significant anemia (ie, hemoglobin < 10 g/dL) has been observed in up to 9% to 13% of patients receiving combination therapy with interferon and ribavirin.[1] Moderate anemia (hemoglobin < 11 g/dL) may be seen in 30%.[7] The mean maximal decrease in hemoglobin can be as high as 3.1 g/dL and 3.7 g/dL with nonpegylated and pegylated interferon, respectively, in combination with ribavirin.[2,8] The hemoglobin generally reaches its lowest level within the first 4 to 8 weeks of therapy, plateauing thereafter and returning to baseline values after treatment discontinuation.

Both ribavirin and the interferons contribute

There are several mechanisms by which anemia occurs during combination therapy for HCV infection. Ribavirin causes a dose-dependent and reversible hemolytic anemia. After entering red blood cells, ribavirin is phosphorylated into its active form, leading to depletion of adenosine triphosphate.[9] This leads to impaired antioxidant mechanisms, resulting in membrane oxidative damage and subsequent extravascular red blood cell removal by the reticuloendothelial system.[9]

Interferons also contribute to anemia, mainly through bone marrow suppression.[10] De Franceschi and colleagues[9] found that interferon impairs compensatory reticulocytosis related to ribavirin-induced hemolytic anemia, suggesting that the bone marrow–suppressive effect of interferon contributes to the anemia associated with combination therapy.

Managing by dose reduction—and the limits thereof

There are widely variable approaches to the management of anemia during combination therapy. The package insert for ribavirin recommends reducing the ribavirin dose at hemoglobin levels less than 10 g/dL and permanently discontinuing the drug at levels less than 8.5 g/dL. As previously noted (see the article by Patel and McHutchison in this supplement), such dose reduction can have adverse implications for SVR, since studies show that higher doses of ribavirin are associated with higher SVR rates. Rates of SVR are higher in patients who receive more than 80% of their full interferon and ribavirin doses for more than 80% of the intended duration of therapy.[11] One report found that SVR rates were higher in patients who received greater than 10.6 mg/kg/d of ribavirin.[1] In fact, delivering the optimal dose of antiviral therapy seems to be most crucial during the first 12 weeks of antiviral therapy, the period of most significant decline in hemoglobin.[12]

A role for erythropoietic growth factors?

An alternative strategy for raising hemoglobin levels without resorting to dose reduction or premature withdrawal is the use of erythropoietic growth factors.

Epoetin alfa. Recombinant human erythropoietin, commercially available as epoetin alfa, is used to treat anemia associated with chronic renal failure, zidovudine therapy for HIV infection, or cancer chemotherapy, as well as to reduce the need for blood transfusions in anemic patients undergoing elective surgery.

Two studies have evaluated the use of epoetin alfa as an adjunct for the management of anemia (defined as hemoglobin < 12 g/dL) during combination therapy for chronic hepatitis C. Dieterich and colleagues[13] compared epoetin alfa therapy (40,000 units weekly) with standard-of-care anemia management in 64 patients in terms of the effects on hemoglobin levels and ribavirin dose. They found that patients receiving epoetin alfa had increases in hemoglobin level and maintained their ribavirin dose. At 16 weeks after randomization, the patients who received epoetin alfa had significantly higher mean hemoglobin levels (14.2 vs 11.2 g/dL) and a higher mean ribavirin dose (895 vs 707 mg/d) compared with the patients who received standard anemia management. Also, significantly fewer patients in the epoetin alfa group had their ribavirin dose reduced (5.7% vs 33.3%), and significantly more patients in the epoetin alfa group maintained a daily ribavirin dose of 800 mg or greater (83% vs 54%).

In the other study,[14] 186 patients from several centers were randomized to receive epoetin alfa (40,000 to 60,000 units weekly) or placebo. After 8 weeks, patients receiving epoetin alfa showed improvement in their anemia and were more likely than placebo recipients to maintain their ribavirin dose from randomization. These patients also had higher mean hemoglobin levels and higher mean ribavirin doses than the placebo recipients. This study had an open-label period during which patients receiving epoetin alfa who were responding to this treatment continued their medication and those receiving placebo who developed anemia and/or required ribavirin dose reduction were started on epoetin alfa. During follow-up in the open-label period, no further changes were

noted in patients previously taking epoetin alfa, whereas patients who previously had taken placebo showed significant increases in hemoglobin levels. The investigators also found that improvement in hemoglobin was an independent predictor of improvement in health-related quality of life as measured by the Linear Analog Scale Assessment and the Medical Outcomes Survey Short Form–36.[15] They suggested that since epoetin alfa increases hemoglobin levels in anemic HCV-infected patients receiving combination therapy, it may also improve health-related quality of life in these patients.

Neither of these two studies was designed to evaluate the effect of epoetin alfa on virologic response. Epoetin alfa was generally well tolerated in both studies.

Darbepoetin alfa. Darbepoetin alfa is a novel erythropoietic protein recently approved by the US Food and Drug Administration for treatment of anemia associated with chronic renal failure and cancer chemotherapy. Darbepoetin alfa is a hyperglycosylated protein, which gives it a threefold longer circulating half-life, higher in vivo potency, and less-frequent dosing compared with epoetin alfa.[16] Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. In a number of clinical trials of patients receiving cancer chemotherapy, darbepoetin alfa had the same efficacy and safety profile as epoetin alfa but required less-frequent dosing.[16]

Preliminary data from a recent study[17] show that darbepoetin alfa therapy (3 μg/kg every other week) in patients with chronic hepatitis C increases hemoglobin levels and also allows for maintenance of the optimal weight-based dose of ribavirin in 83% of patients, suggesting that it may be beneficial as an adjunct to combination therapy for HCV infection. Improvements in health-related quality of life also were noted after initiation of darbepoetin alfa. To date, no significant toxicity has been noted with the use of darbepoetin alfa in this study.

Darbepoetin alfa's increased half-life and less-frequent dosing may simplify anemia management, potentially offering greater convenience to both patients and health care providers.

Additional issues to address. These studies are promising and should provide impetus for larger trials that can adequately address issues such as the optimal dose and duration of erythropoietic growth factor therapy, the effect of improvement in anemia on SVR, quality of life, treatment adherence, efficiency of care delivery, and cost-effectiveness. The hemoglobin level that should trigger the initiation of growth factor therapy and the target hemoglobin level to be achieved are other important issues to consider.

NEUTROPENIA

Interferon therapy is associated with a reduction in peripheral white blood cell counts (both neutrophils and lymphocytes). This has been attributed to bone marrow suppression or a reversible impairment in the release of neutrophils and lymphocytes.[10] Peginterferons result in a greater degree of neutropenia than does nonpegylated interferon. Similar to hemoglobin levels, neutrophil counts decline rapidly within the first 2 weeks of therapy, stabilize for the duration of therapy, and rapidly return to baseline levels after treatment discontinuation.

Reducing the interferon dose is a common strategy

Because of concerns about the association between neutropenia and infections, the package inserts of both peginterferon preparations (alfa-2a and alfa-2b) recommend dose reduction for patients with neutrophil counts less than 750 cells/mm^3 and drug discontinuation for those with counts less than 500 cells/mm^3. In the pivotal trials of combination therapy with peginterferon and ribavirin, neutropenia was the most frequent reason for reducing the peginterferon dose.[1,2] Neutropenia-related dose reductions took place in 24% and 18% of patients receiving peginterferon alfa-2a and alfa-2b, respectively. Less than 1% of patients required permanent drug discontinuation.

Although reducing the dose of peginterferon can, like ribavirin dose reduction, also reduce the likelihood of SVR, this impact has been less clearly established. In the large multicenter study of peginterferon alfa-2b and ribavirin,[1] patients who were randomized to peginterferon 1.5 mg/kg/wk for 1 month followed by 0.5 mg/kg/wk had significantly lower SVR rates than did those who received 1.5 mg/kg/wk for the duration of therapy. This suggests that maintenance of the optimal dose of peginterferon for the entire duration of treatment may also be a determinant of long-term virologic response.

The neutrophil count threshold used for dose modification was extrapolated from data in cancer patients who developed neutropenia related to chemotherapy. The implications of these data for interferon-related neutropenia in patients with hepatitis C are not wholly clear. In a systematic analysis of bacterial infections in 119 patients receiving interferon and ribavirin, none of the 22 infections that occurred during treatment were observed in neutropenic patients.[18] The only bacterial infection that required hospital admission was in a patient with cirrhosis who had a neutrophil count

greater than 1,000 cells/mm^3. These findings suggest that neutropenia may be better tolerated by HCV-infected patients receiving combination therapy than it is by cancer patients receiving chemotherapy.

Management looks to granulocyte colony-stimulating factor

The management of neutropenia, like that of anemia, is variable. While some clinicians tolerate more profound neutropenia before recommending dose reduction, others are using filgrastim to raise the neutrophil count in HCV-infected patients receiving combination therapy.

Filgrastim is a recombinant human granulocyte colony-stimulating factor (G-CSF) that is used to increase white blood cell and neutrophil counts in cancer patients with chemotherapy-associated neutropenia. Very few studies have reported the use of filgrastim in patients with chronic hepatitis C. Van Thiel and colleagues[19] evaluated filgrastim as an adjunct to interferon in HCV-infected patients with advanced liver disease. All 30 patients had histologically confirmed cirrhosis. They were randomly assigned to receive interferon alfa-2b alone or with 300 mg of filgrastim given twice a week. The dose of interferon alfa-2b was 5 MU daily. Although the mean and peak white blood cell counts were higher for the patients receiving filgrastim, the nadir values were the same between the two treatment groups. A higher proportion of patients receiving filgrastim (53% vs 40%) achieved SVR, but this difference was not statistically significant. Filgrastim appeared to be fairly well tolerated in this study.

In a more recent study,[20] the use of filgrastim allowed patients to resume and maintain their full dose of peginterferon. In an additional study,[17] filgrastim was used to manage neutropenia in 39 patients who were treated with peginterferon alfa-2b and ribavirin. Preliminary results from this study demonstrate that 89% of patients receiving filgrastim had significant improvement in their neutrophil count (Younossi, unpublished data, 2004).

Together, these results indicate that filgrastim may be safe and effective in raising neutrophil counts in HCV-infected patients undergoing antiviral therapy. Nevertheless, future research will be important to better understand the clinical implications and management of neutropenia in these patients.

THROMBOCYTOPENIA

A decrease in platelet count also may be observed in patients who are receiving interferons, and such decreases are more prominent with the peginterferons. The decrease is caused primarily by a reversible bone marrow suppression, although autoimmune-related thrombocytopenia may also occur. The concurrent use of ribavirin may blunt the thrombocytopenic effect of interferons as a result of reactive thrombocytosis.

With peginterferons, the platelet count decreases gradually over 8 weeks, stabilizing thereafter and returning to baseline values within 4 weeks of stopping therapy. Bleeding complications as a result of thrombocytopenia are uncommon.[1,2]

In randomized clinical trials of the peginterferons, the rate of dose reduction attributed to thrombocytopenia ranged from 3% to 6%.[1,2] However, most patients in clinical trials are carefully selected, and these trials excluded patients with more advanced liver disease. Patients with cirrhosis may have baseline thrombocytopenia due to hypersplenism from portal hypertension, and these patients may develop more significant decreases in platelet counts owing to bone marrow suppression during therapy. For these patients, an alternative approach to dose modification would be beneficial to avoid dose reduction or discontinuation, both of which reduce the chance of SVR.

Early, unencouraging results with interleukin-11

Data are even more limited on the use of growth factors for the management of interferon-related thrombocytopenia than for the management of interferon-related anemia and neutropenia. Oprelvekin, or recombinant human interleukin-11, is approved for use in cancer patients receiving chemotherapy to enhance platelet production. It also may be useful as adjuvant therapy in HCV-infected patients receiving combination therapy.

Oprelvekin was evaluated in an open-label study of 13 HCV-infected patients undergoing therapy with interferon (3 MU three times per week) and ribavirin (1,000 to 1,200 mg/d) for 48 weeks.[21] All patients had low baseline platelet counts (< 100,000 cells/mm^3). Oprelvekin was given concurrently at a dose of 50 mg/kg subcutaneously three times per week. The researchers noted improvement in platelet counts: the mean count at 2 weeks was higher than the baseline count (98,600 vs 73,600 cells/mm^3; $P < .05$). The main side effect was fluid retention, which was noted in all patients, with 10 of 13 patients requiring diuretic therapy.

Given this side-effect profile in patients with HCV-related cirrhosis, there currently is not much enthusiasm for oprelvekin's use. Newer growth factors

with more promising safety and efficacy profiles are in development.

CONCLUSIONS

Hematologic abnormalities are common during combination antiviral therapy for chronic hepatitis C. Although dose reduction or discontinuation can easily treat these side effects, they can adversely affect the efficacy of combination antiviral therapy. This is especially true in the management of ribavirin-induced anemia. Recent evidence has led to increasing recognition that optimal dosing of ribavirin is a crucial determinant of viral clearance. Preliminary data suggest that hematopoietic growth factors may be useful for managing the hematologic side effects of combination therapy (especially anemia). The current data are limited and further study will be required, particularly with respect to the potential impact on SVR, cost-effectiveness, health-related quality of life, and other patient-related outcomes.

REFERENCES

1. **Manns MP, McHutchison JG, Gordon SC, et al.** Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358:958–965.
2. **Fried MW, Shiffman ML, Reddy KR, et al.** Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975–982.
3. **Fried MW.** Side effects of therapy of hepatitis C and their management. Hepatology 2002; 36(suppl 1):S237–S244.
4. **Martin LM, Younossi ZM, Price L, et al.** The impact of ribavirin-induced anemia on health-related quality of life. Hepatology 2001; 34(suppl):600A. Abstract.
5. **Bernstein D, Kleinman L, Barker CM, Revicki DA, Green J.** Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology 2002; 35:704–708.
6. **Gaeta GB, Precone DF, Felaco FM, et al.** Premature discontinuation of interferon plus ribavirin for adverse effects: a multicentre survey in 'real world' patients with chronic hepatitis C. Aliment Pharmacol Ther 2002; 16:1633–1639.
7. PEG-Intron (peginterferon alfa-2b) package insert. Kenilworth, N.J.: Schering Corporation; October 2003.
8. **Maddrey WC.** Safety of combination interferon alfa-2b/ribavirin therapy in chronic hepatitis C-relapsed and treatment-naive patients. Semin Liver Dis 1999; 19:67–75.
9. **De Franceschi L, Fattovich G, Turrini F, et al.** Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. Hepatology 2000; 31:997–1004.
10. **Peck-Radosavljevic M, Wichlas M, Homoncik-Kraml M, et al.** Rapid suppression of hematopoiesis by standard or pegylated interferon-alpha. Gastroenterology 2002; 123:141–151.
11. **McHutchison JG, Manns M, Patel K, et al.** Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002; 123:1061–1069.
12. **Davis GL, Wong JB, McHutchison JG, et al.** Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003; 38:645–652.
13. **Dieterich DT, Wasserman R, Brau N, et al.** Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus–infected patients receiving ribavirin plus interferon alfa. Am J Gastroenterol 2003; 98:2491–2499.
14. **Afdhal NH, Dieterich DT, Pockros PJ, et al.** Epoetin alfa treatment of anemic HCV-infected patients allows for maintenance of ribavirin dose, increases hemoglobin levels, and improves quality of life vs placebo: a randomized, double-blind, multicenter study. Gastroenterology 2003; 124(suppl 1):A-714. Abstract.
15. **Afdhal NH, Klopfer A, Tang L, Younossi Z.** Hemoglobin increase is independently associated with increased health-related quality of life in anemic interferon/ribavirin-treated hepatitis C virus-infected patients treated with epoetin alfa. Hepatology 2003; 38(suppl 1): 312A. Abstract.
16. **Glaspy JA.** Hematopoietic management in oncology practice. Part 2. Erythropoietic factors. Oncology (Huntingt) 2003; 17:1724–1739.
17. **Younossi ZM, Ong JP, Collantes R, et al.** Darbepoetin alfa for ribavirin-induced anemia in patients with chronic hepatitis C treated with pegylated interferon and ribavirin: a preliminary analysis. Gastroenterology 2004; 126(suppl 2). Abstract.
18. **Soza A, Everhart JE, Ghany MG, et al.** Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002; 36:1273–1279.
19. **Van Thiel DH, Faruki H, Friedlander L, et al.** Combination treatment of advanced HCV associated liver disease with interferon and G-CSF. Hepatogastroenterology 1995; 42:907–912.
20. **Senkbeil LE, Moss JG, Gaglio PJ, et al.** Erythropoietin maintains ribavirin dose and sustained virologic response during HCV treatment. Hepatology 2003; 38(suppl 1):744A. Abstract.
21. **Rustgi VK, Lee P, Finnegan S, Ershler W.** Safety and efficacy of recombinant human IL-11 (oprelvekin) in combination with interferon/ribavirin in hepatitis C patients with thrombocytopenia. Hepatology 2002; 36(4 Pt 2):361A. Abstract.