

Anemia Institute Review

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LETTER FROM THE EDITOR:

There is a great deal of interest in the problems that anemia causes in the treatment of patients with chronic hepatitis C. This problem is even more severe in patients with combined hepatitis C-HIV infection. However, although not mentioned in any of the reviews in this edition of the Anemia Institute Review, the problem also extends to other population groups, such as patients with thalassemia, and other red blood cell diseases, patients with renal failure, and other chronic diseases. Anemia limits the option to treat hepatitis C, since the ribavirin will predictably exacerbate a pre-existing anemia, and may actually result in a fall in hemoglobin that is unacceptable. As a result, patients with anemia have often not been offered treatment for hepatitis C.

Anemia often complicates anti-viral therapy for hepatitis C, again more often and more severely in patients who are co-infected with HIV. Anemia may result in dose reductions of ribavirin and even in withdrawal of ribavirin completely. Such modifications to anti-viral therapy may reduce the likelihood of achieving a sustained virological response.

Erythropoietin may provide a means to prevent or treat some of these problems. Erythropoietin is the hormone which normally controls production of red blood cells. When the hemoglobin falls there is an outpouring of erythropoietin from the kidney, which stimulates the production of new red cells to repair the anemia.

The induction of anemia during anti-viral therapy should trigger an erythropoietin response. Two studies described here describe the erythropoietin response, one study showing that the response is adequate, and the other study showing just the opposite, that the response is suboptimal. It is not clear why such disparate results were obtained. Even if the erythropoietin response is normal, it may be that the bone marrow is unable to respond normally to the erythropoietin, because of the suppressive effect of interferon.

Thus we need additional data to understand exactly how the body responds to the anemia induced by anti-viral therapy, so that we can tailor our treatment to reduce the impact of the anemia and provide adequate supportive therapy to those who need it.

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Anemia in the Treatment of Hepatitis C Virus Infection

Sulkowski MS.

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Hepatitis C virus (HCV) infection is a significant worldwide health care problem. Nearly one-third of all patients infected with human immunodeficiency virus (HIV) are coinfecting with HCV. Compared with HIV-monoinfected persons, coinfecting individuals experience more rapid progression of fibrosis and higher incidence of cirrhosis and death as a result of liver disease. Treatment for HCV infection includes ribavirin (RBV) plus interferon alfa (IFN- α) or pegylated IFN, a combination treatment associated with anemia that may require

RBV dose reduction or discontinuation. IFN-RBV-associated anemia is more profound among co-infected patients, who have a high prevalence of pretreatment anemia and may also be taking other medications causing anemia. Epoetin alfa administration to HCV-infected patients with IFN-RBV-related anemia can significantly increase hemoglobin levels and maintain significantly higher RBV doses compared with patients treated with RBV dose reduction alone. Higher RBV doses and adherence to HCV therapy have been associated with higher sustained virologic response (SVR) rates. Maintenance of RBV dose with epoetin alfa may improve adherence, thereby affecting SVR.

The Anemia Institute is a non-profit organization dedicated to generating and sharing knowledge about anemia as a serious condition - particularly amongst patients and health care professionals dealing with disease and/or treatment related risk factors for anemia.



Evidence that plasma concentration rather than dose per kilogram body weight predicts ribavirin-induced anaemia

Lindahl K, Schvartz R, Bruchfeld A, Stahle L.
J Viral Hepat. 2004 Jan; 11(1):84-87.

Ribavirin in combination with interferon alpha-2 or pegylated interferon is the standard treatment for chronic hepatitis C. The current dosage recommendations for ribavirin are based on body weight (bw). Ribavirin is mainly eliminated by the kidneys and we have recently shown that ribavirin plasma concentrations are determined primarily by renal function. It is therefore reasonable to hypothesize that side-effects of ribavirin, i.e. anaemia, should be more closely related to plasma concentrations of ribavirin than to the dose per kg bw. A total of 108 consecutive patients eligible for treatment of chronic hepatitis C were studied. Ribavirin concentrations in plasma were measured by high-performance liquid chromatography (HPLC)-UV after

solid-phase extraction in trough samples taken 4, 8 and 12 weeks after the treatment commenced. A total of 213 samples were obtained and the change in the haemoglobin level and the creatinine concentration was measured in addition to ribavirin. The dose of ribavirin per kg bw did not correlate with the drop in haemoglobin level induced by ribavirin. The concentration of ribavirin was non-linearly related to the drop in the haemoglobin level as revealed by fitting a standard Hill equation type dose-response curve. The half maximal drop in haemoglobin was obtained at 4.4 microm. The results from this study suggest that the anaemia induced by ribavirin depends primarily on the concentration of ribavirin, and not on the dose per kg bw. This lends further support to the idea that ribavirin should be dosed according to renal function.

Implications of anemia in human immunodeficiency virus, cancer, and hepatitis C virus

Mildvan D.
Clin Infect Dis. 2003; 37 Suppl 4:S293-6.

Anemia is a multifactorial problem in patients with human immunodeficiency virus (HIV) infection, cancer, and hepatitis C virus (HCV) infection. New insights regarding anemia symptoms and quality of life (QOL) have prompted reassessment of traditional triggers for anemia treatment to increase hemoglobin (Hb) and improve QOL. In HIV-positive patients, anemia is independently associated with disease progression and survival. Many HIV-positive patients receiving highly active antiretroviral therapy (HAART) still develop

mild to moderate anemia and associated QOL impairment. Epoetin alfa effectively increases Hb and improves QOL in these patients. Many HIV-positive patients are coinfecting with HCV. Standard HCV therapy (interferon alfa/ribavirin) can cause anemia that may result in treatment alterations and compromised virologic outcome. Epoetin alfa therapy in anemic HCV patients increases Hb levels and may provide other benefits. Neuroprotective effects of epoetin alfa in preclinical models of central nervous system disorders have recently been demonstrated, implying a new therapeutic role for this cytokine.

Treatment of hepatitis C and anemia in human immunodeficiency virus-infected patients

Dieterich DT.
INFECT DIS 2002;185{SUPPL1} S128-137.

Because of shared modes of transmission, co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common. Co-infection with HIV increases HCV virus load, liver-related mortality, and the risk of sexual and perinatal transmission of HCV and it may accelerate HCV disease progression. With combination interferon (IFN)- α 2b/ribavirin or pegylated IFN- α 2b/ribavirin therapy, long-term remission is possible for HCV-infected patients. Preliminary evidence suggests that the combination of IFN-

α 2b/ribavirin can achieve similar response rates in HCV/HIV – co-infected individuals with no adverse effect on HIV RNA concentrations. Although adverse effects are more frequent with combination therapy than with IFN- α monotherapy, most are manageable. In addition, few instances of drug-drug antagonism have been reported among drugs used to treat each disease, although further study is necessary. Ribavirin-associated hemolytic anemia is a potential problem in a patient population that is already susceptible to anemia but is manageable with recombinant human erythropoietin (epoetin alfa).

Erythropoietic Response to Anemia is Decreased in Patients Infected with Hepatitis C Virus (HCV) Receiving Combination Ribavirin and Pegylated Interferon (RBV/PEG-IFN) Therapy

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Poster presented at 54th Annual Digestive Disease Week May 2003

Background: Studies in anemic patients (pts) with cancer and HIV infection show that the inverse relationship between serum erythropoietin (sEPO) and hemoglobin (Hb) seen in control pts with iron deficiency anemia (IDA) is decreased, suggesting that pts with cancer and HIV infection have a blunted erythropoietic response compared with controls (Spivak et al, JAMA 1989; Miller et al, NEJM 1990). The present study was conducted to describe the patterns of change in Hb, sEPO, and reticulocytes (retics) to evaluate if HCV-infected pts treated with RBV PEG-IFN therapy (tx) also show a diminished erythropoietic response to anemia. Historic control pts with IDA were used as a comparator.

Methods: A multicenter, observational, 8-week (wk) study was conducted in 105 HCV-infected pts scheduled to receive their initial course of RBV/PEG-IFN tx. Laboratory parameters were measured weekly for 8 wks or until early withdrawal. Primary variables included changes in Hb, sEPO, and retics.

Results: The analysis included 97 pts (mean age, 47.5y; 46% men). Mean Hb decreased by 2.6 ± 1.4 g/dL from Day 1 (D1) to Wk 8. Mean sEPO and retics increased from D1 to Wk 8; however, regression analysis showed that the estimated erythropoietic response (defined as the slope of the relation between sEPO and Hb) was lower (sEPO = -18.6 Hb + 268 [$r = -.56$]) than in historic control pts with IDA (sEPO = -25.8 Hb + 316 [$r = -.90$], sEPO = -45.0 Hb + 518 [$r = -.71$]). The mean initial dose of RBV was 986 mg/day versus 913 mg/day at Wk 8. A total of 10.4%, 5.2%, and 1.3% of pts had 200, 400, and 600 mg/day RBV dose reductions, respectively, from D1 to Wk 8. There was no change in mean PEG-IFN doses from D1 (1.55 mcg/kg/wk) to Wk 8 (1.53 mcg/kg/wk). There were 20 pt withdrawals from the study.

Conclusion: Similar to pts with cancer and HIV infection, HCV-infected pts treated with RBV/PEG-IFN showed diminished production of endogenous sEPO for their degree of anemia when compared with historic control pts with IDA. These data point to a multifactorial etiology for the anemia seen with combination HCV tx, which, as shown in preliminary studies (Dieterich et al, AASLD 2002; Sulkowski et al, AASLD 2001), could be responsive to treatment with recombinant human erythropoietin (rHuEPO).

How can we identify better those with recurrent hepatitis C who will respond to therapy? What are the optimal treatment regimen and treatment duration?

Wright TL.

Liver Transpl. 2003 Nov; 9(11):S109-13.

1. Treatment responses are lower in immune compromised patients such as those with hepatitis C virus (HCV) disease following liver transplantation than in immune competent patients with HCV disease.
2. Predictors of nonresponse, extrapolated from studies of immune competent patients, are overly represented in liver transplantation patients (high levels of HCV RNA and genotype 1 infection).
3. Tolerability of peginterferon plus ribavirin therapy is lower in transplant patients than in immune competent patients with HCV disease, in part because of a baseline renal insufficiency that increases the likelihood of ribavirin-associated anemia.
4. Clear recommendations regarding optimal treatment

- regimens for patients with posttransplantation HCV disease are problematic since there are few prospective, randomized, controlled trials that evaluated different treatment regimens.
5. If treatment is undertaken, baseline creatinine clearance should be measured and patients should be started on a dose of ribavirin of 400mg bid, or lower if renal function is impaired.
6. Tolerated peginterferon doses may be somewhat lower than for the standard immune competent patients. It is likely that lower doses will not greatly compromise response (1.0 ug/kg/week for peginterferon alfa 2b and 135 ug/week for peginterferon alfa 2a).
7. Optimal treatment duration is unknown. In patients with an on-treatment response, at least 12 months of therapy is recommended.
8. More potent drugs with fewer toxicities are needed for patients with progressive posttransplantation liver disease.

Treatment of Posttransplantation Recurrence of Hepatitis C With Interferon and Ribavirin: Lessons on Tolerability and Efficacy

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Liver Transpl 2002;8:623-629

Recurrence of hepatitis C virus (HCV) infection after orthotopic liver transplantation is a major cause of graft failure. The aim of our study was to determine the safety, efficacy, and tolerability of combination therapy with interferon and ribavirin in the treatment of recurrent hepatitis after liver transplantation. Twenty-six patients (18 men) with histologically established HCV recurrence after liver transplantation for cirrhosis secondary to chronic HCV infection were treated with a combination of interferon alfa-2b (3 million units three times weekly) and ribavirin (800 to 1,000 mg/d). Dosage modifications were according to a standard protocol incorporating laboratory values and clinical side effects. Fifty percent of patients completed 1 year or

more of therapy. On an intention-to-treat basis, nine patients (35%) showed an end-of-treatment virological response. Six of these nine patients completed greater than 6 additional months of follow-up, and all have had sustained virological responses. A histological response (decrease in histological activity index ≥ 2) was seen in 75% of virological responders and 67% of nonresponders. Adverse events requiring dose modification or cessation of therapy occurred in 66% of patients. Adjuvant therapies used to support hemoglobin levels included erythropoietin and red blood cell transfusions. There were no independent pretreatment predictors of a virological response, perhaps because of the small sample size. Combination therapy with interferon and ribavirin may be beneficial in patients with recurrent HCV after liver transplantation. The majority of patients require dose modifications because of side effects. Histological response is common in virological nonresponders.

Normal erythropoietin response in chronic hepatitis C patients with ribavirin-induced anaemia

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Antivir Ther. 2003 Feb; 8(1):57-63.

Background: Ribavirin administration for chronic hepatitis C is associated with the development of haemolytic anaemia, which affects treatment efficacy and tolerability. In a pilot study, the exogenous administration of erythropoietin has been shown to be beneficial, reducing the rate of ribavirin dose reduction. How ribavirin administration affects normal erythropoietin production has not been determined.

Aim: To investigate the endogenous erythropoietin response in hepatitis C patients with ribavirin-induced anaemia.

Methods: Serum erythropoietin was measured before and during interferon-ribavirin treatment in 18 HCV-positive subjects. Mathematical analysis and modelling were applied to compare the degree of erythropoietin increase in HCV-

positive and in otherwise healthy anaemic patients, and estimate the endogenous excess erythropoietin production in response to ribavirin induced anaemia.

Results: Erythropoietin concentration increased significantly in response to anaemia caused by ribavirin. The physiological erythropoietin response to the ribavirin induced anaemia was as adequate in HCV-positive subjects as it is in anaemic subjects without liver disease. The recommended exogenous erythropoietin dose appears three-times greater than the endogenous erythropoietin boost.

Conclusion: Chronic liver damage by HCV does not affect the physiological erythropoietin response to ribavirin induced anaemia. While the rationale for erythropoietin treatment of ribavirin-induced anaemia is not straightforward, the currently recommended dosing regimen should be reassessed.

Folic acid supplementation does not prevent ribavirin-induced anemia

Gonzalez H, Rios ME, Torres EA, Munoz H, Arroyo J, Castro FJ.

P R Health Sci J. 2003 Dec; 22(4):359-62.

Treatment of chronic hepatitis C consists of interferon plus ribavirin. The major adverse effect of ribavirin is hemolytic anemia, a complication that limits therapy. Folic acid supplementation is used to improve erythropoiesis in chronic hemolytic anemia. The aim of this study was to evaluate the effectiveness of folic acid supplementation in the prevention of ribavirin-induced anemia in patients being treated for hepatitis

C. Twenty one patients enrolled in treatment protocols for hepatitis C received folic acid 1 mg daily and 22 did not. Groups were similar in age, gender, ribavirin dose and baseline hemoglobin. Folic acid supplementation had no effect in the decrease in hemoglobin or the measured parameters of hemolysis. No difference between males and females was noted for hemoglobin decrease or lowest hemoglobin levels. In our study, folic acid showed no beneficial effect in the prevention of ribavirin-induced anemia.