Anemia in the Treatment of Hepatitis C Virus Infection

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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 coinfected with HCV. Compared with HIV-monoinfected persons, coinfected 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 coinfected 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.

EPIDEMIOLOGY OF HCV INFECTION

With nearly 4 million people chronically infected with hepatitis C virus (HCV) in the United States, the health care burden resulting from HCV infection is likely to increase substantially in the next 2 decades [1]. This is primarily because ~85% of patients with acute HCV infection will subsequently develop chronic infection, and an estimated 20%–30% of these will develop cirrhosis [1]. Chronic infection may also lead to hepatocellular carcinoma and is now the most common indication for orthotopic liver transplantation in the United States [1, 2]. In addition, the aging of the chronically infected population is estimated to increase the number of patients with HCV-related liver decompensation and to increase mortality ~4-fold by the year 2018 compared with current rates of decompensation and mortality [3].

Of significant concern is the high prevalence of HIV and HCV coinfection, which likely results from the similar modes of transmission for the viruses, particularly in injection drug users and recipients of transfused blood products [4]. A recent report noted that ~16% of a heterogeneous population of HIV-infected patients were coinfected with HCV [5]. The increasing significance of HCV-HIV coinfection is also related to dramatic reductions in morbidity and mortality among HIV-infected patients during the HAART era, resulting in the emergence of HCV as a common pathogen in this population [4]. Relatively more severe HCV disease occurs in this setting, possibly from HIV infection altering the response of T cells to HCV antigens. For example, an imbalance of Th1 (low) and Th2 (high) activation may lead to an ineffective immune response to HCV infection. Although the mechanism has not been fully elucidated, HIV-infected patients have an

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increased risk for HCV disease progression compared with those with HCV monoinfection, leading to higher rates of cirrhosis, liver failure, hepatocellular carcinoma, and mortality.

TREATMENT OF HCV INFECTION

The primary objective of HCV treatment is virus eradication, which is the most effective way to delay or prevent the histologic (i.e., hepatic fibrosis) and clinical (i.e., liver failure, liver cancer, death) consequences of chronic HCV infection. Currently, the most effective therapy for chronic HCV infection is once-weekly (q.w.) pegylated interferon (PEG-IFN)-α-2a or -α-2b in combination with ribavirin (RBV) [6, 7]. In 2 large, randomized controlled trials, a sustained virologic response (SVR), defined as absence of HCV RNA in serum by PCR assay 24 weeks after treatment discontinuation, was achieved in 54%–56% of patients receiving PEG-IFN–RBV for 48 weeks. On the basis of these data, the 2002 National Institutes of Health Consensus Panel on the Management of Hepatitis C recommended that HCV-infected patients, including those coinfected with HIV, be considered for treatment with PEG-IFN–RBV combination therapy [8].

Factors predictive of response to combination PEG-IFN–RBV therapy. Further analysis of individuals who achieved SVR in the 2 randomized trials of PEG-IFN–RBV indicates that the most important pretreatment factors to predict SVR include HCV genotype and quantitative serum HCV RNA level (i.e., HCV load) [6, 7]. SVR rates of 42% and 46% were achieved in patients with HCV genotype 1, compared with rates of 76% and 82% in patients with HCV genotypes 2 or 3. Furthermore, SVR rates were substantially lower among persons with high HCV RNA levels, defined as ≥2 × 10^6 copies/mL, compared with those with lower HCV RNA levels. In the study by Manns and colleagues [7], SVR was achieved in 42% and 78% of PEG-IFN-α-2b–RBV–treated patients with high and low HCV RNA levels, respectively. Similarly, Fried et al. [6] reported SVR rates of 53% and 62% for PEG-IFN-α-2a–RBV–treated patients with high and low HCV RNA, respectively. Thus, patients infected with HCV genotype 1 and high HCV RNA levels represent the patient subgroup that is the most difficult to treat.

In addition to virologic factors, baseline liver histology also appears to be associated with SVR. Patients with evidence of advanced fibrosis or cirrhosis generally have lower SVR rates compared with those with no or minimal fibrosis [6, 7].

Importance of maintaining adequate IFN and RBV doses. In addition to baseline factors, treatment regimen and patient adherence to this regimen are important factors in determining SVR. Emerging data suggest that a key element of successful combination therapy with IFN–RBV is the ability of the patient to maintain adequate doses of both drugs throughout the designated treatment period. Recently, McHutchison et al. [9] demonstrated that patients who received at least 80% of the total doses of both PEG-IFN-α-2b and RBV for at least 80% of the expected duration of therapy had an SVR of 63%, compared with an SVR of 52% for those who received <80% of the total doses of both drugs for at least 80% of the expected therapy duration (P = .04) (figure 1).

The importance of RBV dose was also evident in a recent phase 3 randomized, controlled trial evaluating the efficacy of 2 PEG-IFN-α-2b–RBV dosing regimens (PEG-IFN-α-2b 1.5 μg/kg weekly plus RBV 800 mg/d for 48 weeks [n = 511] or PEG-IFN-α-2b 1.5 μg/kg weekly for the first 4 weeks followed by 0.5 μg/kg weekly for the next 44 weeks plus RBV 1000–1200 mg/d [n = 514]) with that of IFN-α-2b 3 million U sc 3

![Figure 1](image_url)

**Figure 1.** Sustained virologic response rates based on percentage of total doses of IFN-α-2b and ribavirin (RBV) and percentage of the total duration of therapy [9]. SVR, sustained virologic response. Adapted with permission from 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; 123:1061–9 [9].
times weekly (t.i.w.) plus RBV 1000–1200 mg/d \((n = 505)\) for 48 weeks in HCV-infected patients [7]. In this study, the doses of PEG-IFN-α-2b selected reflected their antiviral effect when used as monotherapy [10], whereas the lower 800-mg/d RBV dose was selected because of concern that the higher PEG-IFN-α-2b dose might be associated with anemia that would exacerbate the dose-dependent anemia observed with RBV [7].

Interestingly, patients receiving the higher-dose pegylated product demonstrated higher SVR rates compared with those receiving lower-dose PEG-IFN-α-2b or IFN-α-2b [7]. However, further analysis of the PEG-IFN-α-2b and RBV doses received indicated that adequate doses of both drugs were important and significantly predicted SVR (OR, 1.7, \(P = .002\) for high-dose vs. low-dose PEG-IFN-α-2b and \(P = .015\) for RBV). Plotted as a continuous variable, the likelihood of SVR increased with increasing RBV dose (expressed as mg of RBV received per kg of body weight) (figure 2). Additional logistic regression analysis showed that observed SVR rates generally increased as RBV dose increased up to \(\sim 13\) mg/kg, which corresponds to an RBV dose of \(\sim 1000\) mg/d in a 70-kg person. According to this analysis, the most effective RBV dose range is 11–15 mg/kg, which corresponds to daily doses of 800–1400 mg, depending on body weight. Further analysis showed that the SVR rate was higher in all study groups when the RBV dose was \(> 10.6\) mg/kg; patients receiving higher-dose PEG-IFN-α-2b plus RBV doses \(> 10.6\) mg/kg had an overall SVR of 61%, compared with an SVR of 50% for those receiving the same PEG-IFN-α-2b dose but RBV doses \(= 10.6\) mg/kg.

In addition, the significance of adequate RBV dose in patients with HCV genotype 1 was prospectively demonstrated in a multicenter, double-blind, randomized controlled trial conducted by Hadziyannis and colleagues [11] among previously untreated persons chronically infected with hepatitis C. Study participants \((N = 1284)\) were randomized to 1 of 4 treatment groups comparing 2 RBV dosing schemes (800 mg/d vs. 1000–1200 mg/d) and 2 treatment durations (24 weeks vs. 48 weeks). Study results showed that, among persons infected with HCV genotype 1, the SVR rate was significantly higher for those treated with high-dose RBV (1000–1200 mg/d; SVR, 51%) for 48 weeks, compared with those treated with low-dose RBV (800 mg/d; SVR, 40%) for 48 weeks \((P = .01)\). Conversely, among patients infected with HCV genotype 2 or 3, no difference in SVR rate was observed between low-dose and high-dose RBV treatment groups for 24 or 48 weeks.

Thus, these data, derived from large, randomized clinical trials, indicate that RBV dose and patient adherence are im-

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**Figure 2.** Logistic regression analysis describing sustained virologic response (SVR) as a function of ribavirin (RBV) dose (milligrams of drug per kilogram) and pegylated (PEG) IFN-α-2b doses [7]. SVR rates are presented as moving averages, along with fitted regression lines. The moving average places patients into overlapping intervals on the basis of their RBV dose; observed SVR rates are calculated for each interval on the basis of all patients in the interval. Midpoints of each of the intervals are obtained by dividing the RBV dose axis into 0.5-mg/kg increments; overlapping intervals are formed by including doses within 2 mg/kg above and below midpoints. The size of each of the circles represents the size of the group as well as the precision of these response rates. Reprinted with permission from 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; 358:958–65 [7].
portant factors in achieving SVR, particularly among "difficult-to-treat" patients, such as those infected with HCV genotype 1 and those with high baseline levels of HCV RNA. However, in all studies, the major, and sometimes dose-limiting, toxicity of PEG-IFN–RBV was a dose-dependent hemolytic anemia.

**Hepatitis C in the HIV-infected patient.** Before the advent of HAART, clinicians caring for HIV-infected patients focused their attention on preventing traditional opportunistic infections and delaying progression of HIV disease to AIDS/death. In keeping with that strategy, chronic HCV infection that was presumed to be indolent in many patients was often not treated. However, in the era of HAART, HCV infection has emerged as a major cause of morbidity and mortality among HIV-infected patients. Consequently, HIV care providers have focused increasing attention on HCV treatment, with renewed research efforts to determine the most safe and effective regimen in this population.

Although studies are currently under way, there are few published data addressing the safety and efficacy of IFN-α or PEG-IFN-α and RBV therapy in HIV-infected patients. Several retrospective treatment series suggest that IFN-α–RBV is reasonably well tolerated and may lead to persistent HCV clearance among some HIV-infected patients [12, 13]. In addition, preliminary data from ongoing clinical trials have recently been presented. Kostman and coworkers [14] treated 110 HIV-HCV–coinfected patients with IFN-α-2b plus RBV or placebo. After 12 weeks of therapy, HCV RNA was undetectable in 23% of patients receiving combination therapy, compared with 5% of those receiving monotherapy. Although SVR data are not yet available, the safety profile was similar in both treatment groups, with 18% and 23% of patients discontinuing therapy as a result of adverse events in the placebo and RBV groups, respectively.

More recently, Chung and colleagues [15] presented preliminary data from an ongoing AIDS Clinical Trials Group study, which randomized 134 coinfected adults to standard IFN-α-2a 6 million U t.i.w. for 12 weeks followed by 3 million U for 36 weeks or PEG-IFN-α-2a 180 μg weekly; both groups received RBV 600 mg daily with a possible dose escalation to 1000 mg daily (if tolerated). The majority of patients were white (48%) or black (34%), were male (82%), had a history of intravenous drug use (64%), and were infected with HCV genotype 1 (83%); 10% had cirrhosis. The median age was 45 years. At study entry, 90% were receiving antiretroviral therapy and 59% had undetectable HIV RNA levels. The mean CD4 cell count was 452/mm³. At week 24 of therapy, HCV RNA was undetectable (<60 IU/mL) in 15% and 44% of standard and PEG-IFN plus RBV groups, respectively. Among persons with genotype 1 infection, HCV RNA suppression was observed in 7% and 33% of standard and PEG-IFN recipients, respectively (P = .0014). Among those with HCV genotypes other than genotype 1, HCV RNA suppression was observed in 40% and 80% of standard and PEG-IFN recipients, respectively (P = .06).

Histologic response at week 24 of therapy (defined as ≥2-point reduction in histological activity index score) was observed in 40% and 26% of standard and PEG-IFN virologic nonresponders, respectively. AIDS Clinical Trials Group grade 4 adverse events were observed more frequently among PEG-IFN (n = 17) than among standard IFN (n = 4) recipients. However, premature treatment discontinuation was similar in both groups (12%). No adverse effect on control of HIV replication was observed. Absolute CD4 cell count decreased and CD4 cell percentage increased in both treatment groups (PEG-IFN: −194 cells/mm³, +3.5%; standard IFN: −112 cells/mm³, +2.5%), suggesting no significant impact on immune status. Multivariate logistic regression analysis of HCV genotype found week-24 HCV response was independently associated with PEG-IFN (OR, 0.0004), white race (0.016), Karnofsky Performance Status score of 100% at baseline, and fibrosis score 0–2 (0.021). These preliminary data suggest that PEG-IFN–RBV may produce virologic and/or histologic response in HIV-HCV–coinfected patients, although SVR data are not yet available.

Although adverse effects are common with IFN-RBV, anemia is of particular concern in patients coinfected with HCV and HIV who receive combination IFN-α–RBV therapy, because these patients are already at risk for anemia from HIV-related causes, including chronic disease, nutritional deficiencies, opportunistic infections, and concurrent therapies for HIV infection. In addition, RBV seems to cause more anemia in HIV-infected patients than in individuals not infected by HIV [4]. Thus, the decision to treat coinfected patients with IFN-α–RBV must balance adverse effects of therapy, including anemia, with the potential benefit of effectively managing HCV infection.

**ANEMIA ASSOCIATED WITH IFN-α–RBV THERAPY**

The development of significant treatment-associated anemia is a concern in both HIV-infected and -uninfected persons receiving IFN-RBV. Decreased hemoglobin (Hb) levels have been reported in patients receiving both IFN and RBV, either alone or in combination (figure 3) [16]. Of interest, 25%–30% of HCV-infected patients receiving IFN-α-2b alone demonstrated at least 2-g/dL decreases in Hb levels as a result of IFN-related bone marrow suppression, which limits RBC production [17, 18]. Furthermore, RBV monotherapy results in a dose-dependent, extravascular hemolytic anemia in most patients [19]. Accordingly, patients treated with combination therapy are subject to RBV-related hemolytic anemia as well as IFN-related bone marrow suppression, which may impair the compensatory reticulocytosis that is an expected response to most hemolytic processes. Thus, many patients receiving IFN-RBV experience...
Figure 3. The effect of IFN-α and/or ribavirin (RBV) on hemoglobin (Hb) level in hepatitis C–infected patients. Reprinted with permission from Schalm SW, Hansen BE, Chemello L, et al. Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C: meta-analysis of individual patient data from European centers. J Hepatol 1997; 26:961–6 [16].

Figure 4. Magnitude of hemoglobin decrease during 48 weeks of treatment with IFN-α2b–ribavirin [21]

a “mixed anemia,” with both hemolysis and bone marrow suppression developing simultaneously [20].

The magnitude of treatment-associated anemia was further evaluated in a retrospective analysis of data from IFN-α2b–naive (study 1, n = 192) and IFN-α2b–experienced patients (study 2, n = 485) [21]. Enrolled patients had initial Hb levels >12 g/dL (women, n = 243) or >13 g/dL (men, n = 433) and were treated with standard IFN-α2b–RBV 1000–1200 mg/d; data from 208 women and 386 men were analyzed. In both studies, patients whose Hb levels decreased to <10 g/dL had RBV doses reduced to 600 mg/d. Overall, 54% of all patients had a ≥3-g/dL decrease in Hb level (figure 4), and >27.7% of patients experienced Hb decreases of ≥25% of baseline levels. The incidence of Hb decreases ≥3 g/dL was higher in men (60%) than in women (44%) (RR, 1.4; 95% CI, 1.2–1.6). In addition, nearly 10% of men and 7% of women experienced
an Hb decrease ≥5 g/dL. Thus, many patients receiving combination standard IFN-RBV therapy experience relatively significant declines in Hb levels.

Similarly, anemia is a common complication of combination therapy with PEG-IFN–RBV. In the study by Mans et al. [7], patients receiving RBV doses >10.6 mg/kg had more-frequent dose modifications if they also received PEG-IFN-α-2b compared with standard IFN-α-2b (49% vs. 34%), most commonly as a result of neutropenia and anemia. However, treatment discontinuation was similar in the 2 treatment groups (14% vs. 13%, respectively). In the study by Hadziyannis and colleagues [11], RBV discontinuation as a result of anemia was more common among patients treated for 48 weeks (18% and 19%) than among those treated for 24 weeks (6% and 7%). Thus, treatment-associated anemia among patients taking PEG-IFN–RBV can necessitate RBV dose reduction or discontinuation, which may significantly decrease the probability of achieving an SVR.

MANAGEMENT OF ANEMIA IN HCV-INFECTED PATIENTS

Accordingly, strategies to address HCV treatment–associated anemia are needed. The standard-of-care (SOC) management for patients who develop anemia during HCV therapy with IFN-RBV has been RBV dose reduction to 600 mg/d for Hb levels !10 g/dL and drug discontinuation when Hb levels drop to !8.5 g/dL [18]. However, as discussed above, emerging data indicate that daily RBV doses <1000 mg (for patients <75 kg) and 1200 mg (for patients ≥75 kg) are associated with lower SVR rates in HCV genotype 1–infected patients [6, 7]. Consequently, to avoid RBV dose reduction and to improve symptoms related to Hb decreases, studies are needed to evaluate alternative approaches to the management of anemia in HCV-infected patients receiving IFN-RBV combination therapy.

Recombinant human erythropoietin (epoetin alfa; PROCRIT; Ortho Biotech Products) is effective for the management of cancer-related anemia as well as for anemia in HIV-infected patients receiving antiretroviral therapy. On the basis of experience in these populations, epoetin alfa 40,000 U sc q.w. was administered in an open-label, prospective study of 18 HCV-infected patients receiving IFN-RBV who developed symptomatic anemia (Hb ≤10 g/dL or a decrease in Hb of ≥2 g/dL from baseline) or a decrease in Hb accompanied by decreased exercise tolerance [22, 23]. Patients receiving IFN-RBV (n = 38) who did not meet these anemia criteria did not receive epoetin alfa and served as a comparison group. Patients were followed for a mean of 25.3 and 21.2 weeks, respectively [23]. Among anemic patients, the mean Hb level had declined to 10.6 ± 1.0 g/dL when epoetin alfa therapy was initiated. RBV doses were decreased before epoetin alfa initiation in 8 patients and concurrently with epoetin alfa therapy in 5 patients.

At study completion, mean Hb levels were 12.7 ± 1.7 g/dL in the epoetin alfa group and 13.0 ± 1.4 g/dL in the comparison group. In the anemic group, before initiation of epoetin alfa, the Hb decreased by a mean of 26.5% after IFN-RBV therapy administration; however, with the administration of epoetin alfa, nearly 75% of this Hb decrease was recovered by the end of follow-up. Interestingly, nearly 50% of the observed Hb decrease occurred during the first 2 weeks of RBV treatment, typically with symptoms of dyspnea and fatigue [22, 23]. In

Figure 5. Mean hemoglobin levels for hepatitis C virus–infected patients receiving epoetin alfa 40,000 U sc weekly or standard of care (SOC) [24]
most patients, Hb recovery was rapid and often associated with an improvement in dyspnea.

On the basis of these preliminary results, an open-label, randomized, parallel-group study involving 60 HCV mono-infected patients at 7 centers in the United States was initiated [24]. In this study, patients currently receiving IFN-α-2b–RBV for HCV infection with Hb levels ≤12 g/dL were randomized to receive epoetin alfa 40,000 U sc q.w. for 16 weeks or SOC anemia management. The study objective was to determine the efficacy of epoetin alfa compared with SOC in correcting anemia and minimizing the need for anemia-related RBV dose reduction. At study entry, the mean Hb level was 11 g/dL for both groups. However, at the end of the 16-week study period, patients receiving epoetin alfa had a mean Hb level of 13.9 g/dL, compared with a mean Hb level of 11.3 g/dL for patients receiving SOC (P < .001) (figure 5) [24]. Similarly, mean daily RBV doses were 926 mg/d and 782 mg/d for patients receiving epoetin alfa and SOC, respectively (P < .05) (figure 6). This represents a decrease from baseline RBV doses of 31 mg/d and 179 mg/d for patients receiving epoetin alfa and SOC, respectively (P < .05). Thus, epoetin alfa use was associated with an Hb increase of nearly 3 g/dL and maintenance of the intended RBV dose. Epoetin alfa therapy was well tolerated.

Similarly, preliminary studies have evaluated the role of epoetin alfa in HIV-HCV coinfected patients who developed anemia during IFN-RBV therapy. In a small case series, 5 (23.8%) of 21 HIV-infected patients receiving IFN-α-2b plus RBV for concomitant HCV infection developed significant anemia [25]. After a median of 4 weeks of treatment with epoetin alfa 40,000 U q.w., mean Hb levels increased from 10 to 12.7 g/dL, allowing continuation of combination therapy. Only 1 of the 5 patients discontinued HCV treatment as a result of anemia, suggesting that anemia in HIV-HCV coinfected patients may also be managed with epoetin alfa; additional studies are ongoing in this population.

**SUMMARY**

Chronic HCV infection is an increasingly important cause of liver disease in the United States. Therapy with pegylated IFN-α–RBV can lead to SVR in 54%–56% of treated patients. However, as a result of IFN-related bone marrow suppression and RBV-related hemolysis, anemia is a common complication of IFN-RBV therapy and may be associated with decreased quality of life and the need for RBV dose reduction. Recent data suggest that adherence to therapy and maintenance of the RBV dose are important factors in achieving SVR. Accordingly, epoetin alfa has been studied as a strategy to treat IFN-RBV–related anemia. Preliminary data suggest that epoetin alfa can increase Hb level, improve quality of life, and decrease the need for RBV dose reduction in patients who develop IFN-RBV–related anemia. Studies are currently under way to assess whether these improvements lead to enhanced patient adherence and increased hepatitis C response rates among HCV-infected patients with and without HIV co-infection.

**References**