Hematologic Disorders Associated with Hepatitis C Virus Infection and Their Management

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More than 4 million people in the United States are infected with hepatitis C virus (HCV). During the next 20–30 years, the burden of HCV-related mortality and morbidity will likely double. To date, the most effective treatment for chronic HCV infection is the combination of either interferon (IFN)–α or pegylated IFN-α and ribavirin. For a sustained virologic response, treatment adherence and dose maintenance are essential. However, both IFN-α and ribavirin induce hematologic toxicity, such as anemia, neutropenia, and thrombocytopenia, which can compromise treatment adherence and dose maintenance and could, therefore, potentially influence outcomes. Although there are currently no approved treatments for hematologic complications of HCV therapy, studies have shown that hematopoietic growth factors can provide significant benefits. This review highlights the pharmacology, risks, and benefits of recombinant hematopoietic growth factor therapy in HCV-infected patients.

More than 4 million people in the United States are acutely or chronically infected with hepatitis C virus (HCV) [1, 2]. Of those individuals with acute HCV infection, 54%–86% will develop chronic infection [1], and at least 20% of individuals who are chronically infected will develop cirrhosis [2, 3]. HCV is the most common cause of cirrhosis and is responsible for >50% of liver transplants performed currently [2, 4].

HCV-infected individuals can be asymptomatic for many years or may have mild symptoms, which makes HCV infection difficult to recognize. Rates of disease progression among individuals with chronic HCV infection vary; however, older age at time of infection, chronic alcoholism, and coinfection with HIV or hepatitis B virus appear to be correlated with more rapid progression [3, 5, 6]. It is evident that the burden of HCV-related mortality and morbidity will have a large impact over the course of the next 20–30 years [2, 6]. During the present decade (2000–2010), up to 10,000 HCV-related deaths are expected each year [7], a value that will likely double in the next 2–3 decades.

Anemia, neutropenia, leukopenia, and thrombocytopenia are among the numerous side effects of currently available HCV treatments [8–11]. Preliminary data suggest that the infection itself can also induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia [12–16]. These complications can influence HCV treatment and adherence, which could compromise outcomes. Although no approved treatments for HCV-related hematologic complications exist, this review will summarize the pharmacology, risks, and benefits of the investigational use of hematopoietic growth factors for treating such complications.

CURRENT THERAPIES FOR HCV INFECTION

Approved treatments for HCV include IFN-α2a and IFN-α2b monotherapy, pegylated IFN-α2a (PEG-IFN-
α2a) and PEG-IFN-α2b monotherapy, and IFN-α2b, PEG-IFN-α2b, or PEG-IFN-α2a in combination with ribavirin (Rbv). Although IFN-α monotherapy was the first approved treatment, results of randomized, controlled trials subsequently indicated that the addition of Rbv to IFN-α produces improved sustained virologic response (SVR) rates [17–21]. An SVR is defined as the absence of HCV RNA 6 months after treatment. In 2 large, multicenter trials, the SVR rates for IFN-α monotherapy at 24 and 48 weeks were 6% and 13%–19%, respectively, whereas SVR rates with the combination of IFN-α and Rbv at 24 and 48 weeks were 31%–35% and 38%–43%, respectively [22]. In addition, preliminary evidence suggests that IFN-α/Rbv combination therapy is effective for patients who experience relapse or do not respond to IFN-α monotherapy [23–27]. Combination therapy also produces a greater reduction in liver fibrosis than does IFN-α monotherapy [26, 28].

Pegylation of IFN-α, which increases the half-life of the molecule, resulted in improved SVR rates, compared with those achieved using nonpegylated IFN-α [29]. There are 2 forms of PEG-IFN-α: PEG-IFN-α2a, which has a 40-kDa polyethylene glycol moiety, and PEG-IFN-α2b, which has a 12-kDa polyethylene glycol moiety. Regardless of the size of the polyethylene glycol moiety, the combination of PEG-IFN-α and Rbv demonstrated better efficacy than IFN-α monotherapy or combination therapy with IFN-α and Rbv [10, 30–32]. In one trial, the average SVR rate for conventional IFN-α2b/Rbv treatment was 47%, compared with 54% for PEG-IFN-α2b/Rbv combination therapy (P = .01) [10]. In a recent trial, 48 weeks of PEG-IFN-α2a/Rbv treatment (180 μg of PEG-IFN-α2a once weekly and 1000–1200 mg/day Rbv) resulted in an overall SVR rate of 56%, compared with 44% for IFN-α2b/Rbv and 29% for PEG-IFN-α2a alone [31]. Furthermore, among patients treated with IFN-α monotherapy who were followed up, PEG-IFN-α2b monotherapy at low, medium, and high doses (0.5, 1.0, and 1.5 μg/kg once weekly, respectively) significantly improved SVR rates, compared with IFN-α2b monotherapy (P ≤ .042) [30]. Similar findings have also been demonstrated in comparisons of PEG-IFN-α2a and IFN-α2a [33–35]. Thus, the present standard of care includes subcutaneous injections of either IFN-α 3 times/week or PEG-IFN-α2a or -α2b once weekly in combination with daily oral Rbv.

The current dosing practice for Rbv is weight based. Retrospective analysis has determined that maintenance of Rbv dosages >10.6 mg/kg/day was associated with more-optimal SVR rates [10]. Preliminary analysis from a prospective study of PEG-IFN-α2a and Rbv demonstrated a higher SVR rate for patients infected with HCV genotype 1 who were randomly assigned to receive 1000–1200 mg/day Rbv (51%) than for those receiving 800 mg/day Rbv (40%) for 48 weeks [36].

The most important factors in successful eradication of HCV are adherence to therapy and dose maintenance. Optimal results have been obtained in patients infected with HCV genotype 1 when treatment with at least 80% of the IFN-α dose and at least 80% of the Rbv dose was maintained for at least 80% of the time [37, 38]. However, combination therapy significantly increased the risk of dose modifications and discontinuations due to treatment-related adverse effects [23, 26, 38], and, as has been observed clinically, dose modifications appeared to be less than optimal for HCV eradication. Thus, treatment success may be compromised by the adverse effects of HCV therapy. As detailed in the 2002 National Institutes of Health Consensus Statement on the Management of Hepatitis C [4], “There is a need to assess the effectiveness of supportive therapy to ameliorate the side effects of antiviral therapy.”

ROLE OF HEMATOPOIETIC GROWTH FACTORS IN TREATMENT-INDUCED HEMATOLOGIC DISORDERS

Common Hematologic Adverse Effects of IFN-α, Rbv, and IFN-α/Rbv Combination Therapy

Side effects of IFN-α and PEG-IFN-α (hereafter, where both IFN-α and PEG-IFN-α are meant, “[PEG]IFN-α” is used) include depression, transient flulike symptoms (headache, fatigue, myalgia, chills, and fever), more severe or persistent fatigue, alopecia, and bone marrow suppression leading to anemia and neutropenia [9]. Leukopenia and thrombocytopenia are also common; however, they tend to be mild and generally are not associated with complications [10, 31, 39, 40]. Neutropenia and thrombocytopenia appear to occur at higher rates with use of PEG-IFN-α than with use of nonpegylated IFN-α [10, 31, 33, 41, 42], whereas anemia tends to occur less frequently with PEG-IFN-α than with nonpegylated IFN-α [11, 40–43].

The major side effect of treatment with Rbv is dose-dependent hemolytic anemia [8, 11]. At Rbv doses of ≧800 mg/day, Rbv-induced hemolytic anemia causes a dramatic decrease in hemoglobin levels (of 2–3 g/dL), usually ≤4 weeks of initiation of treatment [11]. When combination therapy with IFN-α/Rbv is used, hemoglobin levels ≤11 g/dL occur in 25%–30% of patients [18, 19]. Anemia has been found to be more pronounced with combination therapy (figure 1) [9] than with IFN-α monotherapy; in one study, the incidence of dose modifications due to anemia increased from 0% with IFN-α monotherapy to 7%–9% with combination therapy [18]. Similarly, the incidence of dose reductions due to anemia increased from 1% with PEG-IFN-α monotherapy to 22% with PEG-IFN-α/Rbv therapy [31]. In addition, as seen in figure 2, dose reductions due to neutropenia and thrombocytopenia were more common in association with PEG-IFN-α/Rbv therapy than with standard IFN-α/Rbv therapy [10]. This finding was similar for both formulations of PEG-IFN-α [31]. The greater incidence of neutropenia and thrombocytopenia associated with PEG-
Blood Disorders Associated with HCV

IFN-α may be due to the longer half-life of the agent, which allows longer bone marrow exposure; however, the recommended weekly dosages for combination therapy of both formulations of PEG-IFN-α (1.5 μg/kg of PEG-IFN-α2b once weekly and 180 μg of PEG-IFN-α2a once weekly) are also greater than the recommended weekly dose of IFN-α (3 million IU of IFN-α2b 3 times/week) [10, 11, 31, 41, 42].

Etiology and Consequences of Anemia, Neutropenia, and Thrombocytopenia

IFN-α/Rbv treatment–induced anemia has been called a “mixed” anemia, because the effects of both drugs contribute to its etiology. In addition to hemolysis (discussed in the previous section), Rbv induces anemia by suppression of erythropoiesis, possibly as a result of down-regulation of erythropoietin receptors [44–46]. IFN-α–induced anemia can occur by various mechanisms, including suppression of hematopoietic progenitor cell proliferation, activation of programmed cell death (apoptosis) in erythroid progenitor cells, provocation of immune hemolysis, and impairment of renal function [47–49].

Some of the consequences of anemia include impaired tissue oxygenation, organ function, and quality of life, as well as increased susceptibility to thrombocytopenic bleeding, increased risk of postoperative mortality, and increased likelihood that blood transfusions will be needed [12, 50–54]. In addition, anemia may be associated with decreased survival rates among patients with HIV infection and cancer [52, 53, 55]. These clinical sequelae of anemia indicate the importance of its treatment, especially in patients with a chronic disease.

The mechanisms by which IFN-α induces neutropenia and thrombocytopenia include direct bone marrow toxicity and autoimmune reactions [39, 56]. In some cases, Rbv may potentiate (PEG)IFN-α–induced neutropenia; however, it appears not to potentiate thrombocytopenia [10, 31, 41, 42]. Although a serious consequence of severe neutropenia (absolute neutrophil count [ANC] <500 cells/mm3) is increased susceptibility to opportunistic infections, decreases in the neutrophil counts seen in patients receiving (PEG)IFN-α therapy for HCV are rarely life-threatening or associated with an increased incidence of bacterial infection [11, 40]. As for thrombocytopenia, spontaneous bleeding may occur more frequently in patients receiving (PEG)IFN-α therapy, but severe thrombocytopenia is very rare [41, 42].

Strategies for Treating Hematologic Disorders in HCV-Infected Patients

Recombinant human erythropoietin. Pharmacologic enhancement of erythropoiesis is an effective strategy for alleviating anemia without exposing the patient to allogeneic blood and the accompanying risks. Erythropoietin is a hormone produced primarily by the kidneys in adults and acts in the bone marrow as an erythroid cell viability (i.e., antiapoptotic) factor and a mitogen, thereby increasing the number of erythroid progenitor cells [12]. Recombinant human erythropoietin behaves like endogenous erythropoietin. The development of recombinant hematopoietic growth factors, such as recombinant human erythropoietin, has allowed the correction of anemia without blood transfusions. Epoetin alfa (recombinant human erythropoietin) was the first recombinant hematopoietic growth factor to be used in a clinical setting (i.e., in patients...
with end-stage renal disease) and is the most well-studied [57, 58]. Epoetin alfa (Procrit; Ortho Biotech) is also the only recombinant human erythropoietin that has been evaluated in clinical trials for the treatment of anemia in patients with HCV. Therefore, in this review, its therapeutic benefits will be used to provide the rationale for treating HCV therapy–associated anemia with such agents.

Epoetin alfa has been shown to be effective and safe for the treatment of anemia in patients with chronic kidney disease, patients with cancer who are receiving chemotherapy, zidovudine-treated HIV-infected patients, and patients scheduled to undergo elective noncardiac, nonvascular surgery. The clinical benefits (e.g., increased hemoglobin and reduced transfusion use) and health-related quality-of-life benefits of epoetin alfa have been demonstrated in HIV-infected patients in whom hemoglobin levels decreased to <12 g/dL or >25% below baseline [54, 59–63], in anemic patients with cancer who were undergoing chemotherapy [50–52, 64], in anemic patients with cancer who were not undergoing chemotherapy [65, 66], and in patients with chronic kidney disease [67].

The use of epoetin alfa to treat patients receiving (PEG)IFN-α/Rbv combination therapy is potentially beneficial for a number of reasons. Both (PEG)IFN-α and Rbv cause anemia, which may result in fatigue, loss of functional capacity, and cognitive impairment. These symptoms are associated with reduced quality of life and could lead to treatment noncompliance. Symptomatic anemia may require blood transfusions. HCV treatment–related anemia may also require Rbv dose reduction or interruption of (PEG)IFN-α/Rbv combination therapy, thereby decreasing adherence to HCV therapy and perhaps decreasing SVR rates. Preliminary evidence in anemic HCV-infected patients who are receiving IFN-α/Rbv treatment has shown that epoetin alfa is effective in ameliorating anemia [68–70]. Although there are no official guidelines for treating HCV therapy–associated anemia, clinical trial data have shown that epoetin alfa therapy is effective when it is initiated when a hemoglobin level of 12 g/dL in men and 11 g/dL in women is reached [69]. If the hemoglobin level does not increase by 1 g/dL after 4 weeks of therapy with 40,000 U of subcutaneous epoetin alfa once weekly, the dose can be increased to 60,000 U. If this dose does not lead to an increase in the hemoglobin level after 4 weeks, epoetin alfa therapy may be discontinued. In addition, epoetin alfa should be withheld if hemoglobin levels rise to >16 g/dL in men and >14 g/dL in women [69]. For patients in whom the hemoglobin level increases ≥1 g/dL 4 weeks after receipt of a starting dose of 40,000 U sc once weekly, if the hemoglobin level subsequently decreases (to <15 g/dL in men and <13 g/dL in women), epoetin alfa therapy should be resumed at a dosage of 30,000 U sc once weekly and titrated in increments of 5000–10,000 U to 40,000 U once weekly [69].

In an open-label, randomized, multicenter study of HCV-infected patients who developed anemia (hemoglobin level ≤12 g/dL) during the first 24 weeks of IFN-α/Rbv therapy [69], patients were randomly assigned to receive either epoetin alfa (40,000 U sc once weekly) or nonpharmacologic management of anemia (Rbv dose reduction or discontinuation or blood transfusions). Patients in the epoetin alfa group could also receive these nonpharmacologic management measures as necessary. The primary end point measured was change from baseline hemoglobin level, and the secondary end point was change in Rbv dose. At weeks 2, 4, 8, 12, and 16, hemoglobin levels were higher in the epoetin alfa group than in the group in which Rbv dose reduction alone was used (P ≤ .01; figure 3). In addition, the percentage of patients who were able to main-
Figure 3. Mean hemoglobin levels among hepatitis C virus–infected patients receiving epoetin alfa or no adjunct therapy (ribavirin [Rbv] discon-
tinuation or dose reduction only) for treatment-induced anemia. In the epoetin alfa group (40,000 U once weekly), the mean hemoglobin level (± SD) at study end was 14.2 ± 1.7 g/dL. In the group not receiving epoetin alfa, the mean hemoglobin level (± SD) at study end was 11.2 ± 1.3 g/dL. These values were found to be significantly different from each other \(P < .01\). Hemoglobin levels at weeks 2, 4, 8, and 12 were also significantly higher in the epoetin alfa group than in the group of patients receiving no adjunct therapy \(P < .01\). Data are from Sulkowski et al. [69]. * \(P < .01\).

tain Rbv dosages >10.6 mg/kg/day was significantly greater in the epoetin alfa group than in the group of patients who were not receiving epoetin alfa \(P < .05\). The mean Rbv dose was significantly greater among patients receiving epoetin alfa than among those who were not receiving epoetin alfa \(P < .05\); figure 4). These findings indicate that the group receiving epoetin alfa had fewer Rbv dose reductions and Rbv therapy discontinuations than the group not receiving epoetin alfa. Quality-of-life parameters, measured by Medical Outcomes Study Short Form scores [71], were higher in the epoetin alfa group, although the study was not powered to demonstrate significant differences in quality of life. Thus, epoetin alfa was effective and well tolerated in anemic HCV-infected patients receiving IFN-α/Rbv therapy. Data reported thus far suggest that maintaining a higher Rbv dosage results in an improved SVR rate, although confirmatory research is warranted [10, 36].

**Granulocyte colony-stimulating factor (G-CSF).** Recombinant human G-CSF (filgrastim [72]), an agent that enhances granulopoiesis in neutropenic patients with cancer who are receiving IFN-α [73], stimulates production of multipotent hematopoietic progenitor cells and mature granulocytes. Although there are no guidelines for the use of G-CSF in the HCV-infected population, the rationale for its use is predicated on its success in patients with cancer who are receiving chemotherapy [74, 75].

A study of the use of IFN-α and G-CSF to treat HCV-infected patients has demonstrated that short-term use of IFN-α can induce G-CSF production. In contrast, long-term use of IFN-α produces a negative feedback effect on G-CSF production [76]. However, it is with use of pegylated forms of IFN-α (especially at higher doses) that higher rates of neutropenia have been observed [10, 33, 41, 42]. Inhibition of granulopoiesis is associated with a decrease in neutrophil count, which can exacerbate immunosuppression and perhaps lead to sepsis, pneumonia, and end-organ compromise. Cancer treatment–related neutropenia (ANC < 500 cells/mm³) typically requires a course of concomitant antibiotics; however, the neutropenia induced by HCV therapy (ANC of 1000–1500 cells/mm³) is typically modest and has not been associated with sepsis [10, 33].

The addition of G-CSF during the course of IFN-α therapy for advanced HCV-associated liver disease has been shown to increase mean and peak WBC counts [77]. With PEG-IFN-α/Rbv combination therapy, dose modifications have been warranted for a few patients who became neutropenic [10, 31, 33]. Clinical experience has demonstrated that a typical dosage of G-CSF is 300 μg sc 2–3 times/week, with dose titration as needed to maintain an ANC of ≥ 750 cells/mm³ [78, 79]. However, controlled trials are warranted to determine the optimal G-CSF dosage. Moreover, the pegylated G-CSF formulation may prove equally efficacious and is convenient, because it is given once weekly [80].

**IL-11.** Recombinant human IL-11 (rhIL-11; oprelvekin [81]) is the only currently approved agent for enhancing platelet production, which it does by stimulating megakaryocytopoiesis [73]. In patients with breast cancer who are receiving chemotherapy, increases in platelet levels occurred 5–9 days after initiation of rhIL-11 therapy [82, 83]. In this population of individuals with cancer, the effective dosage was 25–50 μg/kg/day sc [82, 83]. It should be noted that rhIL-11 does not interact adversely with G-CSF [84].

Dose modification is sometimes required for patients receiving PEG-IFN-α/Rbv combination therapy who become thrombocytopenic; rhIL-11 may be useful in treating this thrombocytopenia and in preventing dose modifications that may decrease...
Figure 4. Use of epoetin alfa treatment to maintain therapeutically optimal ribavirin (Rbv) dosage in hepatitis C virus–infected patients with treatment-induced anemia. In the group of patients receiving epoetin alfa (40,000 U once weekly), the mean Rbv dosage (± SD) at the end of the study (900 ± 238 mg/day) was significantly higher than that in the group not receiving adjunct therapy (707 ± 217 mg/day) (P < .05). Dashed line represents the minimal therapeutic dosage of Rbv (800 mg/day for the average 75-kg patient) [37, 38]. All patients began HCV therapy with IFN-α2b (3 million IU 3 times/week) and Rbv (≥10 mg/kg/day). Data are from Sulkowski et al. [69]. *P < .05.

treatment adherence [10, 33]. Although spontaneous bleeding is very rare in association with HCV therapy, HCV-infected patients are often thrombocytopenic, and further inhibition of platelet production could compromise hemostasis, leading to bleeding episodes that may require platelet transfusions. Experience with rhIL-11 in increasing platelet production has been primarily in patients with breast cancer who are receiving chemotherapy [82, 83]; however, preliminary evidence from a pilot study has indicated that rhIL-11 can increase platelet levels safely in HCV-infected patients with IFN-α–induced thrombocytopenia [85]. Thus, further investigation will be needed to define the role of rhIL-11 in this patient group.

HEMATOLOGIC DISORDERS RELATED TO HCV INFECTION

The influence of HCV infection on the peripheral blood cell count has not been well studied. A recent National Health and Nutrition Examination Survey of HCV-infected individuals in the United States showed that HCV antibody–positive subjects were more likely to have low neutrophil and platelet counts than were HCV-negative individuals, but there was no association between HCV status and anemia [15]. However, independent case studies have demonstrated that patients with chronic HCV infection can develop autoimmune hemolytic anemia in the absence of treatment with IFN-α [12–14, 16]. In these HCV-infected patients, autoimmune hemolytic anemia was reversible with prednisolone therapy [13, 14, 16]. In addition, fatigue, a major symptom of anemia, was recently reported to be the most common extrahepatic complication in HCV-infected patients [86], and, in one study, it was considered by almost one-half (48%) of all untreated HCV-infected patients to be the initial or worst symptom [87].

Anemia of chronic disease (ACD) occurs in association with chronic infections and inflammatory or neoplastic diseases. ACD can be mild or severe (hemoglobin level of 7–12 g/dL) with normochromic/normocytic or normochromic/microcytic RBCs [12]. An inflammatory response, manifesting as increases in levels of TNF-α and IL-1 (which inhibit erythropoiesis), is common among patients with ACD [12]. Patients with HIV infection or cancer typically have bone marrow suppression, which results in ACD [65, 88]. Although it appears that individuals with chronic HCV monoinfection do not demonstrate ACD, it has been shown that HCV can replicate extracellularly, specifically in the bone marrow [89]—the physiologic site of erythropoiesis. Replication of HCV in the bone marrow may also contribute to the etiology of neutropenia and thrombocytopenia observed in HCV-infected patients. One pilot study has shown, however, that HCV infection may result in an increased peripheral clearance or consumption of platelets that is unrelated to autoimmune thrombocytopenia or splenic sequestration [90]. Moreover, this and other small pilot studies have demonstrated that thrombocytopenia in HCV-infected patients is reversed after treatment with IFN-α monotherapy, and this reversal is concomitant to improvement in biological and virologic HCV markers [90–92]. These findings support the hypothesis that HCV infection can itself contribute to thrombocytopenia in the HCV-infected population, but the mechanism is still unclear. Thus, further investigation is warranted to determine the mechanisms by which hematologic disorders are elicited by HCV infection.
CONCLUSION

Due to the slow course of HCV-related liver disease, the burden of comorbidities in patients chronically infected with HCV will have a large impact over the course of the next 30 years. The most effective treatment for HCV infection is combination therapy with (PEG)IFN-α and RBV. The eradication of HCV is possible; however, treatment adherence and dose maintenance are essential. Both IFN-α and RBV induce hematologic disorders that may exacerbate or compound an already fragile hematologic state in the HCV-infected individual and may compromise treatment adherence. Therapies (e.g., epoetin alfa) to counter these disorders (e.g., anemia) have been successful in allowing the maintenance of critical doses of RBV and thus providing optimal HCV treatment that should improve adherence and treatment success. Although this effect is less studied, it appears that HCV infection itself can also induce neutropenia and thrombocytopenia, and benefits may also be gained through the use of G-CSF and rhIL-11 to normalize hematopoiesis, either alone or in the setting of (PEG)IFN-α/ RBV combination therapy.

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