

Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Hynicka LM. et al. (2013) Anemia management in patients with chronic viral hepatitis C. <i>Annals of Pharmacotherapy</i> , 47(2):228-236			
Date of Review:	March 15, 2015			
Reviewer(s):	Christine Hu			
Part A				
Category:	Basic Science <input type="checkbox"/> Clinical Science <input type="checkbox"/> Public Health/Epidemiology <input type="checkbox"/> Social Science <input type="checkbox"/> Programmatic Review <input checked="" type="checkbox"/>			
Best Practice/Intervention:	Focus: Hepatitis C <input checked="" type="checkbox"/> Hepatitis C/HIV <input type="checkbox"/> Other: anemia _____ Level: Group <input checked="" type="checkbox"/> Individual <input type="checkbox"/> Other: _____ Target Population: HCV patients _____ Setting: Health care setting/Clinic <input checked="" type="checkbox"/> Home <input type="checkbox"/> Other: _____ Country of Origin: USA _____ Language: English <input checked="" type="checkbox"/> French <input type="checkbox"/> Other: _____			
Part B				
	YES	NO	N/A	COMMENTS
<i>Is the best practice/intervention a meta-analysis or primary research?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Review of all relevant studies, meta-analyses, systematic reviews, guidelines and review articles to summarize the current strategies for management of anemia associated with antiviral treatment in chronic hepatitis C patients
<i>Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No mentioning of results used for decision-making.
<i>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>Are the best practices/methodology/results described applicable in developed countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methodology and results can be extended to various countries to conduct similar review.
	YES	NO	N/A	COMMENTS
<i>Are the best practices/methodology/results described applicable in developing countries?</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>The research study/tool/data dictionary is easily accessed/available electronically</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Subscription or payment required for download from http://aop.sagepub.com/
<i>Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? Please go to Comments section</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>How is the research study/tool funded? Please go to Comments section</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No funding mentioned
<i>Is the best practice/intervention dependent on external funds?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Other relevant criteria:</i> _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	- Anemia more commonly associated with the use of ribavirin, telaprevir and boceprevir in HCV treatment
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
<i>Are these data regularly collected?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Search of literature from January 1980 to October 2012
<i>Are these data regularly collected at and/or below a national level?</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Are these data collected manually or electronically?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Electronically: MEDLINE/PubMed, EMBASE, and Cochrane databases
RESEARCH REPORTS				
<i>Has this research been published in a juried journal?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Annals of Pharmacotherapy</i>

<i>Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Existing data
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Anemia Management in Patients with Chronic Viral Hepatitis C

Lauren M Hynicka, Emily L Heil

Chronic viral hepatitis C (HCV) is a major cause of morbidity and mortality in the US. It is estimated that between 2.7 million and 3.9 million people living in the US are chronically infected with HCV and that annually it is responsible for approximately 12,000 deaths.¹ The burden of complications from chronic HCV is increasing in the US, with models predicting a doubling in the number of cases of decompensated cirrhosis and primary liver cancer by 2020, with a 2- to 3-fold increase in deaths.² The most recent surveillance data indicate that mortality from HCV has now surpassed that from HIV, further demonstrating the need for patients to receive optimal treatment.³ The anticipated financial impact of chronic liver disease complications, deaths, and health care utilization and costs is substantial.⁴ Chronic HCV is

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OBJECTIVE: To review the literature regarding current strategies for the management of anemia associated with treatment for chronic viral hepatitis C (HCV) in adults.

DATA SOURCES: The MEDLINE/PubMed, EMBASE, and Cochrane databases were searched (January 1980–October 2012) for articles in English using the search terms anemia, ribavirin, dose reduction, erythropoietin stimulating agents, hepatitis C, HIV, liver transplant, telaprevir, and boceprevir.

STUDY SELECTION AND DATA EXTRACTION: All relevant original studies, meta-analyses, systematic reviews, guidelines, and review articles were assessed for inclusion. References from pertinent articles were examined for additional content not found during the initial search.

DATA SYNTHESIS: Standard of care for patients infected with HCV genotype 1 now requires a triple therapy regimen including an HCV NS3 protease inhibitor. These regimens lead to significantly higher rates of anemia compared to prior dual therapy regimens. Development of an optimal management strategy should begin with risk stratification. Ribavirin dose reductions have been recommended in the package inserts for the pegylated interferon products and studies have demonstrated the need for maintenance of 80% of the initial ribavirin dose to achieve optimal sustained virologic response (SVR) with dual therapy. The use of erythropoietin-stimulating agents has been shown to be effective for anemia caused by peginterferon and ribavirin without compromising SVR rates. Limited data have been published regarding the management of anemia with triple therapy; however, efficacy studies for boceprevir and telaprevir have used ribavirin dose reduction and erythropoietin-stimulating agents to successfully manage anemia.

CONCLUSIONS: Anemia is a common adverse event associated with the use of ribavirin, and, more recently, the new HCV protease inhibitors. Ribavirin dose reduction should continue to be used as an initial anemia management strategy, with the use of erythropoietin alfa 40,000 units once weekly reserved for patients whose hemoglobin does not adequately respond to initial management strategies.

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curable. The goal of therapy is to achieve a sustained virologic response (SVR), which is defined as an undetectable viral load 24 weeks after completion of therapy. SVR predicts undetectable HCV RNA, improvement in liver inflammation, and a decrease in decompensated cirrhosis, primary liver cancer, need for liver transplantation, and liver-related mortality rates.

Standard of care for chronic HCV, prior to May 2011, included dual therapy with weekly pegylated interferon injections and twice-daily oral ribavirin for 24 or 48 weeks depending on the infecting HCV genotype. There are 6 HCV genotypes worldwide. HCV genotype 1 is responsible for 70% of HCV cases in the US and is the most difficult to treat, with an SVR of less than 50% with standard of care. The HCV NS3 protease inhibitors boceprevir and telaprevir received Food and Drug Administration (FDA) approval in May 2011. With the advent of these therapies, patients with chronic HCV genotype 1 will receive standard of care with a 3-drug regimen. The addition of either boceprevir or telaprevir to ribavirin and pegylated interferon increases the SVR rates to 63-75% in treatment-naïve patients and 21-67% in treatment-experienced patients, a significant improvement over SVR rates seen with dual therapy.⁵⁻⁹

Despite the potential for increased SVR rates with triple drug therapy, HCV NS3 protease inhibitor regimens pose several challenges for patients and clinicians. Rates of anemia with dual therapy are estimated to be between 20% and 30%, whereas in patients treated with telaprevir and boceprevir, anemia rates are as high as 39% and 49%, respectively.⁶⁻⁹ The anemia is most closely linked to ribavirin, which produces a dose-dependent hemolytic anemia that is reversible within 4-8 weeks of drug discontinuation.¹⁰ However, peginterferon may also contribute to anemia via bone marrow suppression and likely blunts the ability for patients who develop ribavirin-associated hemolytic anemia to achieve compensatory reticulocytosis.¹⁰ The magnitude of the anemia observed with triple therapy is also profound, with an average decrease in hemoglobin of approximately 4 g/dL in clinical trials, compared to a decrease of approximately 3 g/dL seen with dual therapy.¹¹

Various strategies have been described in the literature for the management of anemia associated with treatment of chronic HCV, but no consensus exists regarding the optimal management strategy. Strategies for anemia management include ribavirin dose modification, administration of an agent to stimulate erythropoietin production, or transfusions. The goal for anemia management is maintenance of the hemoglobin level above 10 g/dL, symptom mitigation, and ability to continue ribavirin therapy. With the likelihood of an increased need to treat patients with chronic HCV, an understanding of anemia management will be essential for pharmacists. Here, we review the literature on

the management of anemia related to the treatment of chronic HCV.

Data Sources and Selection

The MEDLINE/PubMed, EMBASE, and Cochrane databases were searched (January 1980-October 2012) for articles in English using the search terms anemia, ribavirin, dose reduction, erythropoietin-stimulating agents, hepatitis C, HIV, liver transplant, telaprevir, and boceprevir. All relevant original studies, meta-analyses, systematic reviews, guidelines, and review articles were assessed for inclusion. References from pertinent articles were examined for additional content not found during the initial search.

Risk Factors for Developing Anemia

Development of an optimal strategy for the treatment of ribavirin-induced hemolytic anemia is critical in the management of these patients. Identifying risk factors for the development of anemia would allow clinicians to target the population who may require more intensive monitoring and more aggressive treatment strategies. Several studies have identified patient characteristics that seem to be predictive of anemia development, which include age, female sex, baseline hemoglobin level, baseline platelet count, baseline creatinine clearance, decrease in hemoglobin of 2 g/dL or more after 2 weeks of treatment, haptoglobin phenotype, and plasma concentration of ribavirin.¹²⁻¹⁶

A more recent and intensely studied area for risk factors associated with the development of ribavirin-associated anemia is genetic variability in inosine triphosphate pyrophosphatase (ITPA), which encodes a protein that hydrolyses inosine triphosphate (ITP). Several gene mutations lead to ITPA deficiency and an accumulation of ITP in red blood cells.¹⁷ Several studies have shown that individuals with ITPA deficiency receive protection from the hemolytic anemia induced by ribavirin.¹⁷⁻²⁵ The ability to predict which patients do not have ITPA deficiency may aid in the identification of those with increased risk for the development of hemolytic anemia; however, optimal use of these data has not yet been determined.

Ribavirin Dose Reduction

Traditionally, dose reduction has been a key strategy to combat the anemia seen in patients with chronic HCV receiving ribavirin as treatment. The package inserts for peginterferon alfa-2b/ribavirin recommend ribavirin dose reduction by 200 mg/day or to 600 mg/day when the hemoglobin decreases to less than 10 g/dL in patients without cardiac risk factors.^{26,27} When this strategy is used, hemoglobin increases by approximately 1 g/dL.¹¹ Discontinuation of therapy is recommended if hemoglobin decreases to

less than 8.5 g/dL, regardless of cardiac risk factors. Ribavirin is a critical component in the drug regimen for the treatment of chronic HCV genotype 1. A study by McHutchison and colleagues in patients with chronic HCV genotype 1 demonstrated that taking greater than 80% of ribavirin and pegylated interferon doses for more than 80% of the duration of therapy also enhanced the rates of SVR.²⁸

Development of a ribavirin analogue has also been discussed throughout the literature. Analogues that have been evaluated in trials include viramidine and taribavirin. Both analogues have shown significantly lower rates of anemia compared to ribavirin; however, they also have lower SVR rates and, as a result, this strategy has been abandoned.^{5,29-31}

Erythropoietin-Stimulating Agents

Given the association of maintaining ribavirin dosage and improved SVR rates with dual therapy, an alternative to ribavirin dose reductions is the use of recombinant human erythropoietin. Recombinant human erythropoietin (epoetin alfa) is the biosynthetic form of the endogenous hormone erythropoietin that stimulates marrow progenitor cell survival, proliferation, and maturation.³² Darbepoetin alfa is a long-acting form of epoetin alfa that has a longer half-life and requires less frequent dosing. It is theorized that the erythropoietin-stimulating agents work to combat the anemia associated with HCV therapy by overcoming the bone marrow suppression caused by peginterferon to allow increased reticulocytosis. Use of these agents is not without risk; they carry a black box warning related to cardiovascular events. Detailed information about the trials discussed can be found in Table 1.³³⁻³⁸

After small, nonrandomized studies suggested that epoetin alfa was effective in increasing hemoglobin in patients developing anemia while receiving interferon and ribavirin.^{39,40} Dieterich et al. performed a larger randomized study to assess once-weekly epoetin alfa, in addition to minimizing ribavirin dose reductions, for anemia in HCV-infected patients.³³ Patients receiving ribavirin capsules plus interferon alfa-2b recombinant injection whose hemoglobin was 12 g/dL or less during the first 24 weeks of therapy were randomized to an epoetin alfa treatment group or to receive standard of care with ribavirin dose reduction/discontinuation and blood transfusions. Patients coinfecting with HIV were excluded from the study. The primary efficacy end point was change in hemoglobin level between treatment groups at week 16. The secondary end point was change in ribavirin dosage. A quality of life analysis was also performed using the 12-Item Short Form (SF-12) questionnaire and the linear analog scale assessment (LASA) scale.

At weeks 2, 4, 8, 12, and 16, hemoglobin levels for patients receiving epoetin alfa were significantly higher than

at study entry and significantly higher compared to hemoglobin levels in the standard-of-care group. The mean decrease in ribavirin dosage from study entry to week 16 was 34 mg/day in the epoetin alfa group, compared to 146 mg/day in the standard of care group ($p = 0.060$). In a post hoc, categoric intent-to-treat analysis, significantly more patients receiving epoetin alfa treatment maintained ribavirin daily dosages above 800 mg, compared with patients receiving the standard of care (83% vs 54%, respectively; $p = 0.022$). Although the study was not powered to demonstrate statistically significant differences in quality of life, at week 16, improvements in quality of life as measured by changes in LASA scores were greater for patients receiving epoetin alfa. This change was specifically noted in the energy score change and activity score change.³³

There were no statistically significant differences in adverse events between patients in the epoetin alfa treatment group and the standard-of-care group. At week 36, using the patients' last available viral load, 69% of patients in the epoetin alfa group and 60% of those in the standard of care group had undetectable HCV RNA (p value not significant). Overall, epoetin was well tolerated but did not have an effect on improving response to ribavirin and interferon alfa therapy.³³

As a follow-up to the Dieterich et al. study, Afdhal and colleagues performed a prospective randomized controlled trial to assess whether epoetin alfa could correct anemia, maintain ribavirin dose, and improve quality of life in HCV-infected patients receiving combination therapy.³⁴ Patients with a hemoglobin level of 12 g/dL or less at the time of randomization (a mean of 12-14 weeks into dual therapy) were randomized to receive epoetin alfa 40,000 units subcutaneously once weekly or placebo for an 8-week parallel-group phase. This was followed by an 8-week, open-label, modified crossover phase. Patients who were in the epoetin alfa group and had a hemoglobin increase of at least 1 g/dL to the blinded epoetin alfa therapy in the first phase were continued on epoetin alfa. Patients in the placebo arm were initiated on epoetin alfa in the parallel-group phase if their ribavirin dose was reduced or they ended the first phase with a hemoglobin level of 12 g/dL or less. Ribavirin was given as a weight-based dose and was adjusted at the investigator's discretion according to the hemoglobin change.

A total of 185 patients were randomized in the double-blind phase of the study and 160 patients continued on to the open-label phase. A significantly greater number of patients in the epoetin alfa group than in the placebo group had a ribavirin dose at the end of the double-blind phase that was greater than or equal to the ribavirin dose at the start of HCV therapy (77% vs 46%; $p < 0.001$). Patients from the placebo group who were initiated on epoetin alfa in the open-label phase of the study experienced a significant increase in the mean ribavirin dose from the end of the

Table 1. Select Studies of Epoetin Alfa for Anemia in HCV

Reference	Design	Population	Treatment	Primary Outcome Results	Secondary Outcome Results
Dieterich (2003) ³³	Open-label, randomized, parallel-group	HCV-infected pts. treated with ribavirin and interferon alfa-2b with Hb levels ≤ 12 g/dL during first 24 weeks of therapy	Epoetin alfa 40,000 units once weekly (n = 36) vs standard of care with ribavirin dose reductions/discontinuation and blood transfusions (n = 28); epoetin alfa withheld if Hb increased to > 14 g/dL (women) and > 16 g/dL (men), and restarted at 30,000 units when Hb decreased to < 13 g/dL (women) and < 15 g/dL (men)	Mean increase in Hb levels at week 16: 2.8 ± 1.8 g/dL in epoetin alfa group vs 11.4 ± 1.3 g/dL in standard-of-care group (p < 0.0001)	Mean Hb level at week 16: 13.8 ± 1.8 g/dL in epoetin alfa group vs 11.4 ± 1.3 g/dL in standard-of-care group (p < 0.0001); mean ribavirin dose at week 16: 891 mg/day in epoetin alfa group vs 779 mg/day in standard of care group (p = NS)
Afdhal (2004) ³⁴	Randomized, placebo-controlled (8-week double-blind phase followed by 8-week open-label phase; placebo pts. crossed over to epoetin alfa)	HCV-infected pts. on ribavirin and interferon therapy who developed Hb ≤ 12 g/dL at time of randomization	Epoetin alfa 40,000 units once weekly (n = 93) or placebo (n = 92); epoetin alfa titrated to 60,000 units once weekly if Hb not increased by 1 g/dL after 4 weeks of treatment; ribavirin doses adjusted at investigator's discretion	More pts. in the epoetin alfa group maintained randomization ribavirin dose (88%) vs placebo (60%); p < 0.001	Mean ribavirin dose at end of double-blind phase: 949 [212] mg/day in epoetin alfa group vs 852 [238] mg/day in placebo group (p not determined); mean Hb levels at end of double-blind phase: 13.0 ± 1.3 g/dL for epoetin alfa group vs 10.9 ± 1.1 g/dL for placebo group (p < 0.001)
Shiffman (2007) ³⁵	Open-label, randomized, controlled	Treatment-naïve pts. with HCV genotype 1 beginning treatment with peginterferon alfa-2b and ribavirin	Group 1 (n = 48): standard weight-based ribavirin (~13.3 mg/kg/day); group 2 (n = 49): standard weight-based ribavirin and epoetin alfa 40,000 units/week; group 3 (n = 49): high-dose ribavirin (~15 mg/kg/day; starting doses 200 mg/day higher than standard dosing) plus epoetin alfa 40,000 units/week In groups 2 and 3, epoetin alfa initiated when HCV treatment was started if baseline Hb level was < 15 g/dL, or when Hb level decreased to < 15 mg/dL during treatment; doses were adjusted to maintain Hb level at 12-15 mg/dL	Rates of SVR between group 1 and group 2: 29% vs 19% (p = NS), but rate of SVR significantly greater in group 3 (49%; p < 0.05); rate of relapse: 8% in group 3 vs 38% for groups 1 and 2 (p < 0.05)	Group 2 had significantly fewer pts. vs group 1 with decline in Hb level to < 10 g/dL (9% vs 34%; p < 0.05) and ribavirin dose reductions (10% vs 40%; p < 0.05)
Falasca (2010) ³⁶	Observational	Chronic HCV pts. undergoing treatment with peginterferon alfa-2a or -2b plus ribavirin with at least a 2 log decline in HCV RNA during the first month of therapy, ≥ 2.5 -g/dL Hb drop from baseline, and Hb level < 11 g/dL	Epoetin beta (n = 22) 30,000 units once weekly or ribavirin dose reduction to 600 mg/day (standard of care; n = 20)	SVR rates: 81.8% in epoetin beta group vs 45% in ribavirin dose reduction group (p = 0.03)	Mean corpuscular volume of erythrocytes was statistically lower in epoetin beta group vs ribavirin dose reduction group at 4 weeks, end of treatment, and after 6 months (p < 0.001)
Bertino (2010) ³⁷	Longitudinal, prospective, randomized, open-label, controlled	Genotype 1b HCV pts. undergoing treatment with peginterferon alfa and ribavirin	Epoetin alfa 10,000 units twice weekly (n = 67) vs ribavirin dose reduction to 800-1000 mg/day (n = 67)	SVR rates in epoetin alfa group were 59.7% vs 34.4% in dose reduction group (p < 0.01)	End of therapy Hb level: 13.8 ± 1.2 g/dL in epoetin alfa group vs 11.5 ± 0.8 g/dL in dose reduction group (p value not determined)
Younossi (2008) ³⁸	Open-label cohort	Chronic HCV pts. undergoing treatment with peginterferon alfa-2b and ribavirin	Pts. with anemia (Hb ≤ 10.5 g/dL) received darbepoetin alfa 3 µg/kg every 2 weeks titrated to achieve a Hb level of 12 mg/dL (n = 41)	Mean Hb level at time of darbepoetin alfa initiation: 10.2 ± 0.4 g/dL; after 81 days Hb level increased by 1.9 ± 1.0 g/dL to 12.1 ± 1.1 g/dL (p < 0.0001)	Pts. receiving darbepoetin alfa had improved vitality domain on Short Form-36 quality of life score

Hb = hemoglobin; HCV = hepatitis C virus; SVR = sustained virologic response.

double-blind phase ($p < 0.001$). In addition, significant improvements in quality of life as measured by the LASA score and SF-36v2 were demonstrated in the epoetin alfa group. There was no statistically significant difference in the proportion of patients with undetectable HCV RNA at the end of the double-blind phase and the open-label phase. The authors concluded that epoetin alfa 40,000 units once weekly for HCV patients with anemia who were receiving treatment with ribavirin and interferon allows maintenance of the ribavirin dose, improves quality of life, and increases hemoglobin levels.³⁴ Both the Dieterich et al. and Afdhal et al. studies excluded patients with anemia attributable to iron deficiency; however, iron status was evaluated during the study periods and patients could receive iron supplementation as necessary.

The preemptive use of epoetin alfa at the start of peginterferon and ribavirin treatment was studied by Shiffman and colleagues to determine whether SVR could be improved.³⁵ Treatment-naïve patients with genotype 1 HCV were randomized to 1 of 3 groups: group 1 was peginterferon plus standard-weight ribavirin, group 2 was peginterferon plus standard-weight ribavirin plus epoetin alfa 40,000 units weekly, and group 3 was peginterferon plus high-dose ribavirin plus epoetin alfa 40,000 units weekly. High-dose ribavirin was, on average, 15.2 mg/kg/day; the starting doses were 200 mg/day greater than the traditional weight-based doses.

The rates of SVR were not statistically significantly different between group 1 and group 2 (29% vs 19%), but the rate of SVR was significantly greater in group 3 (49%; $p < 0.05$). The preemptive use of epoetin alfa did not enhance SVR when used with the standard starting doses of ribavirin. The authors of this study suggest that dose reductions of ribavirin should be the first response to anemia, unless the patient develops rapid, severe anemia that could not be overcome by dose reduction alone, in which case epoetin alfa would be beneficial.³⁵ Since the publication of the Shiffman study, 2 other studies have demonstrated improvements in SVR rates when erythropoietin-stimulating agents were utilized.^{36,37}

Darbepoetin alfa was assessed in an open-label cohort study of patients receiving peginterferon/ribavirin treatment.³⁸ Forty-one patients in the cohort developed anemia and received darbepoetin; however, 9 patients discontinued ribavirin therapy due to persistent anemia despite darbepoetin use. Patients receiving darbepoetin had clinically significant improvements in health-related quality of life, demonstrated by a more than doubling in the vitality domain score of the SF-36.

The cost-effectiveness of epoetin for anemia management in hepatitis C is controversial. A Markov cost-effectiveness model was used to estimate the costs of treating anemia in a model 50-year-old patient with genotype 1 HCV.⁴¹ The investigators determined that the small gains

in SVR rates and quality of life were overshadowed by the high cost of erythropoietin therapy. A decision analytical model was constructed to estimate the cost of treatment for hepatitis C in patients who did and did not develop anemia, and as a secondary outcome to estimate the costs of using epoetin alfa for the treatment of anemia.⁴² The model showed that the incremental cost of treating hepatitis C decreased when ribavirin dose reduction was used to treat anemia, and increased by 5.7% in genotype 1 patients when epoetin was used. The model revealed that the proportion of genotype 2 and 3 patients who respond to epoetin is greater than the proportion of genotype 1 patients who respond, making epoetin more cost-effective in genotype 2 and 3 patients.

The use of erythropoietin-stimulating agents is effective for anemia caused by peginterferon and ribavirin and also improves quality of life during treatment. However, the data regarding the effects of erythropoietin-stimulating agents on SVR are inconclusive. Neither epoetin nor darbepoetin is FDA approved for treating anemia in patients with HCV. The use of these agents also adds another parenteral drug to the patient's treatment regimen and is associated with additional costs and potential for more adverse effects.

Special Populations

The management of anemia in patients coinfecting with HIV is challenging, as HIV-infected patients have a higher incidence of anemia with ribavirin treatment than do patients who are not HIV infected.⁴³ To address anemia management in the HIV/HCV coinfecting population, Vispo and colleagues performed a prospective, multicenter, open-label study assessing preemptive erythropoietin therapy in which HIV/HCV coinfecting patients were randomized to receive either pegylated interferon alfa-2a 180 µg/wk plus ribavirin 1000-1200 mg/day or pegylated interferon alfa-2a 180 µg/wk plus ribavirin 2000 mg/day along with weekly epoetin alfa 30,000 IU for the first 4 weeks of therapy.⁴⁴ At the planned 4-week interim analysis, 149 patients had completed 4 weeks of therapy. The percentage of patients who achieved a rapid virologic response was similar in the high- and standard-dose ribavirin arms (22% and 21%, respectively). The mean drop in hemoglobin in the standard ribavirin group was -2.4, compared with -1.8 in the high-dose ribavirin plus epoetin alfa arm ($p = 0.06$). There was no significant difference in the incidence of severe anemia between the high-dose and standard-dose ribavirin arms (3.3% vs 6.6%; $p = 0.4$), and ribavirin plasma trough concentrations were comparable in both groups (2.4 vs 1.9 µg/mL; $p = 0.2$). The full results of the trial are unpublished at this time; however, the study supports an interesting hypothesis that the preemptive use of epoetin alfa could enhance ribavirin sequestration in erythrocytes from plasma by increasing the number of red blood cells.

The association of anemia with treatment outcomes in HIV/HCV coinfecting patients was studied in a retrospective analysis⁴⁵ of the SLAM-C (Sustained Long-Term Antiviral Maintenance with Pegylated Interferon in HCV/HIV Coinfecting Patients) study (ACTG A5178), which was a prospective, controlled hepatitis C treatment trial. Of the 329 patients enrolled in the trial, 40% developed anemia, with a median hemoglobin decrease of 2.2 g/dL at week 4. Of the patients who developed anemia, 45% were started on an erythropoietin-stimulating agent, with 17% receiving the agent prior to experiencing a drop in hemoglobin that met the study definition of anemia (<11 g/dL for men and <10 g/dL for women). Only 27% of patients completed the study without needing modification of their ribavirin dose; however, SVR rates were similar in those with or without anemia (23% vs 30%; $p = 0.17$). There was no evidence of association between anemia or erythropoietin-stimulating agent use and overall treatment response. In a multi-covariate model, age greater than 40 years, lower body mass index, zidovudine use, and lower baseline hemoglobin levels were significant predictors of anemia in the coinfecting population.

Other special populations at greater risk for developing anemia during hepatitis C treatment include patients with significant cardiac risk factors and those who have undergone liver transplant. In studies of hepatitis C therapy, anemia has not been associated with significant cardiovascular events, but this is likely the result of careful patient selection and the exclusion of patients with significant cardiovascular risk factors. The erythropoietin-stimulating agents carry a black-box warning for increased risk of serious cardiovascular events when administered to achieve hemoglobin levels greater than 11 g/dL. The goal hemoglobin thresholds for epoetin initiation and titration differed in many of the clinical trials. Liver transplant patients are at a higher risk of anemia with hepatitis C treatment due to drug-induced bone marrow suppression and renal insufficiency, which can potentiate ribavirin-induced hemolysis.^{46,47} Trial data indicate that as many as 60% of liver transplant patients treated with ribavirin withdraw from the studies secondary to hemolysis.⁴⁸ In these special populations, more intensive monitoring of the patient's laboratory values and symptoms of anemia may be required.

Anemia Management with Direct-Acting Antivirals

To date, available data for management of anemia in patients treated with triple drug therapy come primarily from the clinical trials that were responsible for FDA approval of telaprevir and boceprevir. ADVANCE and ILLUMINATE (Illustrating the Effects of Combination Therapy with Telaprevir) evaluated the efficacy and safety of telaprevir in treatment-naïve and treatment-experienced

patients, respectively.^{6,49} Anemia management in both studies was restricted to ribavirin dose reduction per package labeling, with use of erythropoietin-stimulating agents prohibited. The rate of ribavirin dose reduction was not provided for treatment-naïve patients; however, 46% of treatment-experienced patients required some reduction in ribavirin dose. In ADVANCE and ILLUMINATE, patients developing a hemoglobin level less than 10 g/dL and less than 8.5 g/dL were reported as 36% and 39% and 9% and 6%, respectively. SPRINT-2 (Serine Protease Inhibitor Therapy 2) and RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2) evaluated the efficacy and safety of boceprevir in treatment-naïve and treatment-experienced patients, respectively.^{7,9} Anemia management in both studies included ribavirin dose reduction (3-step protocol) and/or administration of epoetin alfa 40,000 IU/week. The rate and degree of ribavirin dose reduction was not provided; however, 43% and 41-46% of patients in SPRINT-2 and RESPOND-2 received erythropoietin, respectively. In these trials, 49% of patients in SPRINT-2 and 43-46% of patients in RESPOND-2 developed a hemoglobin level less than 10 g/dL. While these data provide some guidance regarding anemia management in the new era of triple therapy management of hepatitis C, numerous details, including degree of ribavirin dose reduction and treatment response related to dose reductions, are lacking.

However, in an abstract presented at the 2012 European Association for the Study of the Liver, data have emerged comparing ribavirin dose reduction and epoetin alfa in the management of treatment-naïve patients receiving combination therapy with peginterferon, ribavirin, and boceprevir.⁵⁰ Patients who had a hemoglobin level of 10 g/dL or less during triple therapy were randomized to ribavirin dose reduction of 200-400 mg or administration of epoetin alfa 40,000 IU once weekly. Second and third dose reductions for ribavirin of 200 mg each were permitted. Treatment-experienced, HIV-coinfecting, and decompensated patients were excluded from the study. A total of 500 patients were randomized, 26.8% of whom were female and 67.4% of whom were African American. The primary end point was SVR and statistical analysis of an intent-to-treat population was performed. Results indicated no significant difference in SVR regardless of the strategy used, with 71% achieving SVR in both treatment groups. Subgroup analyses evaluated SVR rates in African Americans, who historically have lower SVR rates, and again no significant difference was seen, with 53% SVR in the ribavirin dose reduction group and 49% SVR in the group receiving erythropoietin. No significant difference was noted between the 2 treatment groups in terms of adverse events.

Historically, clinicians have been reluctant to decrease ribavirin doses to less than 80% of original weight-based dos-

ing, based on the study by McHutchison and colleagues.^{28,51} While no such data exist for triple therapy regimens, studies have shown the importance of ribavirin, as studies of dual therapy that included peginterferon and telaprevir resulted in SVR rates of only 36%.^{4,52} However, anemia management strategies used in efficacy studies of direct-acting antivirals have been more aggressive in their protocol recommendations for dose reductions of ribavirin. While the protocol for anemia management in these studies has allowed for aggressive dose reductions, the degree of reduction was left up to individual study investigators and details regarding dose reductions and SVR rates have not been published.

Summary

Anemia is a common event associated with the use of ribavirin, and, more recently, the new HCV protease inhibitors telaprevir and boceprevir. The management of anemia poses a significant challenge for clinicians and patients undergoing treatment for HCV. Optimal strategies for management of anemia should begin with risk stratification of patients for the development of anemia. Traditionally, dose reduction has been a key strategy to combat the anemia seen in patients with chronic HCV treated with ribavirin and should remain the initial anemia management strategy in patients treated with triple therapy secondary to the increased cost, increased regimen complexity, and adverse effects associated with initiation of an erythropoietin-stimulating agent. While it is clear that ribavirin is an integral part of the currently available treatment regimens for HCV, it appears that clinicians may be more aggressive with their dose reduction strategies than was previously possible with dual therapy. Additional research regarding the degree of ribavirin dose reduction with triple therapy relative to SVR is needed to further clarify optimal ribavirin dose reduction in anemia management.

An erythropoietin-stimulating agent should be considered when ribavirin dose reductions have not adequately treated the anemia (ie, hemoglobin levels continue to decrease despite dose reductions). Studies of erythropoietin-stimulating agents have numerous limitations; however, erythropoietin alfa 40,000 units once weekly has the most robust evidence for successful treatment of anemia.

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EXTRACTO

Manejo de Anemia en Pacientes con Hepatitis C Viral Crónica
LM Hynicka, EL Heil

Ann Pharmacother 2013;47:228-36.

OBJETIVO: Revisar la literatura publicada sobre estrategias actuales para el manejo de anemia asociada con el tratamiento de hepatitis C viral crónica en pacientes adultos.

FUENTES DE INFORMACIÓN: Las fuentes de datos MEDLINE/PubMed, EMBASE y Cochrane fueron auscultadas desde enero 1980-octubre

2012 para artículos en inglés utilizando los siguientes términos de búsqueda asociados: anemia, ribavirina, reducción en dosis, agentes estimulantes de eritropoietina, hepatitis C, VIH, trasplante de hígado, telaprevir, y bocéprevir.

SELECCIÓN Y EXTRACCIÓN DE INFORMACIÓN: Se evaluaron para inclusión todos los estudios originales, meta-análisis, revisiones sistemáticas, guías y artículos de revisión relevantes. Se examinaron las referencias de artículos pertinentes para contenido adicional no encontrado en la búsqueda inicial.

SÍNTESIS: El estándar de cuidado para pacientes infectados con virus de hepatitis C (VHC) genotipo 1 actualmente requiere un régimen de triple terapia que incluya un inhibidor de proteasa NS3 del VHC. Estos regímenes tienen una tasa de anemia significativamente más alta comparada con los regímenes previos de terapia dual. El desarrollo de una estrategia de manejo óptimo debe comenzar con una estratificación de riesgo. La información del fabricante de los productos de interferón pegilado recomienda reducción de dosis de ribavirina. Estudios han demostrado la necesidad de mantener un 80% de la dosis inicial de ribavirina para lograr una respuesta virológica sostenida (RVS) óptima con la terapia dual. El uso de agentes estimulantes de eritropoietina (ESAs) han demostrado ser efectivos en el manejo de anemia causado por peginterferona y ribavirina sin comprometer las tasas de RVS. Se ha publicado poca información relacionada al manejo de anemia asociada a terapia triple, sin embargo estudios de eficacia para bocéprevir y telaprevir han utilizado reducción de la dosis de ribavirina y ESAs para manejar exitosamente la anemia.

CONCLUSIONES: Anemia es un efecto adverso comúnmente asociado con el uso de ribavirina, y más recientemente los nuevos inhibidores de proteasa de VHC. La reducción en la dosis de ribavirina debe continuar ser utilizada como la estrategia de manejo de anemia inicial y reservar el uso de eritropoietina alfa 40,000 unidades una vez por semana para pacientes cuya hemoglobina no responde adecuadamente a las estrategias de manejo iniciales.

Traducido por Giselle Rivera-Miranda

SOURCES D'INFORMATION: Une recherche de littérature a été effectuée dans les banques de données PubMed, MEDLINE, EMBASE et Cochrane entre les mois de janvier 1980 et octobre 2012 avec les mots-clés suivants: anémie, ribavirine, dose réduite, agents stimulant l'érythropoïèse, hépatite C, VIH, transplantation hépatique, télaprevir, et bocéprevir.

SÉLECTION DE L'INFORMATION ET EXTRACTION DES DONNÉES: Tous les essais cliniques, les méta-analyses, les revues systématiques, les lignes de traitement et les articles de revue ont été évalués. Les bibliographies des articles identifiés ont aussi été revues afin d'obtenir des références additionnelles.

RÉSUMÉ: Les lignes directrices de traitement des patients infectés par le virus de l'hépatite C chronique de génotype 1 recommandent une triple thérapie incluant un inhibiteur de la protéase NS3. Ces triples thérapies sont toutefois associées à une incidence plus élevée d'anémie comparativement aux traitements antérieurs (bithérapie). Le développement d'une stratégie optimale de traitement devrait comporter une stratification des risques. Des modifications de doses de la ribavirine (80% de la dose initiale) sont recommandées dans les libellés réglementaires pour atteindre une réponse virologique soutenue (RVS) lorsque cet agent est utilisé en association avec les interférons pégylés. L'utilisation des agents stimulant l'érythropoïèse a été démontrée efficace pour traiter l'anémie associée avec l'utilisation de la ribavirine et de l'interféron pégylé, sans toutefois compromettre le taux de RVS. Bien que les évidences soient limitées, les études d'efficacité du bocéprevir et du télaprevir ont utilisé des doses réduites de ribavirine et d'ASE pour traiter avec succès l'anémie.

CONCLUSIONS: L'anémie est un effet indésirable fréquent associé à l'utilisation de la ribavirine et des nouveaux inhibiteurs de la protéase contre le virus de l'hépatite C. Des doses réduites de ribavirine en association avec l'érythropoïétine (administrée à raison de 40,000 unités une fois par semaine) sont recommandées pour les patients chez qui l'anémie n'a pas répondu aux traitements initiaux.

Traduit par Sylvie Robert

RÉSUMÉ

Le Traitement de l'Anémie Chez les Patients Atteints d'Une Hépatite C Chronique

LM Hynicka, EL Heil

Ann Pharmacother 2013;47:228-36.

OBJECTIF: Réviser la documentation scientifique évaluant les différentes stratégies de traitement de l'anémie associée à l'hépatite C chronique chez les patients adultes.