

Recombinant Erythropoietin Criteria for Use for Hepatitis C Treatment-Related Anemia

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

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The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Additional information can be found at www.pbm.va.gov and <http://vaww.pbm.va.gov>

Introduction

Hepatitis C virus (HCV) infection is estimated to affect several million Americans and over 170 million people worldwide. Standard treatment for chronic HCV involves an interferon-based preparation and ribavirin for 24 to 48 weeks. Sustained virologic response (SVR), defined as having undetectable virus at 6 months post-treatment, occurs in 54% to 56% of overall patients treated with peginterferon alfa and ribavirin. Anemia is a common adverse effect of hepatitis C antiviral therapy (occurring in approximately 10%-30%), with interferon causing bone marrow suppression and ribavirin causing hemolysis of red blood cells, typically resulting in hemoglobin (Hgb) declines of 2 to 3 g/dL. However, ribavirin dose reduction to manage treatment-related anemia may reduce SVR, though the impact upon SVR of $\leq 20\%$ dose reduction is unclear. Therefore, maintaining a target dose of $\geq 80\%$ of the original ribavirin dose is reasonable. Clearly, early discontinuation of ribavirin results in a significant reduction in SVR. Preliminary data indicates that recombinant erythropoietic growth factors may overcome treatment-related anemia, maintain higher ribavirin doses and increase patient quality of life.

Patient Selection

- a. Before considering the use of erythropoietic factors, patients must initially undergo evaluation for other causes of anemia (e.g. bleeding, nutritional deficiency, hereditary) and should be treated appropriately
 - o Obtain CBC and the following as indicated: peripheral smear, reticulocyte count, B12, folate.
 - o Assess for adequate iron stores. If evidence of iron deficiency is found (ferritin < 50 ng/mL or transferrin saturation $< 20\%$), replete iron prior to therapy and investigate causes of iron deficiency.
 - o Obtain thyroid function tests as thyroid dysfunction may impact response to erythropoietin. Assess for thyroid abnormalities and treat appropriately.
 - o Measurement of endogenous erythropoietin levels is not routinely indicated.

AND

- b. Patient has failed to respond (i.e. severe anemia persists) within 2 weeks after reducing the dose of ribavirin by 200 mg/day from their initial dose.*

AND

- c. Hgb < 10 g/dL or are symptomatic and have Hgb < 11 g/dL.**

AND

- d. Does not have uncontrolled hypertension, known hypersensitivity to mammalian cell-derived products or known hypersensitivity to albumin or polysorbate 80 (with darbepoetin alfa).

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*Although evidence to determine the best indications for erythropoietin are unavailable, use of erythropoietin may be considered prior to dose reduction in the following situations:

- a. Documented evidence of cirrhosis
- b. Post-liver transplantation
- c. HIV co-infection

**Patients with Hgb <12 g/dL with comorbid ischemic cardiovascular disease or hypoxemic pulmonary disease may be considered for erythropoietin on a case-by-case basis.

Goals of Therapy

1. Resolution of severe anemia with target Hgb 12-13 g/dL
2. Maintain target ribavirin dose (\geq 80% of original dose)
3. Reduce need for transfusion and/or hospitalization
4. Increase energy, activity, overall quality of life
5. Enhance treatment adherence

Dosing (Refer to algorithm below)

- Initiate epoetin alfa 40,000 units subcutaneously once weekly. Response should be assessed at least every 2 weeks until Hgb is stable. Darbepoetin alfa 200 mcg subcutaneously every other week is an available alternative to epoetin, though there are no published studies currently available for its use in the setting of antiviral treatment. In addition, the response to darbepoetin is slower than to epoetin.

Epo responders:

- If there is an increase in Hgb >1 g/dL in any 2-week period and the ribavirin dose is at target, decrease the erythropoietic growth factor dose by 25%-50%. Alternatively, in patients who are below their target ribavirin dose, ribavirin dose may be increased without changing the erythropoietic dosing. Monitor Hgb accordingly.
- If there is an increase in Hgb >1 g/dL from baseline after 3-4 weeks and ribavirin dose remains at target, maintain erythropoietic growth factor dose. Alternatively, in patients who are below their target ribavirin dose, ribavirin dose may be increased without changing the erythropoietic dosing. Monitor Hgb accordingly.
- If Hgb >13 g/dL and target ribavirin dose is achieved, hold epoetin/darbepoetin alfa dose and reinitiate with a 25% dose reduction if Hgb <10 g/dL or Hgb <11 g/dL with symptoms. If not at target ribavirin dose, consider increasing ribavirin and continuing epoetin/darbepoetin. If Hgb is \geq 14 g/dL discontinue epoetin/darbepoetin. Monitor Hgb accordingly.

Epo partial response:

- If increase in Hgb 0-1 g/dL from baseline after 4 weeks and iron stores are adequate, increase epoetin alfa to 60,000 units subcutaneously once weekly. For patients on darbepoetin, if increase in Hgb 0-1 g/dL after 6 weeks, increase darbepoetin alfa to 300 mcg subcutaneously every other week. Monitor Hgb accordingly.
- If inadequate Hgb response after 6-8 weeks while on epoetin alfa 60,000 units once weekly or darbepoetin alfa 300 mcg every other week, consider reducing ribavirin dose as needed AND maintain erythropoietic growth factor dose as appropriate. Monitor Hgb accordingly.

EPO Non-response:

- If Hgb continues to fall despite erythropoietic growth factors, ribavirin dose should be reduced or discontinued AND consider maintaining vs increasing epoetin alfa to 60,000 units once weekly or darbepoetin alfa 300 mcg every other week. Monitor Hgb accordingly.
- In erythropoietic growth factors were initiated for symptom relief, and symptoms have failed to respond and the Hgb is adequate, then discontinue erythropoietic growth factors. Monitor Hgb accordingly.

Safety Issues

The most common adverse effects associated with erythropoietic growth factors include fever, headache, myalgia, hypertension, gastrointestinal upset, and injection site reaction.

Pure red cell aplasia (PRCA) in association with neutralizing antibodies to native erythropoietin have been observed in patients receiving recombinant erythropoietic growth factors. As of May 1, 2005, four cases of PRCA, along with neutralizing antibodies to native erythropoietin, have occurred in patients receiving epoetin alfa manufactured by Amgen Inc. and sold by Ortho Biotech. Two of these cases were in chronic renal failure (CRF) patients and two were in patients receiving interferon-based therapy and ribavirin. As of March 2005, there have been five confirmed cases of PRCA with epoetin alfa manufactured and sold by Amgen Inc. and one confirmed case with darbepoetin alfa occurring in patients with CRF. Patients receiving erythropoietic growth factors should be closely monitored for a paradoxical decrease in Hgb and treatment should be discontinued in patients with evidence of PRCA and neutralizing antibodies to native erythropoietin. Substitution with other erythropoietic agents is not recommended since the potential for cross-reaction may occur.

Erythropoietic therapies may increase the risk of cardiovascular and thrombotic events including myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary emboli. In clinical trials, the risk appears increased with higher hemoglobin levels and/or higher rates of hemoglobin rise. The risk of thrombotic events was significantly higher in adults with ischemic heart disease or congestive heart failure receiving epoetin alfa where the target hemoglobin was 14 g/dL. In patients who had a rise in Hgb >1 g/dL during any 2-week period while on recombinant erythropoietin, there was an increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbation of hypertension, congestive heart failure, thrombotic events, and fluid overload. Neurologic symptoms should be monitored closely. Blood pressure should be closely monitored and controlled while receiving recombinant erythropoietin.

Since epoetin alfa single-dose vials and darbepoetin alfa single-dose vials and prefilled syringes do not contain preservatives, the vial or prefilled syringe should only be used once and any unused portion should be discarded.

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Algorithm for use of recombinant erythropoietin for Hepatitis C Treatment-Related Anemia

