

The Role of Erythropoiesis-Stimulating Agents in the Treatment of Anemia

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Correction of Anemia and Impact on Quality of Life

Proper treatment of anemia can improve a patient's quality of life (QOL).^{1,4} The most common treatment option, other than transfusions, for patients with anemia who are not iron or vitamin deficient are the erythropoiesis-stimulating agents (ESAs), which may provide significant improvements in health-related quality of life (HRQOL) (particularly fatigue) for patients with cancer, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), or chronic kidney disease (CKD).¹

In patients with cancer, clinical trials have demonstrated improved QOL scores following ESA treatment for chemotherapy-induced anemia.^{4,8} Furthermore, Sabbatini showed that the relationship between increased hemoglobin (Hb) levels and improved QOL scores may be independent of tumor response.⁷

In patients with CKD, study results have been inconsistent, but several reports have found that treating anemia improves HRQOL^{6,9,11} and that early detection and treatment of anemia may improve several cognitive and physical measures.^{3,11} More specifically, partially correcting anemia may improve memory and sustain attention,¹² energy level,^{6,9,11,13} work capacity,^{9,11} aerobic capacity,¹¹ and immune function.¹¹

Treatment of anemia with ESAs may also decrease transfusion requirements and significantly improve measures of QOL in patients with HIV/AIDS,¹⁴ improve QOL measures in patients undergoing surgery,¹⁵ and improve diabetic retinopathy, macular edema, and QOL in patients with diabetes.¹⁶

While the above studies show the benefits of controlling anemia, it should be noted that the magnitude of these benefits remains unclear, the literature includes conflicting results, and many studies have not used validated tools to measure QOL. There may also be a threshold QOL level that is reached in patients receiving ESAs. The CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) study showed that trying to achieve a target Hb level of 13.5 g/dL (compared with 11.3 g/dL) increased the risk of cardiovascular problems and did not improve QOL.¹⁷

More important than the discrepancies in QOL scores are the numerous studies questioning the safety of ESAs. The most recent study, the TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) study by Pfeffer et al,¹⁸ demonstrated that patients with diabetes and CKD were at greater risk of stroke following ESA administration and no clear benefit was observed. Furthermore, there

Abstract

For those affected by anemia, receiving the proper treatment can improve quality of life. The most common treatment is erythropoiesis-stimulating agents (ESAs), which can provide significant improvements in health-related quality of life for those who have anemia and comorbidities of either cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, or chronic kidney disease. But the guidelines associated with ESAs can cause confusion for those tasked with prescribing them, so it is imperative that clinicians be more cognizant of the treatment recommendations for different patient populations to make the proper treatment decisions. With the multiple safety issues involved in administering ESAs, our institution prefers to err on the side of caution until these concerns are resolved.

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For author information and disclosures, see end of text.

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is a long and growing list of studies^{17,19,24} that are in stark contrast to earlier studies showing the benefit of ESA use in a variety of patient populations. These conflicting data sets have led to numerous changes in guideline recommendations, Medicare policy, and prescription information that make it difficult for health professionals to be certain they are prescribing ESAs correctly.

To help health professionals better understand the issues associated with treating anemia, the remainder of this article will review the current efficacy and safety of the various treatment options for anemia and review the current guidelines/recommendations for the various patient populations vulnerable to anemia.

Treatment Options for Anemia

Iron Supplementation

Iron supplementation is insufficient for acute treatment of symptomatic anemia. However, it is a safe and effective means to treat iron deficiency anemia over the intermediate and long term. In a recent phase 3, randomized controlled trial, patients with CKD stage 5D and anemia on hemodialysis and a stable ESA regimen received either 2 injections of ferumoxytol within 7 days or 200 mg of elemental oral iron daily for 21 days.²⁵ At day 35, intravenous ferumoxytol was associated with an increase in Hb of more than 1 g/dL, which was significantly higher than the 0.5-g/dL increase observed with oral iron supplements. Ferumoxytol and oral iron supplements demonstrated comparable tolerability.

Blood Transfusion

Blood transfusion provides the patient with erythrocytes and Hb sufficient to acutely treat anemia. While very common in acute trauma settings, it has many disadvantages. For example, blood transfusions are associated with increased costs; largely due to longer intensive care unit and hospital stays.²⁶ In addition, exposure to allogeneic leukocytes may trigger an immune response that may be detrimental.²⁶ Transfusions have also been associated with increased risk of blood-borne infections¹⁴ and may also be associated with acute lung injury and volume and iron overload.

Erythropoiesis-Stimulating Agents

Erythropoietin is a glycoprotein hormone produced primarily by the kidneys that stimulates red blood cell production. The 2 most commonly available recombinant ESAs are epoetin alfa (Procrit) and darbepoetin alfa (Aranesp). They are closely related analogs of erythropoietin and have similar efficacy and safety profiles. ESAs provide a convenient means

to treat anemia in a variety of patient populations and reduce the need for costly transfusions.

As stated previously, several clinical trials¹⁷⁻²¹ and meta-analyses²²⁻²⁴ have shown that ESA treatment is not as safe as first assumed. Reports by the US Food and Drug Administration (FDA)²⁷ have addressed many of these concerns, and, where appropriate, changes to the prescribing information have occurred.²⁸⁻³² Recently, the FDA announced that all ESAs are to be prescribed and used under a risk management program, known as Risk Evaluation and Mitigation Strategies (REMS), to ensure the safe use of these drugs.³³ Several guidelines³⁴⁻³⁷ are also available to help clinicians understand the benefits and risks associated with the treatment of anemia.

Due to the recent safety concerns, the use and acceptance of ESAs for treating anemia have declined. This concern for safety is appropriate, but clinicians should not refrain from using ESAs; rather, they need to be aware of the concerns and make appropriate treatment decisions using evidence-based analyses. Following is a review of the efficacy and safety of ESAs, which are indicated for the treatment of anemia in 4 patient populations.

ESAs for Patients With Anemia of Chronic Renal Failure

Efficacy. ESAs increase Hb levels in patients with chronic renal failure (CRF) and anemia. In a 26-week, double-blind, placebo-controlled trial, 118 dialysis patients with anemia (mean Hb 7 g/dL) were randomized to either epoetin alfa or placebo. By the end of the study, Hb increased to approximately 11 g/dL in the epoetin-alfa group and remained unchanged in the placebo group. Similar results were reported in 4 clinical trials in patients with CRF not requiring dialysis.³⁸ The ability to increase the Hb level has not been matched by clear improvements in outcomes other than reduction in blood transfusions and perhaps improved QOL.

Safety. Patients with uncontrolled hypertension should not receive ESAs, and approximately 25% of patients may require an antihypertensive medication (or adjustment) after starting ESA treatment.³⁸ Seizures have been reported in some patients at the beginning of ESA treatment.³⁸ Finally, during hemodialysis, some patients may require increased anticoagulation with heparin to prevent clotting of the artificial kidney. Patients are at greater risk for serious cardiovascular events, stroke, and possibly death if goal levels of 13 g/dL or higher are targeted.^{18,38} Because studies have generally not assessed intermediate levels of Hb targets, it is unclear whether car-

■ **Table 1.** Percentage of Patients Receiving Chemotherapy and Requiring Transfusion^a (pooled data from 6 trials [n = 131])³⁸

Chemotherapy Regimen	On Study ^b		During Months 2 and 3 ^c	
	Epoetin Alfa	Placebo	Epoetin Alfa	Placebo
Regimens without cisplatin	44 (15/34)	44 (16/36)	21 (6/29)	33 (11/33)
Regimens with cisplatin	50 (14/28)	63 (19/30)	23 (5/22) ^d	56 (14/25)
Combined	47 (29/62)	53 (35/66)	22 (11/51) ^d	43 (25/58)

^aLimited to patients remaining in the study at least 15 days.

^bIncludes all transfusions from day 1 through end of the study.

^cLimited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.

^dUnadjusted 2 sided, $P < .05$.

diovascular risk may also be present with targets in the 10- to 13-g/dL range as well.

ESAs for Patients With Anemia Due to Chemotherapy

Efficacy. The main purpose of giving ESAs to patients with anemia and cancer is to reduce the need for transfusion.³⁸ **Table 1** shows the reduced need for transfusion associated with ESA use in patients receiving chemotherapy.³⁸

Safety. **Table 2** lists the changes in survival rates and/or tumor progression that have been observed in patients with cancer receiving an ESA.³⁸ Many of these studies have led to the label changes discussed in the next section. Namely, targeted Hb should not exceed 12 g/dL, and treatment should not begin until Hb levels are less than 10 g/dL.

ESAs for Patients With Anemia Due to Zidovudine-Treated HIV Infection

Efficacy. Four clinical trials in HIV-infected patients with anemia receiving zidovudine (n = 297) showed ESAs to significantly reduce the need for transfusion. In patients requiring transfusions at baseline and receiving an ESA, 43% were transfusion-independent by the second and third months of treatment compared with only 18% in the placebo group.³⁸

Safety. No safety concerns have been observed in zidovudine-treated HIV-infected patients receiving ESAs.³⁸

ESAs for Patients Undergoing Surgery to Reduce the Need for Allogeneic Blood Transfusion

Efficacy. In surgery patients with Hb levels between 10 and 13 g/dL who are unwilling or unable to receive transfusions, treatment with epoetin alfa significantly reduced the need for transfusion (23% of patients given ESAs vs 45% with placebo).

Safety. Patients receiving epoetin alfa and undergoing

orthopedic surgery are at increased risk for deep vein thrombosis (DVT), and DVT prophylaxis is advised.³⁸

Understanding Regulatory Changes for ESA Use

As stated earlier, numerous clinical studies and meta-analyses have questioned the safety of ESAs. The FDA, the manufacturers of ESAs, as well as many professional and regulatory organizations have made adjustments to address these concerns. Below is a summary of the major changes to the prescribing information along with a summary of the guidelines available that address the efficacy and safety of ESAs in different patient populations.

Letters to Doctors

After reviewing safety data with the FDA, the makers of ESAs (Ortho Biotech Products, LP; Amgen Inc) quickly responded with label changes to ensure clinicians prescribe ESAs appropriately. The most recent Letters to Health Professionals regarding the safety of ESAs are the following:

Letter to Health Professional, August 2004²⁸

- Adjust or interrupt dosing if Hb rises more than 1 g/dL in 2 weeks
- Also, target range should be 10 to 12 g/dL. Hb levels should not rise above 12 g/dL and dosing should be withheld if Hb level exceeds 13 g/dL.

Letter to Health Professional, March 2008²⁹

- ESAs shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small-cell lung, head and neck, lymphoid, and cervical cancers when dosed to target an Hb level of 12 g/dL or more.

Letter to Health Professional, March 2008³⁰

- ESAs should not be used in patients with cancer until the Hb level is less than 10 g/dL.

Table 2. Safety Concerns From Randomized Controlled Trials Targeting Hemoglobin Levels >12 g/dL in Patients With Cancer³⁸

Tumor, n	Hemoglobin Target, g/dL	Achieved Hemoglobin (median [Q1, Q3]), g/dL	Primary Outcome	Adverse Outcome in Treatment Arm
Chemotherapy				
Metastatic breast cancer (n = 939)	12-14	12.9 (12.2, 13.3)	12-month overall survival	Decreased 12-month overall survival
Lymphoid malignancy (n = 344)	13-15 (Male) 13-14 (Female)	11.0 (9.8, 12.1)	Proportion of patients achieving hemoglobin response	Decreased overall survival
Early breast cancer (n = 733)	12.5-13	13.1 (12.5, 13.7)	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
Cervical cancer (n = 114)	12-14	12.7 (12.1, 13.3)	Progression-free, overall survival, and locoregional control	Decreased 3-year progression-free, overall survival, and locoregional control
Radiotherapy alone				
Head and neck cancer (n = 351)	≥15 (Male) ≥14 (Female)	Not available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival. Decreased overall survival
Head and neck cancer (n = 522)	14-15.5	Not available	Locoregional disease control	Decreased locoregional disease control
No chemotherapy or radiotherapy				
Non-small-cell lung cancer (n = 70)	12-14	Not available	Quality of life	Decreased overall survival
Nonmyeloid malignancy (n = 989)	12-13	10.6 (9.4, 11.8)	Red blood cell transfusions	Decreased overall survival

Letter to Health Professional, April 2009³¹

- Spontaneous reports of antibody-mediated pure red cell aplasia and transfusion-dependent anemia have been reported in patients with hepatitis C infection who receive treatment with ribavirin and interferon or pegylated interferon and an ESA concurrently. ESAs should not be provided for these patients.

Letter to Health Professional, December 2009³²

- Patients with CKD are at greater risks for death, serious cardiovascular events, and stroke when administered ESAs to target Hb levels of 13 g/dL or more.

Risk Evaluation and Mitigation Strategies

As part of the REMS for ESAs, a medication guide explaining the risks and benefits of ESAs must be provided to all patients receiving ESAs.³³ In addition to the medication guide, the ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs) Oncology program was instituted for healthcare

professionals who prescribe ESAs for patients with anemia and cancer.

Under the ESA APPRISE Oncology program, the manufacturers of ESAs will ensure that only those hospitals and healthcare professionals who have enrolled and completed training in the program will prescribe and dispense ESAs to patients with cancer.³³ The manufacturers of ESAs are also required to oversee and monitor the program to ensure that hospitals and healthcare professionals are fully compliant with all aspects of the program.

Additional detail on the REMS for ESAs is located in the article by Fatodu³⁹ in this supplement.

Guidelines—Patients With CKD

In 2006, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) published guidelines that focused on QOL measures with regard to ESA treatment and stated the targeted Hb levels should be more than 11 g/dL and that occasional levels above 13 g/dL should be

Table 3. Medicare and the Use of Erythropoiesis-Stimulating Agents in End-Stage Renal Disease⁴⁰

Hct Exceeds 39.0% or Hb Exceeds 13.0 g/dL	ED Modifier? ^a (Hct >39.0% or Hb >13.0 g ≥3 cycles)	EE Modifier? ^b (Hct >39.0% or Hb >13.0 g <3 cycles)	GS Modifier? ^c (dosage reduced and maintained)	Action
No	N/A	N/A	N/A	Do not reduce reported dose
Yes	No	No	No	Return to provider for correction. Claim must report either ED or EE
Yes	No	No	Yes	Return to provider for correction. Claim must report either ED or EE
Yes	No	Yes	Yes	Do not reduce reported dose
Yes	No	Yes	No	Reduce reported dose 25%
Yes	Yes	No	Yes	Reduce reported dose 50%
Yes	Yes	No	No	Reduce reported dose 50%

Hct indicates hematocrit; Hb, hemoglobin.

^aDefined as an Hct level that has exceeded 39.0% (or Hb level has exceeded 13.0 g/dL) for 3 or more consecutive billing cycles immediately prior to and including the current billing cycle.

^bDefined as an Hct level that has exceeded 39.0% (or Hb level has exceeded 13.0 g/dL) for less than 3 consecutive billing cycles immediately prior to and including the current billing cycle.

^cDefined as a dosage of epogen or darbepoetin alfa that has been reduced and maintained in response to Hct or Hb level.

Source: Centers for Medicare & Medicaid Services. Monitoring of erythropoietin stimulating agents for beneficiaries with end stage renal disease. http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=11. Accessed January 27, 2010.

expected. The guidelines also stated that there are increased risks if levels above 13 g/dL are continuously targeted.³⁴

In 2007, the KDOQI updated the guidelines³⁵ and stated the following: (1) selection of the Hb target and Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in QOL and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events); (2) in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL; and (3) in dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should be no more than 13.0 g/dL.³⁵

Guidelines—Patients With Cancer

The National Comprehensive Cancer Network (NCCN)³⁶ currently states that ESAs are recommended only for patients given chemotherapy without curative intent. Patients undergoing radiation therapy, or those undergoing chemotherapy with a curative intent, should not receive ESA treatment. Furthermore, the NCCN stated that clinicians are advised to describe to patients the risks and benefits associated with ESAs. Specifically, ESAs are associated with an increased incidence of thrombotic events, decreased survival, and shorter time to tumor progression. Their use, however, can obviate the need

for blood transfusion and produce gradual improvements in fatigue. No targeted Hb level is recommended by the NCCN; however, they recommend an ESA dose that provides the lowest possible Hb level necessary to avoid a transfusion.

In addition, if Hb levels rise more than 1 g/dL over a 2-week period, the dose should be reduced 25% to 50%. The NCCN emphasized that the primary goal of ESA treatment should be to reduce the need for transfusion.

The American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) published guidelines in 2008.³⁷ Their recommendations are stricter than those of the NCCN, and state that ESA treatment for cancer patients with anemia should not begin until Hb levels approach, or are below, 10 g/dL.

Centers for Medicare & Medicaid Services

Patients With End-Stage Renal Disease

Presently, Medicare allows patients to have higher targeted Hb levels (≤13 g/dL); however, if the Hb level remains high for 3 billing cycles, the payment will be removed unless the dose is lowered by 25% or 50% (Table 3).⁴⁰

Patients With Cancer

The Centers for Medicare & Medicaid Services has stipulated that ESA treatment should not begin until Hb levels

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are <10 g/dL in patients with cancer. This recommendation is similar to the ASCO/ASH guidelines and current prescribing information for ESAs in patients with cancer undergoing chemotherapy; however, their focus on the Hb lower limit to start treatment is in contrast with the other guidelines, which focus on upper limits to finish/adjust treatment.⁴¹

The Economics of Anemia Treatment

ESA treatment is very costly. In 2005, Medicare spent more than \$2 billion on ESAs just for patients with end-stage renal disease.⁴² This large sum illustrates that the costs associated with ESA treatment are formidable and the monies involved may be perceived as impacting policy. While the manufacturers of ESAs have worked closely with the FDA to ensure that the products are used properly and safely, they have also sponsored the NKF guidelines—and that may be perceived as influencing the recommendations. As a result, any changes to the guidelines, regulations, or coverage may be perceived as biased. For example, attempts to increase the use of ESAs by keeping Hb target levels high to improve a patient's QOL may be perceived as lobbying on the part of the pharmaceutical industry. At the other extreme, attempts to reduce the use of ESAs by lowering Hb target levels to reduce the risk of cardiovascular events may be perceived as too frugal and potentially depriving patients of QOL benefits.

Conclusion

There have been numerous changes in prescribing information, guidelines, and Medicare policies for the use of ESAs in treating anemia. The good news about these changes is that they illustrate that the system works. Namely, as new safety concerns have been reported in clinical trials, the FDA and the manufacturers of ESAs have quickly addressed these concerns by adjusting dosing instructions where appropriate. Unfortunately, these numerous changes, along with guidelines that are not updated promptly, can be confusing to health professionals. Adding to the uncertainty is that different patient populations with anemia have different dosing regimens. At present, it is imperative for health professionals to be cognizant of both the historical and current treatment options for anemia in different patient populations so that they can make informed treatment decisions.

Currently, prescription information, guidelines, and Medicare policies for treating anemia in patients with cancer are focused on starting therapy at appropriate lower Hb levels (ie, <10 g/dL), whereas in patients with CKD, the focus is on preventing patients from reaching the upper Hb limits (12-13 g/dL). In our practice with nondialysis patients with CKD, we

prefer to start ESA administration when the Hb level is less than 10 g/dL and stop when Hb levels of 10 to 11.5 g/dL are achieved. Furthermore, the main purpose of treating anemia in our practice is to avoid blood transfusion and improve QOL. This is in contrast to other studies that have shown early initiation of ESAs (at Hb levels of 10-11 g/dL rather than <10 g/dL) was associated with faster achievement of optimal Hb level, lower transfusion requirements, and maintained QOL.⁹ However, until the safety issues with ESAs are better resolved, our institution prefers to err on the side of caution.

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