REVIEW

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Maximizing response to erythropoietin in treating HIV-associated anemia

ABSTRACT

Anemia, a common complication of HIV infection, is associated with morbidity and shortened survival. HIV-associated anemia can often be corrected with erythropoietin (EPO) therapy, which is safer than blood transfusion. Because the response to erythropoietin may be impaired by a number of treatable factors, all HIV patients with anemia should undergo careful evaluation for these factors. This article reviews evaluation and treatment strategies to maximize response to EPO and thus limit the need for blood transfusion.

KEY POINTS

In HIV-infected patients, erythropoietin (EPO) is preferable to blood transfusions, which accelerate the progress of disease and suppress the immune system.

Treating deficiencies of micronutrients and androgens maximizes the response to EPO.

Zidovudine monotherapy is associated with anemia.

Even with careful attention to risk factors, the reason for suboptimal response to EPO may not be identified in a small proportion of patients with HIV-associated anemia.

ERYTHROPOIETIN (EPO) can often alleviate or cure the anemia associated with human immunodeficiency virus (HIV) infection, but unfortunately, a number of factors can impair the response to EPO. These factors must be identified and managed before EPO therapy is initiated.

Treating anemia reduces fatigue, enhances quality of life, and improves survival,[1–5] and early treatment with EPO can prevent the need for risky blood transfusions.[5–7]

This review examines the pathogenesis and clinical results of anemia in HIV infection and presents strategies for maximizing the response to EPO.

PREVALENCE OF HIV-ASSOCIATED ANEMIA

The prevalence of anemia varies, affecting up to 30% of patients with asymptomatic HIV infection and as many as 90% of those with advanced HIV disease.[1,3] Although highly active antiretroviral therapy (HAART) appears to be associated with a somewhat lower risk of anemia, anemia remains common in the HAART era.[3]

PATHOGENESIS OF HIV-ASSOCIATED ANEMIA

The pathogenesis of anemia in HIV infection is multifactorial.[4,8,9] The principal causes of anemia may differ with the stage of HIV disease, and these causes should be identified to select the most appropriate therapy and determine whether the patient is likely to respond well to EPO.

The causes of anemia in HIV infection fall into five broad categories:

- Increased destruction of red blood cells

- Direct or indirect suppression of red cell production
- EPO deficiency or unresponsiveness to EPO
- Micronutrient deficiencies
- Blood loss.

Increased destruction of red blood cells

Hemolysis may be caused by treatment with sulfa drugs, deficiency of glucose-6-phosphate dehydrogenase, bacteremic sepsis, thrombotic thrombocytopenic purpura, or disseminated intravascular coagulation.

Positive results on the direct Coombs test (also called the direct antiglobulin test) are very common in HIV infection, but many of these positive test results are benign. Therefore, Coombs-positive hemolytic anemia should not be diagnosed unless hemolysis can be confirmed by other tests (such as the presence of spherocytes on peripheral blood smears, or an increased reticulocyte count when there is no bone marrow suppression, with a high indirect bilirubin level).

Direct or indirect suppression of red cell production

Up to 90% of persons with advanced HIV disease have anemia

Erythropoiesis may be impaired by infiltrating diseases of the marrow, malignancy, drugs, and infections, both bacterial and viral. The mechanism by which infections reduce erythropoiesis is unclear,[9,10] but it has been proposed that the cause is the proinflammatory cytokines produced during the infection.[9,10]

Red blood progenitor cells often show decreased or defective growth in HIV disease; this phenomenon has been attributed in part to HIV infection in the stromal cell layers, which induces these cells to produce cytokines and increases the rate of apoptosis.[11,12,13]

Whether HIV directly infects any of the hematopoietic progenitor cells remains unknown and hotly debated.[11,14–16] Human hematopoietic progenitor cells do in fact express $CD4^+$ receptors and coreceptors, both of which are necessary for HIV to enter the cell, so direct infection is plausible.[14,17–19] Some in vitro experiments suggest that direct infection can occur,[14,17,20] but others do not,[20–21] and supportive clinical evidence is lacking.

It has also been postulated that antibodies to HIV may be directed against some hematopoietic stem cells, thereby contributing to their decreased growth.

The drugs used to treat HIV may also contribute. For example, zidovudine monotherapy is associated in a dose-dependent fashion with anemia and macrocytosis.[6] However, because multiple drug combinations are standard today, it is difficult to identify the role of each drug in HIV-associated anemia.

EPO deficiency or unresponsiveness to EPO

Ordinarily, EPO production rises during anemia, but in some HIV-infected patients, the EPO rise is blunted for unknown reasons. Furthermore, some patients with normal or high levels of EPO have ineffective erythropoiesis.[9,22,23]

Unresponsiveness to EPO has been attributed to the suppressive effects of proinflammatory cytokines or to decreased production of the cytokines necessary for normal erythropoiesis (as occurs in anemia of chronic disease). Support for this theory is provided by the fact that stromal cells (microphages, fibroblasts, and T lymphocytes) are readily infected by HIV-1, and when infected, they produce less granulocyte colony-stimulating factor and interleukin 3.[11–13]

Micronutrient deficiencies

Deficiencies of iron, vitamin B_{12}, and folate may develop in HIV-infected patients as a consequence of malabsorption or protein-calorie malnutrition.[24,25]

Blood loss

Gastrointestinal bleeding may be overt or occult.

Symptoms of blood loss can occur when many blood samples are drawn for laboratory tests. Patients who are frequently hospitalized are especially at risk.

EFFECTS OF ANEMIA IN HIV DISEASE

Large studies of HIV-infected patients confirm that anemia is a strong independent predictor of death.[2,3,26–28] Mocroft et al[3] found that severe anemia was also associated with a much faster rate of HIV disease progression.

Uncorrected anemia results in multisystemic disabling symptoms and fatigue, increased risk of HIV dementia, and poor quality of life.[5,29–31]

PROBLEMS WITH BLOOD TRANSFUSIONS

Before the availability of recombinant EPO, the mainstay of anemia therapy in HIV infection was blood transfusion. Although effective, blood transfusions carry risks such as hepatitis C virus transmission and allergic reactions.

Worse, they have deleterious effects that are specific to patients with HIV infection. In HIV-infected patients, blood transfusion increases risk of death, accelerates progression of HIV disease, suppresses T cell numbers, increases the incidence of opportunistic infections, and increases the risk of transmission of cytomegalovirus.[7,32,33] In addition, blood transfusion decreases the activity of natural killer cells, monocytes, and helper T cells, with the cumulative effect of suppressing the immune system.[32,33]

Thus, avoiding blood transfusion is desirable in HIV-infected persons, and identifying factors that impair response to EPO is a subject worthy of continued exploration.

Unfortunately, blood transfusions must still be used to correct anemia in HIV-infected patients who have a suboptimal response to EPO or who cannot afford EPO.[6,7]

BENEFITS OF RECOMBINANT EPO

Using recombinant EPO to correct HIV-associated anemia improves survival and quality of life and reduces the need for potentially harmful blood transfusions.[2,3,5,6,31]

Revicki et al[5] used EPO in 251 patients with AIDS and anemia (defined as hematocrit < 30%), and found that those whose hematocrit rose above 38% reported having more energy and better health perceptions, home management, and role function than did those with lower hematocrits.

A 4-month study of 221 patients with HIV infection and anemia (defined as hemoglobin < 11 g/dL) showed that anemia correction was associated with significant improvements on a total quality of life score and a physical well-being subscale score.[31] The improvements were independent of changes in $CD4^+$ counts and of the baseline hemoglobin level.

Unfortunately, the response to EPO therapy is variable.[5,6,30,34–36] EPO therapy results in lower-than-targeted hematocrits in as many as 60% of HIV-infected patients.[5,6] Revicki et al[5] reported that only about one third of EPO-treated patients with HIV infection achieved the target hematocrit of 38% after 24 weeks.

WHEN TO BEGIN EPO THERAPY

Neither the hematocrit at which EPO treatment should be started nor the target hematocrit has been established. Currently, most clinicians start EPO treatment only after the hematocrit falls below 30%, but evidence from studies of anemia-induced morbidity in other patient populations suggests that patients might benefit more if treatment were started earlier.

Pending further studies, I recommend a threshold hematocrit of 33% and a target hematocrit of 38%. Adult patients should be started on 40,000 U of EPO subcutaneously once a week, with dose reductions as hematocrit increases.

I recommend starting EPO if the hematocrit falls below 33%

MAXIMIZE RESPONSE WITH A THOROUGH EVALUATION

Before starting EPO, conduct a thorough evaluation to identify the immediate cause of the anemia and any factors that will impair the response to EPO. Continue to monitor the response throughout the treatment period.

History and physical examination

A comprehensive baseline history and physical examination may help reduce the number of laboratory tests needed. Possible non–HIV-related causes of anemia, such as sickle cell disease, should be ruled out.

The physician should also document all previous and current drug use (including prescription drugs, over-the-counter drugs, and alternative medicine products). Zidovudine is known to be associated with anemia,[32] but the effects of other HIV drugs and drug combinations are not clear and require further study.

Laboratory testing

Helpful laboratory procedures include stool testing for occult blood, examining the peripheral blood smear, and taking a reticulocyte count. Measuring endogenous EPO may also be helpful (see next section).

Testing for iron

Iron deficiency impairs the response to EPO in any patient population, including HIV patients. To evaluate iron stores, test for transferrin saturation, ferritin levels, and total iron-binding capacity. Transferrin saturation below 20% or ferritin below 100 ng/mL are considered inadequate.

Absolute iron deficiency is uncommon in HIV infection, except in cases of substantial blood loss.[4,8] However, some patients with HIV infection may have functional iron deficiency, a failure to mobilize iron to marrow sites for erythropoiesis despite the presence of adequate iron stores. Because this condition is not detected by commonly measured indices of iron availability, distinguishing it from absolute iron deficiency is difficult except by bone marrow biopsy.

IV iron therapy impairs the immune system and should be avoided in HIV patients

Oral and intravenous iron therapy. If patients on EPO have an unexplained failure to respond to therapy, oral iron supplements may be tried. However, intravenous iron should be avoided because it impairs the immune system and increases the risk of infection.[37–45] No data are available about the specific risks of intravenous iron in HIV patients, but a study of hemodialysis patients[8] found that those who received intravenous iron for 4 to 6 months had a 35% higher risk of death from infection than did those who received iron for 1 to 3 months. Also, repeated doses of intravenous iron dextran increase hepatic deposition,[45] and excess hepatic iron may promote viral hepatitis infection.[38]

Testing for other micronutrients

Deficiencies of vitamin B_{12} or folate also impair EPO response. Although many HIV-infected patients have low serum vitamin B_{12} levels,[46] anemia attributable to vitamin B_{12} deficiency is uncommon, and megaloblastosis is rare. Furthermore, using parenteral vitamin B_{12} to treat HIV-infected patients with low serum vitamin B_{12} is often ineffective.

Testing for hypogonadism

Hypogonadism, a common disorder in men with HIV infection, may be associated with persistent anemia during EPO therapy. The pathogenesis of this androgen-associated problem is unknown, but androgen replacement therapy may ameliorate anemia in EPO-treated patients.

OTHER PREDICTORS OF RESPONSE TO EPO

Many researchers have sought to identify other predictors of response to therapy with recombinant EPO, but much of the work in this field is still controversial.

Endogenous EPO level

Although some early research suggested that endogenous EPO levels were a strong predictor of response, more recent work has failed to confirm the relationship.

In the original clinical trials of recombinant EPO in patients with HIV infection receiving zidovudine, patients with serum endogenous EPO levels above 500 IU/L had less response to recombinant EPO than did those with lower EPO levels.[6] The authors speculated that elevated EPO levels reflected bone marrow unresponsiveness associated with zidovudine.

But several other studies in zidovudine-treated HIV-infected patients have found no correlation between level of endogenous EPO and response to EPO therapy.[35,47,48] Furthermore, the zidovudine dose is not correlated with the endogenous EPO level, and the proposed relationship between the endogenous EPO level and responsiveness to recombinant EPO is not linear.[6,47] An additional reason for doubt is that no similar inverse relationship is found in patients with renal failure or viral hepatitis.[49,50] Therefore, it is likely that if endogenous EPO levels do in fact predict responsiveness, the relationship is limited to HIV-infected patients treated with zidovudine.

Infection

Coexisting viral or bacterial infection in HIV patients may impair response to EPO.[51,52] However, some patients with HIV infection and persistent febrile illness still respond well

to EPO.[34] The suppressive effect of infection thus may be partial or minimal in some patients and easily overwhelmed by the effects of more critical factors.

Stage of HIV disease

The frequency of different causes of anemia in HIV-infected patients may vary according to the stage of the disease, but several studies confirm that neither the duration of HIV disease nor its severity as assessed by CD4 count affects response to EPO.[5,6,34]

Renal failure

HIV is an important cause of renal failure; renal failure impairs the response to EPO in most patient groups and may also do so in HIV infection.

Detecting renal insufficiency in AIDS may be complicated by HIV-associated wasting syndrome,[24,25] which may result in apparently normal serum creatinine concentrations (from 0.6 to 1.4 mg/dL) even in patients with severe renal failure. For example, a cachectic HIV-infected patient whose body weight is only 50 kg may have already lost more than 50% of renal function even with a serum creatinine concentration of 0.8 mg/dL. In such patients, the only way to detect renal insufficiency is by measuring creatinine clearance.

Risk groups

African-Americans, women, and injection drug users with HIV infection respond less well to EPO. Whether the differences are biological or sociological in origin is not known. African-Americans and injection drug users have an increased incidence of HIV-associated renal failure.[53–55]

Wasting syndrome

Wasting syndrome itself may also impair responsiveness to EPO by causing malabsorption of the nutrients essential for erythropoiesis or inducing direct marrow changes.

Use creatinine clearance, not serum creatine, to estimate renal function in cachectic HIV patients

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