

Anti-Erythropoietin Antibodies and ESA Hyporesponsiveness in Hemodialysis Patients: A Review Article

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Abstract

Background: Anemia is a common complication in chronic kidney disease and is associated with reduced quality of life, worse renal survival, increased morbidity and mortality, and higher healthcare costs. The mechanisms involved in CKD-related anemia are diverse and complex, including decreased endogenous erythropoietin production, absolute or functional iron deficiency, inflammation, increased hepcidin levels, shortened red blood cell survival, and impaired bone marrow response. Erythropoiesis-stimulating agents and iron supplementation remain the main therapeutic approaches, but some patients show poor response despite treatment. This review aims to discuss anemia of chronic kidney disease with special focus on erythropoiesis-stimulating agent hyporesponsiveness, its major causes, clinical consequences, and the role of anti-erythropoietin antibodies as a rare but clinically significant immune-mediated mechanism of ESA resistance.

Conclusion: ESA hyporesponsiveness is a multifactorial problem in patients with chronic kidney disease and hemodialysis. Iron deficiency, infection, inflammation, inadequate dialysis, hyperparathyroidism, malnutrition, medications, and pure red cell aplasia may all contribute to poor response. Anti-erythropoietin antibodies represent an uncommon but important cause of severe ESA resistance, particularly when associated with pure red cell aplasia. Early recognition and systematic evaluation of ESA hyporesponsiveness are essential to optimize anemia management and reduce transfusion requirements.

Keywords: Anti-erythropoietin antibodies; ESA hyporesponsiveness; Chronic kidney disease; Hemodialysis; Anemia; Pure red cell aplasia.

Anemia of Chronic Kidney Disease

Anemia is a common complication in CKD, and is associated with a reduced quality of life, a worse renal survival, an increase in morbidity and mortality, and higher costs. The mechanisms involved in anemia associated to CKD are diverse and complex. They include a decrease in endogenous EPO production, absolute and/or functional iron deficiency, and inflammation with increased hepcidin levels, among others [1].

Anemia may be a risk factor for progression of CKD, including to ESKD. The mechanism for a faster decline in kidney function with more severe anemia is not known with certainty, but might involve low-grade kidney ischemia or effects of underlying inflammation causing both anemia and CKD progression. From animal models of ischemic and nephrotoxic kidney injury, various mechanisms by which erythropoietin might have renoprotective effects have been proposed. These include reduced apoptosis, increased tubular regeneration, decreased caspase activity, and decreased interstitial fibrosis [2].

Patients are most commonly managed with oral or intravenous iron supplements and with erythropoiesis-stimulating agents. However, these treatments have associated risks, and sometimes are insufficiently effective. In recent years, there have been remarkable advances in the treatment of CKD-related anemia, including hypoxia-inducible factor prolyl hydroxylase inhibitors. These agents induce, among other effects, an increase in the production of endogenous EPO, improve iron availability and reduce hepcidin levels [3].

Definition and Prevalence

Most nephrologists use the World Health Organization criteria to define anemia. Anemia is defined by WHO as a hemoglobin concentration <13 g/dL for adult males and postmenopausal females and a hemoglobin concentration <12 g/dL for premenopausal females. However, the WHO definition of anemia does not define goals of treatment among patients on hemodialysis. Multiple studies have shown that, among patients with CKD, including those on hemodialysis, using ESAs to correct hemoglobin to normal increases the risk of adverse outcomes [4].

It is more common in patients with impaired kidney function, especially when GFR falls below 60 mL/min. It is rare at GFRs higher than 80 mL/min, but as the GFR falls, the severity of the anemia worsens and its prevalence increases: almost 90% of patients with a GFR less than 30 mL/min are anemic. An analysis of the cross-sectional data from the National Health and Nutrition Examination Survey in 2007–2008 and 2009–2010 revealed that anemia was twice as prevalent in patients with CKD as in the general population. The prevalence of anemia raised with the progression of CKD: 8.4% at stage 1 to 53.4% at stage 5 [5].

Pathophysiology of Anemia in CKD

The mechanisms of anemia in CKD are multifactorial. While anemia in CKD can result from multiple mechanisms including iron, folate, or vitamin B12 deficiency, gastrointestinal bleeding, severe hyperparathyroidism, systemic inflammation, and shortened red blood cell survival, decreased erythropoietin synthesis is the most important and specific etiology causing CKD-associated anemia [6].

Some CKD patients may also present with a functional EPO deficiency or EPO resistance, where normal range EPO levels coexist with low hemoglobin levels, indicating that the bone marrow response to endogenous and exogenous EPO is blunted in patients with CKD. The mechanisms that have been hypothesized for EPO resistance are various; proinflammatory cytokines are thought to induce apoptosis as well as to have a direct toxic effect via the induction of labile free radical nitric oxide on erythroid progenitor cells [7].

Proinflammatory cytokines are thought to downregulate the expression of EPO receptor on their surface too. It has also been shown that cytokines can induce the production of antagonistic peptides that bind to the EPO receptor and inhibit the EPO-dependent proliferation. Moreover, hepcidin, whose production is enhanced by inflammation, might also contribute to EPO resistance by directly inhibiting erythroid progenitor proliferation and survival. Lastly, neocytolysis is a homeostatic physiological process that leads to selective hemolysis of young circulating red blood cells, that has been found to contribute to resistance in CKD patients receiving exogenous EPO [8].

The search for new therapeutic options for these patients is essential. Some molecules of the HIF system have already been studied as new targets for anemia treatment with a view to increase endogenous EPO production and presumably improve the utilization of iron stores [6].

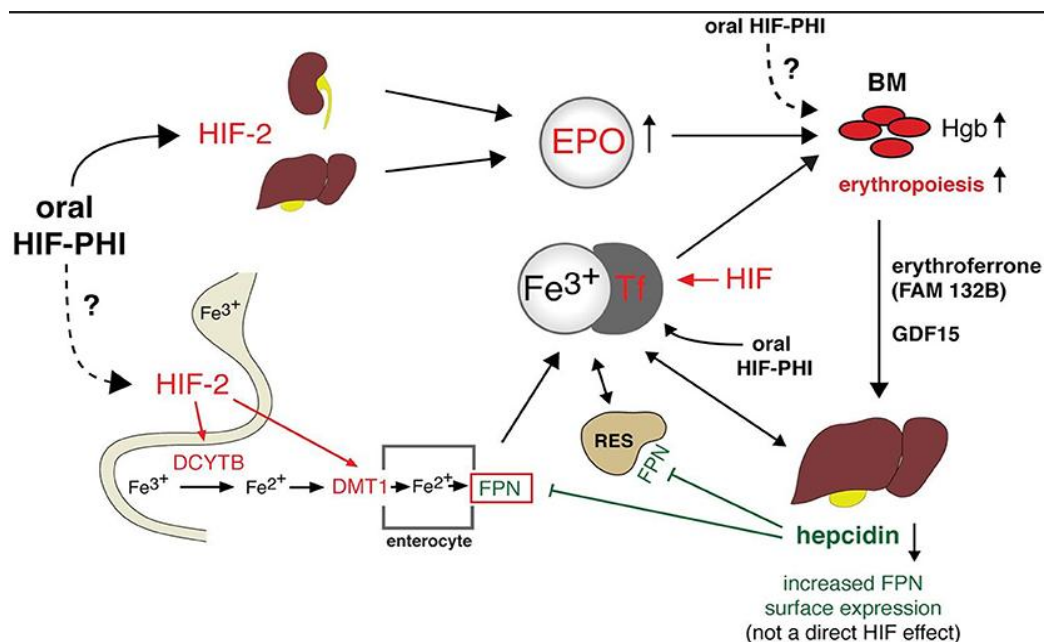


Figure 1: Integrated model for CKD-anemia physiology and actual and potential treatments. HIF, hypoxia-inducible factor; Fe, iron; HIF-PHI, hypoxia inducible factor prolyl hydroxylase inhibitor; EPO, Erythropoietin; Tf, transferrin; DCYTB, duodenal cytochrome b; DMT1, divalent metal transporter 1; BM, Bone marrow; FPN, ferroportin; GDF15, Growth differentiation factor 15; Hgb, hemoglobin; RES, Reticuloendothelial system; FAM132B, Gene that codes for erythroferrone ^[6].

Iron Metabolism and CKD Anemia

Iron is required for an adequate erythropoietic response to EPO, and in anemic conditions having iron deficiency corrected allows lower exogenous EPO supplies. Furthermore, iron is required in other essential non-erythropoietic effects that may help explain symptoms such as impaired exercise performance, cognitive impairment or decreased quality of life, and an increased risk in hospitalization or death in patients with heart failure and reduced ejection fraction, independent of anemia. Thus, these advocate for the need to correct iron deficiencies independent of hemoglobin status ^[9].

Iron supplementation is advised for all CKD patients with anemia. Guidelines generally recommend intravenous iron supplementation as the preferred treatment for CKD patients on dialysis, while both intravenous and oral iron supplementation are appropriate for patients with non-dialysis CKD ^[10].

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

In recent years, new drugs have been developed for the treatment of anemia. These are the so-called HIF-prolyl-hydroxylase inhibitors. These drugs inhibit the action of prolyl-hydroxylase, which leads to an increase in the levels of HIF, and therefore, to an increase in endogenous EPO. There are currently four HIF-PHIs: roxadustat, daprodustat, vadadustat and molidustat. All of them are administered orally. However, they have differences in pharmacodynamics and pharmacokinetics, which probably determine differences in their interaction with the HIF system, and thus lead to differences in efficacy and safety profiles ^[11].

From a mechanistic point of view, the inhibition of prolyl-hydroxylases prevents HIF from degradation, leading to an increase of endogenous EPO within the physiological range, rather than the pharmacological levels achieved by current ESAs. Therefore, the rate of adverse events related to the high EPO levels should be expected to be lower than with ESAs. However, HIF also modulates many other non-erythropoietic genes. This activity would explain the potential beneficial effects seen in pre-clinical and early clinical studies such as improved iron utilization, HDL and LDL lowering effect, ischemia protection, protective effect on CKD progression, improved neovascularization or better blood pressure control ^[12].

Hyporesponse to Erythropoiesis-Stimulating Agents in CKD

ESA hyporesponsiveness is a term used to describe patients who do not achieve the desired hemoglobin concentration despite higher than usual doses of ESAs or who require increasingly higher ESA doses to maintain a target hemoglobin concentration ^[13].

Criteria for ESA hyporesponsiveness are not well defined. Kidney Disease Outcomes Quality Initiative criteria include inability to achieve or maintain a desired hemoglobin concentration using a maximum dose of 450 units/kg per week intravenous erythropoietin or 300 units/kg per week subcutaneous erythropoietin ^[14].

ESA hyporesponsiveness may also be considered when there is no increase in hemoglobin concentration after the first month of appropriate weight-based dosing and/or when the patient requires two increases in ESA doses up to 50 percent beyond the dose at which the patient had originally been stable.

Causes of ESA Hyporesponsiveness

Iron deficiency and infection and/or inflammation are the two most common causes of ESA hyporesponsiveness.

Iron deficiency is a common cause of ESA hyporesponsiveness. Iron deficiency may be absolute, often due to external blood losses, or functional, related to ESA administration or anemia of chronic disease. All patients with ESA hyporesponsiveness should be assessed for absolute and functional iron deficiency ^[13].

Absolute iron deficiency is characterized by a significant reduction or absence of iron stores, whereas functional iron deficiency occurs when iron stores are sufficient, but iron availability for erythropoiesis is impaired, primarily due to elevated hepcidin levels ^[15].

The criteria for diagnosing iron deficiency in CKD differ from those used in individuals with normal renal function. In CKD patients, absolute iron deficiency is defined by a transferrin saturation of $\leq 20\%$ and serum ferritin levels of ≤ 100 ng/mL in pre-dialysis and peritoneal dialysis patients, or ≤ 200 ng/mL in hemodialysis patients. Functional iron deficiency, also referred to as iron-restricted erythropoiesis, is identified by a transferrin saturation of $\leq 20\%$ accompanied by elevated ferritin levels ^[10].

Chronic inflammation is common among hemodialysis patients and is an important cause of ESA hyporesponsiveness. Immune dysregulation and inflammatory activation in CKD are influenced by multiple factors including genetic background, diet, lifestyle, and environmental factors, which represent epigenetic influences. Reduced renal clearance leads to elevated levels of circulating cytokines, though increased cytokine production has also been observed. The uremic environment induces oxidative and carbonyl stress, both of which are strongly pro-inflammatory. Additionally, metabolic acidosis is recognized as a significant contributor to inflammation in CKD ^[16].

Patients with CKD, particularly those undergoing dialysis, are at increased risk of frequent infections and thrombotic events, which further stimulate inflammatory responses. These events include catheter-related bloodstream infections, access site infections, thrombosed intravenous fistulas and grafts, and episodes of peritonitis in peritoneal dialysis patients ^[17].

Uremic toxins have been implicated in contributing to intestinal dysbiosis in CKD, potentially leading to the translocation of gut bacteria and bacterial components into the bloodstream, which can trigger systemic inflammation ^[18].

Inadequate dialysis may cause ESA hyporesponsiveness. However, an increase in the dialysis dose is unlikely to increase ESA response in patients who are already being adequately dialyzed. Changes in the dialysis modality also may affect ESA responsiveness, with beneficial effect of short daily and long nocturnal hemodialysis on anemia and ESA response. The use of ultrapure dialysate has been associated with improved hemoglobin concentrations and reduced ESA requirements. This association is believed to be related to reduced inflammation ^[19].

Other conditions associated with ESA hyporesponsiveness are relatively uncommon. These include severe hyperparathyroidism with osteitis fibrosis cystica, malignancy, bone marrow disorders such as myelodysplastic syndrome and multiple myeloma, and hemoglobinopathies, such as sickle cell disease. Vitamin B12 and folate deficiencies have also been reported in ESA hyporesponsive patients [13].

Pure red cell aplasia is a condition of complete ESA hyporesponsiveness and has been associated with the subcutaneous administration of a particular brand of ESA, which is no longer available [13].

Certain medications may decrease responsiveness to ESAs. Proton pump inhibitor therapy was associated with a higher prevalence of ESA hyporesponsiveness. Some reports suggest that the administration of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists may cause relative ESA hyporesponsiveness, but this does not seem to be clinically important or common [20].

Approach to ESA Hyporesponsiveness

Management of ESA hyporesponsiveness should begin with exclusion of both absolute and functional iron deficiency and treatment with iron, if present. Even in the absence of documented absolute iron deficiency, some patients will have an increase in hemoglobin concentration with additional iron supplementation given intravenously [20,21].

Patients should be adequately dialyzed. Among patients who are not achieving the minimum Kt/V, the dialysis prescription should be modified to increase the amount of delivered dialysis. A careful physical examination should be performed to exclude occult infection, with particular attention to thrombosed arteriovenous grafts. Observational studies suggest that removal of old grafts is associated with improved ESA responsiveness. Among those with a hemodialysis catheter, placement of arteriovenous access and removal of the catheter may also improve ESA responsiveness [20,21].

Optimal parathyroid hormone concentrations should be restored with pharmacologic therapy or parathyroidectomy when indicated. Treatment of hyperparathyroidism improves ESA response. For patients on dialysis with an unknown or untreatable cause of ESA hyporesponsiveness who have symptomatic anemia or require red blood cell transfusions, a trial of hypoxia-inducible factor prolyl hydroxylase inhibitor therapy may be reasonable. In patients with ESA hyporesponsiveness, the ESA can be stopped or continued at a low dose that helps to minimize transfusion requirements with use of transfusions as needed to manage anemia-related symptoms [20,21].

Outcomes of ESA Hyporesponsiveness

ESA hyporesponsiveness is associated with increased mortality. In one observational study of hemodialysis patients in the United States, patients who had hemoglobin <9.5 g/dL and received larger ESA dose changes over an 11-month period had a higher mortality risk [22].

In another study that used data from the Normal Hematocrit Cardiac Trial, a higher erythropoietin-responsiveness measure, defined as the ratio of the weekly hematocrit change per ESA dose increase, was associated with lower mortality. The effect of ESA hyporesponsiveness on mortality among peritoneal dialysis patients has not been well studied. One study from Korea suggested that ESA hyporesponsiveness was associated with higher mortality among hemodialysis patients but not peritoneal dialysis patients [23,24].

Anti-Erythropoietin Antibodies and Pure Red Cell Aplasia

Among the rare but clinically significant causes of ESA hyporesponsiveness is the development of anti-erythropoietin antibodies. These antibodies may interfere with the biological activity of endogenous and exogenous erythropoietin and may lead to severe anemia. The most severe clinical manifestation is antibody-mediated pure red cell aplasia, which is characterized by severe anemia, reticulocytopenia, and marked suppression of erythropoiesis.

Pure red cell aplasia is a condition of complete ESA hyporesponsiveness and has been associated with recombinant erythropoietin therapy. It should be suspected in patients receiving ESA therapy who develop severe

unexplained anemia, loss of response to ESA treatment, and low reticulocyte count after exclusion of other common causes of anemia.

Treatment of anti-EPO antibody-mediated pure red cell aplasia may require discontinuation of ESA therapy, transfusion support, and immunosuppressive therapy. The highest recovery rates were associated with combination of prednisone plus oral cyclophosphamide, and the highest rates of EPO responsiveness on rechallenge were in those patients whose anti-EPO antibody levels were undetectable [25].

The optimal duration of immunosuppressive therapy and monitoring for anti-EPO antibody-mediated PRCA is unknown. However, reasonable recommendations include continuing treatment until antibody levels become undetectable, monitoring hemoglobin weekly to assess transfusion requirement and response to therapy, and monitoring reticulocyte count and anti-EPO antibody levels every one to two weeks during treatment to assess response or lack thereof. Since the majority of patients who respond to treatment do so within three to four months, immunosuppressive therapy should probably be discontinued if there is no response within this time [26].

With the introduction of biosimilar epoetins and increasing use of unlicensed epoetin products in certain parts of the world, ongoing vigilance must be maintained for new occurrences of anti-EPO antibody-mediated PRCA [27].

Hypoxia-inducible factor prolyl hydroxylase inhibitors are a class of oral drugs that stimulate the production of endogenous erythropoietin and are an alternative option to ESAs for patients with EPO-associated PRCA. However, data on their use in patients with CKD who are not on dialysis remain limited, because the safety of HIF-PHIs in this population has not been established [28].

Conclusion

Anemia of chronic kidney disease is a frequent and clinically significant complication, resulting from multiple mechanisms including reduced endogenous erythropoietin production, iron deficiency, inflammation, hepcidin-mediated iron restriction, and impaired erythroid response. ESAs and iron therapy remain essential in the management of CKD-related anemia, while HIF-PHIs represent a newer therapeutic approach.

ESA hyporesponsiveness is a major clinical challenge and should be approached systematically. Iron deficiency, infection, inflammation, inadequate dialysis, hyperparathyroidism, bone marrow disorders, nutritional deficiencies, medications, and pure red cell aplasia should be considered and corrected when possible.

Anti-erythropoietin antibodies represent a rare but important immune-mediated cause of severe ESA hyporesponsiveness. Their clinical significance is greatest when they cause antibody-mediated pure red cell aplasia, leading to severe anemia and transfusion dependence. Recognition of this condition is important in patients with unexplained loss of response to ESA therapy, particularly when associated with reticulocytopenia. Further studies are needed to clarify optimal diagnostic and therapeutic strategies for anti-EPO antibody-associated anemia in hemodialysis patients.

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