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Review Article

Anemia of Chronic Kidney Disease

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Abstract

Anemia of chronic kidney disease(CKD) is a complex pathophysiological disorder which causes a significant increase in morbidity and mortality, cost of care, and decrease in quality of life. Anemia of CKD results primarily from decrease in total iron and accessible iron, as well as a relative decrease in erythropoietin. The effect of the chronic inflammatory state associated with CKD results in a number of detrimental effects on iron handling. There are important open questions in the management of anemia of CKD, particularly the parameters for use of iron repletion, the appropriate targets of therapy, and minimization of risks associated with both anemia and its treatment.

Keywords: Anemia, Chronic kidney disease, Erythropoietin, Iron, Iron deficiency, Hepcidin, Hypoxia inducible factor.

Background

Anemia is a state characterized by a reduced mass of red blood cells (RBCs) and hemoglobin (Hgb), resulting in reduced oxygen-carrying capacity and delivery to the body's tissues and organs. The National Kidney Foundation's clinical practice guidelines define anemia as a Hgb concentration lower than 13.5 g/dl for adult men and less than 12.0 g/dl for adult women. Anemia is associated with increased morbidity and mortality, including increased risk of fractures, cardiovascular events, and mortality in outpatients, as well as in cardiac patients [1-5].

Introduction

Renal anemia is a major complication in patients with chronic kidney disease (CKD), particularly dialysis patients. The prevalence of anemia, defined as an Hgb concentration < 12 g/dl in men and < 11 g/dl in women, increased from 1% in patients with an eGFR of 60 ml/min per 1.73 m^2 to 9% at an eGFR rate of 30 ml/min/1.73 m^2 and to 33% for men and 67% for women at an eGFR of 15 ml/min/1.73 m} [6]. Hsu and coworkers studied 12,055 adult ambulatory subjects from health clinics in Boston and monitored the effect of progressively decreasing creatinine clearance and hematocrit. They found that as Glomerular Filtration Rate (GFR) falls below 60 mL/min in men and 40 mL/min in women the hematocrit starts falling as well. Moderately severe anemia (Hct<33%) was common (present in >20% of patients) when GFR was severely depressed (<30 mL/min in women and <20 mL/min in men) [7].

The natural history of anemia in severe CKD and ESRD results in patients with very low Hgb and a dependence on periodic transfusions. Outcomes with the severe anemia in CKD common before the advent of erythropoietin stimulating agents (ESAs) are well documented, and include increased mortality, increased cardiac events, and decreased quality of life [8-12].

Although all causes of anemia must be considered in patients with CKD, the causes of anemia particular to renal disease include decreased renal EPO-producing capacity, shorter lifespan of red blood cells, hypo-responsiveness of erythroid progenitor cells to EPO, malnutrition, and iron deficiency, and other factors, which may include circulating inhibitors of erythropoiesis [13-15].

The most important causes of anemia in CKD involve iron and erythropoietin (EPO). EPO and iron are both vital to erythropoiesis. They are involved at different stages of the process of differentiation and maturation from pluripotent stem cell to erythrocyte. EPO is crucial over an approximately 10- to 13-day period when burst-forming unit–erythroid (BFU-E) cells are transforming into colony forming units– erythroid (CFU-E) that differentiate into proerythroblasts [16,17]. In contrast, iron incorporation into Hgb synthesis is evident during the second, shorter (3– 4 days) stage as erythroblasts develop into reticulocytes [18,19]. Deficiency of iron can impair full hemoglobinization of the RBCs, leading iron deficiency anemia, and thus treating anemia in CKD requires adequate levels of both iron and EPO for proper erythropoiesis.

Iron Handling

In the healthy adult, only 1–2 mg iron per day is absorbed from the intestinal tract, yet the total body stores are about 800- 1000mg. Muscle myoglobin contains about 300 mg of elemental iron, and 600 mg resides in storage within reticuloendothelial macrophages in ferritin. The great majority of body iron, 1,800 –2,000 mg, is incorporated as Hb in circulating erythrocytes [20]. The major transporter protein for Iron is Transferrin. Around 20–25 mg iron/day must be delivered to the bone marrow for synthesis of Hb in new RBCs whereas 20–25 mg iron is returned to macrophages through removal of old RBCs. Yet the total amount of iron bound to transferrin at any moment is only 3 mg. Thus, during normal erythropoiesis, transferrin-bound iron must turn over six to seven times per day. Because of this, access to iron stores in the body is critical for effective erythropoiesis.

Ferritin is a protein that is the chief means of storage of iron within cells. Serum ferritin, in turn, correlates with total body iron stores. Low values of ferritin are associated with decreased iron stores, while elevated levels are seen in patients with iron overload, including those with hemochromatosis or dependence on frequent transfusions. Complicating the use of ferritin as a diagnostic marker of iron stores is its response to inflammatory mediators, as mediated by hepcidin (see below). In inflammatory states in general, and in

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CKD in particular, ferritin levels are typically elevated relative to the level of total body iron stores [21].

Transferrin, on the other hand, is a negative acute-phase reactant; its concentration is low in patients with CKD, especially those on dialysis, because of the chronically inflamed state. In the cytokine milieu in CKD, iron-binding capacity is also likely to average about 220 mcg/dl, versus the normal value, 330mcg/dl. Thus in CKD patients have increased serum ferritins and decreased iron transport capacity.

Hepcidin is a peptide, secreted by the liver, which is a part of the innate immune system, decreasing the availability of iron for invading organisms and thus decreasing their ability to multiply. Hepcidin is induced by markers of infection and inflammatory mediators such as TNF-α, IL-1 and IL-6, as well as by iron overload [22]. Hepcidin decreases availability of iron through multiple pathways (Figure 1). It increases production of ferritin, thus increasing the ability to sequester ironintracellularly. It decreases levels of transferrin, this decreasing the intravascular transport of iron. It decreases the body's ability to absorb iron from the gut or access existing stores of iron by causing the binding, internalization, and degradation of ferroportin, the only means by which iron can be exported from cells, whether from enterocytes involved in iron absorption from the gut, or from macrophages of the reticuloendothelial system or hepatocytes [23]. Hepcidin is elevated in chronic inflammatory state, in particular in CKD and ESRD, leading to a decreased ability to access iron stores in these patients, and an effective iron deficiency.

Absolute iron deficiencyis defined as the percent transferrin saturation (plasma iron divided by total iron binding capacity x 100, TSAT) below 20 percent and the serum ferritin concentration <100 ng/ml[9] [24,25]. However, it is helpful to divide iron deficiency into two parts, total body iron deficiency, as reflected by a low ferritin, and accessible iron deficiency, as reflected by a low TSat. In inflammatory states, because of the actions of hepcidin, there is often an accessible iron deficiency in the presence of a normal or elevated, often markedly elevated ferritin.

Iron and CKD

Iron deficiency is common among CKD patients with anemia. According to data from the National Health and Nutrition Examination Survey 3 study [26], 35%–40% of CKD grade 3–4 patients (men and women) meet the KDOQI criteria for iron deficiency, that is, they have a TSAT <20% and a ferritin level <100 ng/ml[9]. This proportion increases as patients approach the need for dialysis. The increased prevalence of iron deficiency in CKD is related to increased hepcidin in the inflammatory state of CKD, resulting in decreased ferroportin in enterocytes, and thus decreased absorption of dietary iron. In patients on hemodialysis, the prevalence of iron deficiency is still higher, both from an increased severity of chronic inflammation but also from chronic blood loss in the hemodialysis circuit.

Because of the aforementioned decrease in bioavailability of oral iron in CKD, the use of intravenous iron becomes more important. Several studies in CKD patients with or without hemodialysis and anemia has established that in patients who are being treated with an ESA, intravenous iron is more effective than oral iron in raising the Hb level [27-29]. The main risk with intravenous iron has been anaphylactic reaction to dextran the carrier of iron in solution. Because of this risk many have moved to other formulations of intravenous iron, including sodium ferric gluconate complex in sucrose, iron sucrose and ferumoxytol. These formulations have not had significant anaphylactic reactions reported. Sodium ferric gluconate complex in sucrose and Iron sucrose are commonly used in USA. The chief theoretical risk to intravenous iron use is its impact on infections; in animal models of sepsis intravenous iron can worsen sepsis [30-31]. While this has never been established as clinically important in humans, it nevertheless seems prudent to avoid the use of intravenous iron in patients with sepsis. One recent study did demonstrate an association between the bolus dosing strategy of intravenous iron and increased risk of infection, compared with no iron exposure. There was no difference in risk of infection between patients getting maintenance dosing of intravenous iron and patients getting no iron [32].

While the prevalence of absolute iron deficiency is increased in CKD patients, the prevalence of accessible iron deficiency is still higher, again related to elevated hepcidin. The ferritin may be normal or slightly elevated, reflecting relatively low total iron stores in an inflammatory state, may be moderately elevated, suggesting normal total iron stores in an inflammatory state, or may be markedly elevated, pointing to iron overload and/or severe inflammation. Based on literature review, iron deficiency in patients with ESRD probably is rare when serum ferritin is >500 mcg/L but not excluded [33]. Fishbane et al. found that sensitivity of serum ferritin in excluding iron deficiency was 90% at 300 mcg/L and 100% at 500 mcg/L. Serum ferritin levels >100 mcg/L are recommended for patients with CKD and >200 mcg/L for dialysis patients to prevent absolute iron deficiency [34]. The indication for iron in absolute iron deficiency is clear, but the safety of iron administration with higher levels of ferritin is uncertain. Iron overload is extremely harmful, exemplified by hemochromatosis, which can cause diabetes, cirrhosis, and CHF. Iron overload promotes oxidative stress and inflammation, cardiovascular disease, immune dysfunction, and progression of renal disease. These are insidious and chronic effects, and thus careful long-term RCTs are required to explore fully the effects of IV iron on outcomes in CKD and ESRD populations [35].

While the long-term safety of intravenous iron in CKD patients with higher ferritins has yet to be established, its efficacy in these situations has been proven. The Dialysis patients Response to IV Iron with Elevated Ferritin (DRIVE) study examined the effect of intravenous iron administration in patients with elevated ferritins, between 500 and 1200 [36–38]. The results of the DRIVE study show that IV iron administration results in increased hemoglobin concentrations and decreased dose requirements of ESAs, without any safety concerns through the 12 week course of the study. Based on these results, dialysis patients with low TSat and higher ferritins are now routinely treated with intravenous iron, despite the lack of data on longer-term safety.

Although normal body stores of iron are 800 to 1000 mg, approximately 1000 mg is required among hemodialysis patients to raise hemoglobin levels from approximately 8 g/dL to 11 to 12 g/dL with the initiation of ESA therapy [34]. After target hemoglobin levels are achieved, approximately 250 to 500 mg of iron may be required

every three months to maintain adequate iron stores to support erythropoiesis with ESA therapy.

Based upon the 2005 USRDS Annual Report, approximately 70 percent of hemodialysis patients in the United States received parenteral iron. There are several different approaches to iron replacement in ESRD, including bolus dosing of iron (e.g. 1 gram over 3 weeks) versus maintenance dosing (e.g. 50-125 mg weekly) and high-dose versus low dose (>200 mg/month versus <200 mg/month [39]. Bolus dosing was associated with higher average adjusted hemoglobin (+0.23 g/dL; 95% confidence interval [CI], 0.21-0.26), transferrin saturation (+3.31%; 95% CI, 2.99-3.63), serum ferritin (+151 mg/L; 95% CI, 134.9-168.7), and lower average epoetin dose (-464 units; 95% CI, - 583 to - 343) compared with maintenance. Similar trends were observed with high-dose iron versus low-dose (>200mg/ month vs < 200mg/ month). Iron sucrose was associated with higher adjusted average hemoglobin (+0.16 g/dL; 95% CI, 0.12-0.19) versus ferric gluconate. The limitations in this study were that it had short follow up so the long term safety uncertain. The mean adjusted difference in achieved hemoglobin was only 0.2 mg/dL between groups of patients receiving either high or bolus dosing, and those receiving low or maintenance dosing. This benefit, however, comes at a potential cost, a 2- to 3-fold greater intravenous iron exposure. It remains to be seen if increasing the laboratory parameters with more aggressive use of intravenous iron will result in improved survival from improvement in anemia or increased adverse events from long term toxic effects of iron overload.

EPO and Anemia in CKD

Erythropoietin is a glycoprotein with the main function of stimulating the proliferation and differentiation of erythroid precursors in the bone marrow. It is a 165 amino acid monomeric polypeptide that has one consensus O-linked glycosylation site and three N-linkedconsensus glycosylation sites.EPO has also been shown to be anerythrocyte survival factor, by modulating pro- and anti-apoptotic mechanisms, and apro-angiogenic factor. It has also been associated with wound healing, as well as a protective effect on cardiac and neuronal cells [40-42].

Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor". EPO transcription and release of EPO into the bloodstream are both induced by hypoxic conditions. Theerythropoietin gene has a hypoxia-responsive element, a sequence which induces expression when bound to Hypoxia-inducible factor- 1(HIF-l), a transcription factor, which will be discussed more fully below.

There are two types of EPO receptors, high affinity, high specificity receptors, expressed predominantly on hematopoietic cells, and low affinity low specificity receptors expressed more broadly on non-hematopoietic cells. The high affinity receptors will respond to lower levels of EPO, while the low affinity receptors require a much higher level to induce a response. The non-hematopoieticcells expressing the erythropoietin receptor include those of the female reproductive tract (placental trophoblasts, cervical squamous epithelium, uterine glandular epithelium, endometrium,ovarian follicles), breast (mammary epithelium), prostatevasculature (endothelium), nervous system (neurons, astrocytes,oligodendrocytes, microglia), pancreas (islet cells), and kidney (cortex, medulla, papilla).The erythropoietin receptors expressed on these tissues are functional although their role is not identified [43].The primary effect of EPO, inducing erythropoiesis, is likely induced by binding to the high-affinity receptors, while the other effects may be due to binding to the low-affinity, more broadly expressed receptor.

There are two erythropoietin products currently approved in the U.S. The first approved agent was epoetinalfa, which is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name EPOGEN. The same epoetinalfa product is also marketed and distributed by Ortho Biotech, L.P., a subsidiary of Johnson & Johnson, under the proprietary name PROCRIT. EPOGEN/PROCRIT was licensed in June 1989, with the following indication: "treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis." This was expanded in April 1993 to include asupplemental indication for the treatment of anemia associated with cancer chemotherapy [44].

The second product was darbepoetinalfa, which is manufactured and distributed by Amgen, Inc., under the proprietary name Aranesp. Darbepoetinalfa, an erythropoietin analog, contains two additional N-linked glycosylation sites resulting from amino acid substitutions in the peptide backbone. These additional oligosaccharide side chains increase the molecular weight of the protein from approximately 30 kDa to 37 kDa. Darbepoetin has a three-fold longer terminal half-life than erythropoietin alfa, and a five-fold lower affinity for erythropoietin receptors. Aranesp was licensed in September 2001 with the following indication: "for the treatment of anemia associated with chronicrenal failure, including patients on dialysis and patients not on dialysis". This was expanded in July 2002 to include a supplemental indication for the treatment of anemia associated with cancer chemotherapy [44].

EPOGEN/PROCRIT are first generation and typically have shorter half lives, requiring frequent dosing 1 to 3 times weekly. Darbepoietinalfa, a second generation ESA, has been modified from EPO to give it a longer half life and can be administered once weekly to every two weeks. Recently, a third generation ESA that is modified from EPO by insertion of a large pegylation chain to make it longer acting, called continuous EPO receptor activator (Cera) has been approved for marketing as Miorcera (Roche) [45].

The most common side effects of ESAs include exacerbation of HTN, injection site reactions, seizure, headache, thrombosis, and flu-like illness. Hypertension may be related to increased red cell mass, effects on endothelin, and nitric oxide, and direct effects on vascular smooth muscle cells. Seizure and headache are likely related to elevated blood pressure. Injection site reactions and flu-like illness are likely related to direct reaction to the molecule or carrier [46]. There are some reports of pure red cell aplasia, mainly associated with the use of epoetin beta but reported with other ESAs, related to formation of neutralizing antibodies to native erythropoietin.

Irrespective of the type of ESA used, the goal of therapy is to reduce the morbidity, mortality, and decreased quality of life caused by anemia of CKD. Prior to the development of therapeutic ESA, patients with ESRD generally had severe, transfusion-dependent anemia, with Hgb under 9. This was associated with left ventricular hypertrophy (LVH) and congestive heart failure (CHF), as well as a

markedly decreased quality of life. When Epoetin was introduced, correction of anemia in these patients to 11-12 was found to decrease mortality, decrease morbidity associated with LVH and CHF, and improve quality of life [47-49], precisely as would have been predicted given the proven effects of anemia. With this evidence in hand, the next obvious question is whether complete reversal of anemia would give still more improvement in morbidity, mortality, and quality of life. There have been multiple studies addressing this question (Table 1). The initial study addressing this question, the NORMAL trial, randomized patients on hemodialysis to a target hematocrit of 42% or 30%. The trial was stopped prematurely, unexpectedly showingantrend to increased mortality and myocardial infarction with normal hematocrit compared with hematocrit target of 30% [50]. Other interesting findings were decreasing mortality within each randomization arm as Hgb increased and decreased adequacy of dialysis in the normal Hgb arm. Because of the incongruity of the results with the expected pathophysiological model, the hypothesis of complete reversal of anemia resulting in improvement of outcome was tested again in several studies of patients with CKD.

The CHOIR trial [51] was an open-label, randomized trial to study the risks and benefits of the correction of anemia in patients with CKD who were not receiving dialysis. They studied 1432 patients at 130 sites in the US. 715 were randomly assigned to receive a dose of epoetinalfa targeted to achieve a hemoglobin level of 13.5g/dL and 717 were assigned to receive a dose targeted to achieve a level of 11.3 g/dL. Primary endpoint was a composite of death, myocardial infarction, hospitalization from CHF (without renal replacement therapy) and stroke. A total of 222 composite events occurred with 125 events in the high hemoglobin group as compared with 97 events in the low hemoglobin group (hazard ratio 1.32, 95% CI 1.03 to 1.74; p=0.03). This demonstrates that there is an increased of the primary composite endpoint in the high hemoglobin group as compared to the low hemoglobin group. Death and hospitalization from CHF accounted for 74.8% of the composite events. There was no added improvement in the quality of life in the higher hemoglobin group [51].

The CREATE trial [52] enrolled 605 patients with CKD Stage III and IV (eGFR 25-35 ml/min) at 94 centers in 22 countries. Patients were randomly assigned to an early or a late anemia correction group. The early group received epoetin beta therapy for a target Hgb 13-15g/dL. The late anemia group did not receive epoetin beta until their Hgb<10.5g/dL with aHgb target of 10.5-11.5g/dL. The primary end point was the time to a first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more. At the end of the study, 105 patients had had a CV event, 58 in the higher hemoglobin group and 47 in the lower hemoglobin group (hazard ratio, 0.78; 95% CI, 0.53 to 1.14; adjusted p=0.20). Their results indicate that the early and complete correction of anemia to Hgb levels between 13.0 and 15.0 g/dL has no beneficial effect on the time to a first cardiovascular event. Quality of life was better in the higher Hgb group than in the lower Hgb group and this was maintained for the duration of the study [52].

In contrast, The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [53] is a placebo-controlled double blind randomized study that comprised 4038 patients with diabetes, CKD, and anemia. 2012 patients were randomly assigned to the group to receive darbepoetinalfa to aHgb concentration of >13g/dl and 2026 patients to the group to receive rescue darbepoetinalfa if the Hgb went below 9g/dL. The primary endpoints were the composite outcomes of death or a cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease. Death or a CV event occurred in 632 patients assigned to darbepoetinalfa and 602 patients assigned to placebo (hazard ratio 1.05, 95% CI 0.95-1.19; p= 0.41). There was no overall significant difference in the hazard rates for CV or renal event or in the rates of death, heart failure, myocardial infarction, admission for myocardial ischemia, or end-stage renal disease.It was noted that there was a significantly higher rate of stroke in patients treated with darbepoetin. Fatal and non-fatal strokes occurred in 101 patients assigned to darbepoetin and 53 patients on placebo (HR 1.92, p<0.001). There was a modest improvement in patient reported fatigue in the darbepoetinalfa group as compared to the placebo group.

In CREATE, the hazard ratio for the primary endpoint in the higher hemoglobin arm was 0.78 (95% confidence interval [CI] 0.53 to 1.14), in CHOIR 1.34 (95% CI 1.03 to 1.74), and in TREAT 1.05 (95% CI 0.94 to 1.17), respectively. According to this, targeting a higher Hb concentration with ESAs was certainly not associated with benefit but perhaps increased risk. In TREAT, there was no benefit in terms of hard outcomes. In CHOIR, a higher risk of death and heart failure was observed in patients targeted to a higher Hb (13.5 g/dl), whereas, in TREAT, a higher risk for stroke was observed [50]. CHOIR and CREATE were open-label studies comparing one Hb target with the other, whereas TREAT was double-blind in design that compared darbepoetin against placebo.

The heterogeneity in results from the three trials could be because of the different use of ESAs which have known biologic differences. In CHOIR, epoetinalfa was tested, in TREAT, darbepoetinalfa was used, and in CREATE, epoetin beta was used to target higher Hgb levels. Another reason for the heterogeneity can be the enrollment of different populations. In TREAT, all enrolled patients had diabetes, in CHOIR, approximately half of patients had diabetes, and in CREATE, only 25% of patients had diabetes. All three trials also used different dosages of ESA. In CHOIR, the higherHgbarm received a median of 10,952 U/wk; in TREAT, the median dosage was 8800 U/wk in the darbepoetin arm; and in CREATE, a median dosage of 5000 U/wkepoetinbeta was used in the higher Hb arm [54].

The higher rate of stroke and thromboembolic events and possibly a higher risk for cancer in TREAT with only very modest benefits to quality of life tip the scale in favor of no ESA treatment of anemia in most non-dialysis patients with CKD. However, it is important to point out that patients in the TREAT trial were able to receive rescue therapy with darbepoietin for Hgb<9. Furthermore, the importance of avoiding transfusions in patients with CKD cannot be minimized. Aside from the usual risks of transfusion, patients receiving transfusions are more likely to develop antibodies against HLA proteins, and thus are more likely to have difficulties with renal

transplantation after progression of CKD. With all these factors in mind, it seems clear that ESAs should not be used routinely in patients with CKD, but should certainly be used to prevent symptomatic anemia and need for blood transfusions. KDIGO guidelines recommend individualized therapy based on symptoms, quality of life, and comorbid conditions. Generally, CKD patients should be given ESAs to keep Hgb>9 to prevent need for transfusions, and the target Hgb should be less than 11.5. History of or risk for stroke would increase the bar for initiation of treatment and lower the target, given the increased absolute risk of stroke in patients with history of stroke and receiving ESAs [55]. Patients with active malignancy should be given ESAs only with great caution, particularly when oncologic cure is the goal [55].

Another open question for investigation is the reason why a higher Hgb target would be associated with increased stroke, death, myocardial infarction, and hospitalization for CHF. The worse outcomes could be related to the increased Hgb itself from increased viscosity. This is perhaps less likely given that the treatment target for polycythemia verais a hematocrit less than 45% in males and 40% in females, equivalent to Hgbs of 15 and 14 in men and women respectively [56], well above targets in the high Hgb arms. Furthermore, in the NORMAL and CHOIR trials, outcomes within each arm improved as Hgb increased, suggesting that absolute value of Hgb is not the problem. Patients in the higher Hgb arms were exposed to more iron, and the oxidative stress associated with iron could certainly explain the increased risks above. Alternatively, the increased morbidity and mortality could be related to the increased dosage of ESAs. The increased risk of stroke can certainly be explained by the increased blood pressure associated with use of ESAs; increased blood pressure correlates with increased risk of stroke [57]. Increased blood pressure could explain the other adverse outcomes as well. It is also conceivable that the increased dosage of ESAs leads to increased stimulation of the low-affinity receptors, causing non-hematopoietic effects leading to the worse outcomes. A thoughtful post-hoc analysis of the CHOIR trial suggested that the difference in outcomes between arms remained after adjusting for iron administration but disappeared after adjusting for dose of ESA. This suggests that there may be adverse effects of higher doses of ESAs, or that patients requiring higher doses of ESAs, e.g. those with relative EPO resistance, were more likely to have bad outcomes [58].

The route of administration of ESA has to be taken into account when giving them to patients with CKD. According to Tonelli et al., the subcutaneous route usually results in less frequent injections, reduces ESA requirement and is cost effective than the intravenous route. In addition, the peak level of ESA is much higher when given intravenously. However, many dialysis patients use the intravenous route since it is convenient leaving the subcutaneous route for CKD patients not on dialysis and patients on peritoneal dialysis. In patients who do not adequately respond to intravenous ESA administration despite dose adjustment, consideration should be given to switching the subcutaneous route. In this case, the subcutaneous dose should be reduced by 30% to avoid a sudden rise in the Hgb above target (44).

One key sub-population of concern in CKD patients is those CKD patients who are anemic but ESA-resistant. ESA resistance is defined by the KDIGO guidelines as having no increase in Hgb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing, or requiring 2 increases in ESA doses up to 50% beyond the prior maintenance dose, after a stable treatment with ESA, in order to maintain a stable Hgb concentration [55]. One study found a prevalence of ESA hyporesponsiveness in ESRD of 25% [59]. ESA resistance is a powerful predictor of cardiovascular risk and mortality [60], reproduced by analysis of the TREAT trial [61] and the Normal Hematocrit trial [62]. This may well be due to the comorbidities that cause ESA hyporesponsiveness, but could also be attributed to the higher doses of ESAs administered, as suggested by the reanalysis of the CHOIR trial noted above [51]. The most common cause of ESA hyporesponsiveness is iron deficiency, whether related to absolute iron deficiency or inability to access iron stores due to a chronic inflammatory state. Another fairly common cause of ESA hyporesponsiveness in CKD patients is severe hyperparathyroidism. As always, other causes of anemia must be ruled out, including other vitamin deficiencies, occult bleeding, hemoglobinopathies, and bone marrow disorders. While absolute iron deficiency is easily remedied with IV iron, a decrease in accessible iron due to inflammation and elevated hepcidin can be problematic, given the potential risk of iron administration in the face of greatly elevated ferritin. It can be helpful to try to decrease the inflammatory state, whether by looking for and treating any smoldering infection, e.g. osteomyelitis or periodontitis, or by increasing delivered dose of dialysis to treat subclinical underdialysis. Given the significant prevalence of ESA hyporesponsiveness, its impact on morbidity and mortality, as well as increased costs related to higher doses of ESAs, hospitalization, and transfusions, ESA hyporesponsiveness is an important issue to be addressed.

HIF and Anemia of CKD

Hypoxia-inducible factor (HIF) is a protein which is stabilized in hypoxia and acts as a transcriptional activator critical in local and systemic responses to hypoxia [63]. HIF has two main isoforms of its alpha subunit, HIF-1α and HIF-2α. Under normal conditions, HIF is rapidly hydroxylated by prolyl hydroxylase enzymes, and then ubiquitinated and degraded, while in the presence of hypoxia the prolyl hydroxylase enzymes are inactivated, allowing HIF to remain stable and active as a transcriptional activator via hypoxia response elements.

HIF has two general roles, responding to local ischemia and global hypoxia. In the face of local ischemia, HIF-1α induces transcription of proteins involved in glycolysis and shunting away from the citric acid cycle, thus pushing cells toward anaerobic metabolism, as well as increasing angiogenic factors such as VEGF, to increase local tissue perfusion. As a response to global hypoxia, as manifested by decreased oxygen delivery globally, HIF-2α increases red blood cell production through effects on EPO as well as effects on iron metabolism and handling. The impact of stabilizing HIF-2α through inhibiting prolyl hydroxylases is broad and profound. It directly induces synthesis of EPO, and also has multiple effects on iron handling. It upregulates transferrin and ceruloplasmin, allowing increased plasma transport of iron to tissues [64-67], upregulatesferrochelatase, which inserts iron into heme [68], increases intestinal absorption of iron by upregulating duodenal cytochrome b and divalent metal transporter-1 [69,70], and downregulateshepcidin expression, thus decreasing the multiple effects of hepcidin on iron sequestration [71-73]. Given the multitude

of effects on erythropoiesis, stabilizing HIF-2α holds great promise for the treatment of anemia in CKD. Not only does increased effect of HIF-2α cause a physiologic increase in EPO levels, rather than the supraphysiologic peak seen with ESAs, especially when given intravenously, it also will decrease the sequestration of iron seen in chronic inflammation, and seen so commonly in patients with ESA hyporesponsiveness.

One obvious, if logistically difficult, way to increase HIF-2α effect is to move to high elevations. Winkelmayer et al. showed a graded increase in hematocrit along with a decrease in EPO dose as the residential elevation increased, suggesting increased native EPO synthesis and/or increased ESA responsiveness. Furthermore, they also observed improvement in relative mortality in US patients receiving dialysis as the residential elevation increased, adjusting for multiple other factors, suggesting that increased HIF-2α function improved mortality in ESRD patients [74].While moving CKD patients to high altitudes might improve ESA hyporesponsiveness and mortality rates, is would be more convenient to increase HIF-2α effect pharmacologically. There are currently several molecules in development which block the action of prolyl hydroxylase inhibitors. Because of the impact of HIF-2α on both EPO and EPO responsiveness, these drugs hold out great promise in the treatment of anemia of chronic kidney disease.

Summary

Anemia is a disorder commonly seen in CKD which has significant adverse effects on quality of life, morbidity, and mortality. It is often multi-factorial, but the most common causes of anemia in CKD are from absolute iron deficiency, relative iron deficiency related to inflammation and mediated by hepcidin, and relative deficiency of EPO. Current therapy consists of iron repletion, generally given intravenously, and ESAs. However, the hemoglobin level triggering initiation of therapy and target hemoglobin level with therapy remain uncertain. Although one would expect that a complete remediation of anemia with normalization of Hgb would result in the best outcomes, multiple studies have shown that not to be the case. The reason for this has yet to be elucidated, although it seems most likely related to adverse effects related to higher doses of ESAs. One possible means to improve outcomes related to anemia may lie with stabilization of HIF-1α, which will increase endogenous EPO and improve accessibility of iron stores, thus overcoming a major cause of EPO resistance.

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