Mechanisms of Anemia in CKD

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ABSTRACT

Anemia is a common feature of CKD associated with poor outcomes. The current management of patients with anemia in CKD is controversial, with recent clinical trials demonstrating increased morbidity and mortality related to erythropoiesis stimulating agents. Here, we examine recent insights into the molecular mechanisms underlying anemia of CKD. These insights hold promise for the development of new diagnostic tests and therapies that directly target the pathophysiologic processes underlying this form of anemia.


Anemia was first linked to CKD over 170 years ago by Richard Bright.1 As kidney disease progresses, anemia increases in prevalence, affecting nearly all patients with stage 5 CKD.2 Anemia in CKD is associated with reduced quality of life and increased cardiovascular disease, hospitalizations, cognitive impairment, and mortality.2

Anemia in CKD is typically normocytic, normochromic, and hypoproliferative. The demonstration of a circulating factor responsible for stimulating erythropoiesis, and the kidney as the main source of erythropoietin (EPO) in the 1950s3,4 engendered the hypothesis that EPO deficiency is a predominant cause of anemia in CKD. Purification and cloning of EPO in the late 1970s and 1980s5–7 enabled the development of immunologic assays for quantitating levels of circulating EPO. Although generally normal or slightly increased in anemia of CKD, EPO levels are considered inappropriately low relative to the degree of anemia, because similarly anemic patients with normal kidney function have 10–100 times higher EPO levels.8–10 One important limitation of such assays is that they measure all immunogenic EPO fragments, which do not all correlate with biologic activity.11,12

Anemia management was revolutionized in the late 1980s with the introduction of recombinant human EPO. This and related erythropoiesis stimulating agents (ESAs) greatly benefited patients by improving their debilitating symptoms, and freeing them from dependence on blood transfusions with their associated complications (secondary iron overload, infections, and sensitization impeding transplantation).2,13–15 However, even in the initial studies, adverse effects were noted in patients receiving ESAs, including worsening hypertension, seizures, and dialysis access clotting.14,15 In addition, ESAs do not reduce adverse outcomes associated with anemia, such as mortality, nonfatal cardiovascular events, left ventricular hypertrophy, hospitalizations, and progression of kidney disease, in prospective randomized controlled trials.2 In fact, recent trials in both hemodialysis and predialysis CKD patients demonstrate an increased risk of death, adverse cardiovascular events, and stroke by administering ESAs to target hemoglobin levels >11 g/dl.16–19 Secondary analyses of these studies suggest that elevated hemoglobin per se does not confer the increased risk, but rather higher doses of ESAs and relative resistance to ESAs, although this has not been studied directly.20,21 In addition, ESAs have been associated with increased progression of malignancy and death in cancer patients.22

Why would ESAs have these adverse effects? Although relative EPO deficiency may contribute to the anemia of CKD,23 it is not the sole cause. Indeed, anemia of CKD is resistant to ESAs in approximately 10%–20% of patients.2 It seems likely that supraphysiologic doses of ESAs, especially at very high doses or in patients resistant to treatment, have off-target effects in other tissues. These findings have renewed interest in understanding the molecular mechanisms of anemia in CKD, with the hope of developing new therapies that more closely target the underlying pathophysiology of low hemoglobin.

Aside from EPO deficiency, what else contributes to the anemia of CKD? Numerous studies suggest that circulating uremic-induced inhibitors of erythropoiesis contribute to the anemia, although this has been disputed in some...
hemo-dialysis patients.23 Whereas hemo-dialysis routine use of supplementation in hemodialysis patients historically developed secondary iron overload from recurrent blood trans-fusions, the modern era of ESA treatment has uncovered an increasingly recognized role for disordered iron homeostasis as a major contributor to the anemia of CKD.

Based on its ability to donate and accept electrons, iron is essential for many im-portant biologic reactions, including oxy-gen transport, cellular respiration, and DNA synthesis. However, this same prop-erty makes excess iron toxic by generating free radicals that can damage or destroy cells. Systemic and cellular iron levels must therefore be tightly regulated. The majority of iron (20–25 mg) is provided by recycling from senescent red blood cells, which are phagocytosed by reticuloendothelial macrophages to store iron until it is needed, with lesser amounts provided by dietary absorption in the duodenum (1–2 mg) and release from liver stores. Plasma iron, which circulates bound to transferrin, is relatively limited at 3 mg, and therefore must be turned over several times to meet the daily re-quirements for erythropoiesis. With no regulated mechanism for iron removal, typical iron losses are 1–2 mg daily, mainly from intestinal and skin cell shed-ding and menstruation in reproductive-age women. Systemic iron balance is therefore maintained by regulating dietary iron absorption and iron release from storage sites in the liver and reticuloendo-thelial macrophages.26

CKD patients have increased iron losses, estimated at 1–3 g per year in he-modialysis patients, due to chronic bleeding from uremia-associated plate-let dysfunction, frequent phlebotomy, and blood trapping in the dialysis appa-ratus.23 CKD patients, particularly hemodialysis patients, also have im-paired dietary iron absorption. Indeed, oral iron was no better than placebo and was less effective than intravenous iron at improving anemia, improving or pre-venting iron deficiency, or reducing ESA dose in hemodialysis patients.25 In addition, many CKD patients receive ESAs, which deplete the circulating iron pool by increasing erythropoiesis. Thus, CKD patients are prone to true iron deficiency, and iron supplementation is part of mainstay of anemia treatment in CKD. Intravenous iron is preferred for hemo-dialysis patients because of im-paired dietary iron absorption.2

In addition to true iron deficiency, many CKD patients have functional iron deficiency, characterized by im-paired iron release from body stores that is unable to meet the demand for erythropoiesis (also called reticuloendo-thelial cell iron blockade). These patients have low serum transferrin saturation (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores). Some of these patients are treated with intravenous iron, a trend that seems to be increasing with the recent controversy surrounding ESAs. However, for patients with high serum ferritin ≥500–800 ng/ml, management is less clear.2 Concerns about treating these patients with iron include poor ef-fectiveness and the potential for adverse effects, including oxidant-mediated tis-sue injury from excess iron deposition and increased risk of infection. One limi-tation is that high serum ferritin is not specific for increased body iron stores because ferritin is also affected by infec-tion, inflammation, liver disease, and malignancy.2

Recent data suggest that hepcidin ex cess may account for the impaired dietary iron absorption and reticuloendothelial cell iron blockade present in many CKD patients. Discovered independently by three groups in 2000–2001,30–32 hepcidin is the main hormone responsible for maintaining systemic iron homeosta-sis.26 Produced by the liver and secreted into circulation,30–32 hepcidin binds and induces degradation of the iron exporter, ferroportin, on duodenal enterocytes, reticuloendothelial macrophages, and hepatocytes to inhibit iron entry into the plasma.33 Inflammatory cytokines directly induce hepcidin transcription,26 presumably as a mechanism to sequester iron from invading pathogens, leading to the iron sequestration, hypoferremia, and anemia that are hallmarks of many chronic diseases including CKD.

The development of assays to mea-sure bioactive hepcidin in the last 2–3 years has ignited a profusion of studies investigating the role of hepcidin excess in the anemia of CKD. Numerous stud-ies now show that hepcidin is elevated in CKD patients.26,34–36 Mechanisms sug-gested to account for this are increased expression by inflammatory cytokines and reduced renal clearance.26,34–36 Studies are ongoing to determine whether hepcidin measurement will have diagnos-tic utility in CKD patients regarding iron status, inflammatory status, or ESA re-sponsiveness or resistance. Complicating factors are the lack of uniformity in hep-cidin measurements by different assays,37 and the complex interplay of various fac-tors that influence hepcidin levels in CKD patients, including iron, inflammation, and reduced renal clearance that tend to increase hepcidin, and anemia, ESAs, di-alysis clearance, and hypoxia that tend to reduce hepcidin.26

Recognition of a key role for hepcidin excess in causing the functional iron de-ficiency and anemia of CKD has ignited interest in targeting the hepcidin-ferroportin axis as a new treatment strategy for this disease. By blocking hepcidin and/or increasing ferroportin activity, these agents could improve dietary iron ab-sorption and iron mobilization from the patients’ own body stores, thereby mini-mizing the need for supraphysiologic doses of intravenous iron and ESAs with their potential adverse effects. Im-portantly, in CKD patients with hepcidin excess, large intravenous boluses of iron would be predicted to have limited effec-tiveness because much of the iron is rap-idly taken up by the liver and sequestered, and the remainder that is incorporated into red blood cells would be recycled in-effectively. In addition, intravenous iron itself would further increase in hepcidin
levels and worsen this phenomenon. Several strategies under investigation include antagonizing hepcidin directly, inhibiting hepcidin production, interfering with the hepcidin/ferroportin interaction, or stabilizing ferroportin. Initial small studies suggest that targeting this pathway can increase iron mobilization and hemoglobin in animal models of anemia of chronic disease. The side effect profiles and whether these strategies will prove effective for treating anemia of CKD in humans remain unknown.

In summary, anemia of CKD is a multifactorial process due to relative EPO deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis. Recent work has identified hepcidin excess as a main contributor to the disordered iron homeostasis and anemia of CKD by impairing dietary iron absorption and iron mobilization from body stores (Figure 1). Improving our understanding of the molecular mechanisms underlying anemia of CKD holds promise for developing new pharmacologic agents that more closely target the underlying pathogenic mechanisms of this disease for improved efficacy and reduced treatment-related adverse outcomes.

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DISCLOSURES

J.L.B. and H.Y.L. have ownership interest in a startup company, Ferrumax Pharmaceuticals Inc., which has licensed technology from the Massachusetts General Hospital based on work cited here and described in prior publications.

REFERENCES

14. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM: Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by...