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 pathophysiologic processes of CKD.
Hemodialysis patients.23 Whereas hemodialysis is the main hormone responsible for maintaining systemic iron homeostasis.26,34–36 Studies are ongoing to determine whether hepcidin measurement will have diagnostic utility in CKD patients regarding iron status, inflammatory status, or ESA responsiveness or resistance. Complicating factors are the lack of uniformity in hepcidin measurements by different assays,37 and the complex interplay of various factors that influence hepcidin levels in CKD patients, including iron, inflammation, and reduced renal clearance that tend to increase hepcidin, and anemia, ESAs, dialysis clearance, and hypoxia that tend to reduce hepcidin.26

Recognition of a key role for hepcidin excess in causing the functional iron deficiency 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 absorption and iron mobilization from the patients’ own body stores, thereby minimizing the need for supraphysiologic doses of intravenous iron and ESAs with their potential adverse effects. Importantly, in CKD patients with hepcidin excess, large intravenous boluses of iron would be predicted to have limited effectiveness because much of the iron is rapidly taken up by the liver and sequestered, and the remainder that is incorporated into red blood cells would be recycled ineffectively. 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 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.

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