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MANAGEMENT OF KIDNEY DISEASE AND ITS ASSOCIATION WITH ANEMIA

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ABSTRACT

Chronic kidney disease (CKD) is a major global health issue, with anemia being a frequent and debilitating complication. The impaired production of erythropoietin (EPO) in CKD reduces red blood cell production, contributing to anemia, especially in advanced stages, where prevalence can reach up to 90%. Iron deficiency, common in CKD, worsens anemia due to disruptions in iron metabolism, including elevated hepcidin levels that hinder iron absorption and release from stores, further limiting its availability for red blood cell production. Recent treatment options for CKD-related anemia include erythropoiesis-stimulating agents (ESAs) and hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), both aimed at enhancing red blood cell production. ESAs, like epoetin and darbepoetin, have improved anemia management, with long-acting formulations offering convenience and stable hemoglobin levels. However, challenges such as "therapeutic inertia," where patients do not receive adequate ESA or iron supplementation despite clear indications, and concerns about cardiovascular risks at higher ESA doses, persist. Effective anemia management in CKD requires early detection, iron supplementation, and careful ESA use. Addressing anemia alongside controlling blood pressure and diabetes can enhance patient outcomes, improve quality of life, and reduce healthcare costs. This review examines the pathophysiology of anemia in CKD and evaluates current therapeutic approaches.

INTRODUCTION

Kidney disease is a significant global health issue, profoundly affecting the quality of life and survival rates of millions worldwide. One of its most common and debilitating complications is anemia, which is intricately linked to the progression and management of chronic kidney disease (CKD). CKD, defined by the gradual loss of renal function, impairs the production of erythropoietin, a hormone critical for red blood cell production, leading to anemia in a substantial proportion of patients.[1,3] Recent advances in medical research have introduced innovative therapies, including erythropoiesis-stimulating agents (ESAs) and hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), alongside a renewed focus on managing iron deficiency—a prevalent contributor to anemia in CKD. CKD affects approximately 10% of the global population, equating to about 850 million individuals at various stages of the disease.[4] Alarmingly, 85% of cases occur in low- and middle-income countries, where healthcare systems often struggle to address the growing burden. The impact of CKD is particularly pronounced in older populations. Among individuals over 60, the prevalence of CKD is approximately 26%, with the risk of end-stage kidney disease (ESKD) escalating sharply with age.[5] Over the past 50 years, chronic kidney disease (CKD) has emerged as a significant public health concern due to its steadily increasing global burden. This is reflected in CKD's rise as a leading cause of mortality, moving from 17th place in 1990 to 12th in 2017, and ranking 16th in terms of years of life lost globally. Analysis of the Global Burden of Disease (GBD) data over this period highlights substantial growth: the incidence of CKD rose by 89%, prevalence by 87%, mortality by 98%, and disability-adjusted life years (DALYs) by 62%. Globally, CKD (stages 1–5) affects an estimated 13.4% of the population, with stages 3–5 accounting for 10.6%. According to the International Society of Nephrology's Global Kidney Health Atlas, around 10% of the global population faces a lifetime risk of developing CKD, though prevalence varies widely across regions and countries.[6,7]

Anemia, a common complication of CKD, also shows significant regional variation in prevalence. For example, anemia affects 14% of CKD patients in the United States, 39.36% in India, 51.5% in China, 43.18% in South Africa, and 79% in Cameroon.[8] The prevalence of anemia correlates with the progression of CKD, occurring in 22.4% of patients in stage 3, 41.3% in stage 4, and 53.9% in stage 5. By 65 years, around 3% of individuals require dialysis, a figure that rises to 5% by 80 years, underscoring the urgent need for effective management strategies. CKD also has a strong interconnection with systemic conditions such as diabetes and cardiovascular disease, which are leading causes of morbidity and premature mortality among affected individuals. Diabetes, the primary global driver

of CKD, is projected to rise significantly, particularly in Asia. Between 2000 and 2035, South Asia is expected to see a 150% increase in diabetes prevalence, with China and India emerging as epicenters. Anemia, frequently coexisting with CKD, significantly influences disease progression and patient outcomes. Insufficient erythropoietin production and iron deficiency are the primary causes, leading to fatigue, reduced quality of life, and increased cardiovascular risk. Anemia prevalence rises with CKD severity, affecting up to 90% of patients in advanced stages.[9,12] Effective management of CKD and anemia requires a multifaceted approach, including early detection, optimizing blood pressure and glycemic control, and addressing anemia through iron supplementation and ESAs.[13] Dietary modifications, lifestyle changes, and pharmacological therapies also play pivotal roles in slowing disease progression and improving outcomes. Timely intervention and attention to modifiable risk factors are crucial to alleviating the dual burden of CKD and anemia, enhancing patient quality of life, and reducing the broader socioeconomic impact.[14] This review delves into the complex interplay between CKD and anemia, focusing on their pathophysiological mechanisms and advancements in treatment. A deeper understanding of these relationships enables tailored interventions, ultimately improving health outcomes for individuals with CKD.

PATHOPHYSIOLOGY OF ANAEMIA IN CKD

Erythropoietin dysfunction

Erythropoietin (EPO) primarily produced by fibroblast-like interstitial cells in the kidneys and, to a lesser extent, by hepatic perisinusoidal cells, binds to receptors on erythroid progenitor cells in the bone marrow to stimulate red blood cell survival, proliferation, and differentiation. EPO production is regulated at the transcriptional level, primarily in response to oxygen levels, with hypoxia-inducible factors (HIFs) serving as central mediators. Under hypoxic or anemic conditions, the HIF system activates. HIF1, a complex of HIF1α and HIF1β subunits, regulates the expression of hypoxia-sensitive genes, including the EPO gene. While HIF1β is constitutively expressed, HIF1α is typically degraded under normal oxygen conditions. Hypoxia stabilizes HIF1α, enabling its dimerization with HIF1β. The resultant complex binds to hypoxia response elements (HREs) in DNA, enhancing the transcription of genes critical for oxygen homeostasis, such as EPO, transferrin, vascular endothelial growth factor (VEGF), and endothelin-1. HIF1α stability is oxygen-dependent, regulated by prolyl hydroxylase domain (PHD) enzymes, which hydroxylate HIF1α to signal its degradation via the von Hippel-Lindau (pVHL) complex. Among the three PHD isoforms—PHD1, PHD2, and PHD3—PHD2 is the primary regulator. Under hypoxia, PHD activity decreases, allowing HIF1α to accumulate, translocate to the nucleus, and activate target genes.[14] Factor-inhibiting HIF (FIH) also modulates HIF1α by hydroxylating it, reducing its transcriptional activity. Of the three HIF α subunits (HIF1α, HIF2α, and HIF3α), HIF1α is ubiquitous, HIF2α predominantly regulates renal and hepatic EPO production, and HIF3α generally acts as a repressor. Dysregulation of this system in chronic kidney disease (CKD) impairs EPO synthesis, contributing to anemia.[15] In CKD, alterations in renal oxygen delivery maintain normoxic gradients, preventing adequate HIF pathway activation. Pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β) further inhibit EPO production. Despite these challenges, some CKD patients exhibit partial EPO production under conditions like high-altitude exposure or severe blood loss, where enhanced HIF signaling reactivates dormant EPO-producing cells.[17] Observations indicate that CKD patients at higher altitudes require lower doses of recombinant human EPO (rhuEPO) due to increased endogenous production. EPO resistance, a significant concern in CKD, is characterized by reduced hemoglobin levels despite normal or elevated EPO levels. Mechanisms include inflammation-induced toxicity to erythroid progenitor cells, reduced EPO receptor expression, antagonistic peptide production, hepcidin-mediated erythropoiesis suppression, and neocytolysis (selective destruction of young red blood cells). Emerging therapies, such as HIF prolyl hydroxylase inhibitors (HIF-PHIs), aim to enhance endogenous EPO production by stabilizing HIF1α, offering a novel approach to anemia management in CKD patients. These advancements underscore the intricate relationship between oxygen sensing, hypoxia-responsive gene regulation, and erythropoiesis.[18,19]

Iron metabolism dysfunction

Iron is an essential element for hemoglobin synthesis and plays a critical role in supporting the erythropoietic response to erythropoietin (EPO). Its significance extends beyond erythropoiesis, influencing various physiological functions.[20] In chronic kidney disease (CKD), iron deficiency is a common issue, contributing to reduced quality of life, increased hospitalizations, and prolonged recovery periods. Iron can be obtained from dietary sources, released from internal stores, or salvaged from senescent erythrocytes. However, it is continuously lost through exfoliation of the intestinal epithelium and blood loss. CKD patients are particularly prone to significant iron losses due to uremia and recurrent bleeding episodes.[21] Chronic inflammation in CKD exacerbates iron dysregulation by increasing the production of hepcidin, a key acute-phase protein and master regulator of iron homeostasis. Elevated hepcidin levels inhibit intestinal iron absorption and iron release from macrophages and hepatocytes, leading to functional iron deficiency.[22] Hepcidin is primarily synthesized in hepatocytes near the portal vein, with smaller contributions from macrophages and adipocytes. Its production is modulated by several factors, including hypoxia, anemia, erythropoietin levels, transferrin saturation, and liver iron stores. In CKD, these regulatory mechanisms are often disrupted. Inflammation-associated hepcidin overproduction, triggered by

cytokines and bacterial lipopolysaccharides, further disrupts iron utilization by promoting ferroportin internalization and degradation. Ferroportin, the only known iron exporter, is essential for releasing iron into circulation from enterocytes, macrophages, and iron stores. Hepcidin-mediated ferroportin inhibition leads to iron sequestration, limiting its availability for erythropoiesis and contributing to EPO resistance. Additionally, declining estimated glomerular filtration rate (eGFR) in CKD reduces renal clearance of hepcidin, amplifying its effects. This imbalance between increased production and impaired elimination of hepcidin significantly impairs erythropoiesis, worsening anemia in CKD patients.[23,26]

MANAGEMENT OF ANAEMIA IN CKD

Erythropoiesis-Stimulating Agents

Erythropoiesis-stimulating agents (ESAs) are available in both short-acting and long-acting formulations, each with distinct clinical applications. Short-acting ESAs, such as epoetin α/β and epoetin κ, require more frequent administration, whereas long-acting options, like darbepoetin and epoetin β pegol, offer the advantage of extended dosing intervals due to their prolonged half-life. This extended interval simplifies dosing schedules, reduces the burden on healthcare providers in hemodialysis centers, and promotes better hemoglobin stability. However, the choice between these formulations can influence patient outcomes.[27,29] Long-acting erythropoiesis-stimulating agents (ESAs) possess distinct pharmacokinetic and pharmacodynamic profiles, including prolonged half-lives and greater affinity for erythropoietin receptors, enabling less frequent dosing and improved convenience for non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.[33] Notably, the conversion between short-acting and long-acting ESAs is non-linear, with long-acting ESAs demonstrating greater dose efficiency at higher doses. Despite these theoretical advantages, evidence supporting the superiority of one ESA formulation or dosing pattern over another remains inconclusive.[34] For instance, a study by Sakaguchi et al. reported higher mortality rates in patients treated with long-acting ESAs compared to those receiving short-acting formulations, highlighting the need for individualized treatment strategies.[30] Despite differences in administration frequency, the efficacy of ESAs in maintaining hemoglobin levels appears consistent across types and dosing intervals, particularly in patients undergoing chronic peritoneal dialysis. Nevertheless, safety concerns persist, including the potential for adverse cardiovascular events and cancer progression at higher doses. This risk may be linked to the expression of erythropoietin receptors on neoplastic cells, suggesting a mechanism that warrants further investigation.[31] Another significant challenge in ESA therapy is "therapeutic inertia," where patients with chronic kidney disease (CKD) and anemia do not receive adequate ESA or iron supplementation despite evident need. This inertia can lead to erratic hemoglobin levels and adverse outcomes, including progression to renal failure. Studies indicate that treatment gaps are prevalent, with research by Stauffer and Fan showing that only 22.8% of CKD patients with anemia had been treated within three months prior to assessment. Furthermore, a subset of patients, approximately 10%, exhibits poor responsiveness to ESA therapy despite high doses, underscoring the complexity of anemia management in CKD. To optimize outcomes, it is crucial to address therapeutic inertia through timely and appropriate ESA and iron supplementation.[32]

Various Cochrane meta-analyses have reported insufficient evidence to favor any specific ESA formulation or administration approach in terms of efficacy and safety. Observational studies offer conflicting results. For example, a Japanese dialysis registry study reported a 20% higher mortality risk associated with long-acting ESAs compared to short-acting ones. Conversely, an Italian study in NDD-CKD patients suggested that high-dose short-acting ESAs were linked to increased risks of end-stage kidney disease (ESKD) progression and mortality. These findings should be interpreted cautiously due to potential biases inherent in observational study designs.[35,36] In contrast, a recent randomized controlled trial (RCT) comparing monthly administration of continuous erythropoietin receptor activator (CERA) to shorter-acting agents, such as epoetin alfa/beta and darbepoetin alfa (DA), found no significant differences in achieving hemoglobin (Hb) targets, major cardiovascular events, or all-cause mortality in both NDD-CKD and dialysis-dependent (DD-CKD) patients. However, the trial noted an increased risk of cardiovascular events and mortality in patients failing to achieve Hb levels above 10 g/dL or requiring the highest quartile of ESA doses, regardless of the ESA type. These findings underscore the need for further high-quality RCTs to better delineate the relative benefits and risks of different ESA formulations and dosing regimens, particularly for patients requiring high-dose ESAs. Enhanced understanding of individualized ESA dosing strategies may improve outcomes while minimizing adverse effects in CKD populations.[37]

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) represent an innovative therapeutic class for treating anemia, particularly in chronic kidney disease (CKD) patients. These oral agents—roxadustat, daprodustat, vadadustat, molidustat, and desidustat—work by inhibiting prolyl hydroxylase, stabilizing hypoxia-inducible factor (HIF), and mimicking the body's natural hypoxic response.[38,39] This mechanism enhances the transcription of erythropoiesis-related genes, notably increasing endogenous erythropoietin (EPO) production within physiological levels, thereby promoting red blood cell production and addressing anemia's underlying cause. Compared to traditional erythropoiesis-stimulating agents (ESAs), which require intravenous or subcutaneous administration, HIF-PHIs

offer the convenience of oral dosing, improving adherence and patient comfort.[40,41] Roxadustat, one of the most studied HIF-PHIs, has shown efficacy in raising hemoglobin levels in CKD patients regardless of dialysis status. Clinical trials have highlighted its potential to reduce hepcidin levels, improve iron utilization, and address inflammation-driven anemia, making it particularly effective for patients with ESA resistance.[46] Daprodustat has proven non-inferior to ESAs in maintaining hemoglobin levels during hemodialysis, with improved patient compliance due to its oral administration. Trials, such as the ASCEND-NHQ, highlighted its additional benefit in reducing fatigue without a significant increase in adverse events compared to placebo. Meta-analyses indicate comparable safety profiles among HIF-PHIs, ESAs, and placebos, with no substantial differences in cardiovascular or renal adverse events. Beyond erythropoiesis, HIF-PHIs demonstrate ancillary benefits, including improved iron mobilization, lipid profile modulation (e.g., HDL and LDL lowering), and potential protective effects on CKD progression, ischemia, and blood pressure regulation. However, concerns regarding long-term safety persist.[42,45]

Activation of HIF may influence non-erythropoietic pathways, raising questions about its impact on cancer progression and cardiovascular health. While initial findings suggest a lower rate of high EPO-related adverse events compared to ESAs, further research is essential to establish comprehensive safety profiles [48]. Roxadustat has been approved in China and Japan and has demonstrated efficacy in phase III studies. In non-dialysis-dependent CKD (NDD-CKD) patients, it significantly increased hemoglobin levels compared to placebo over nine weeks. In dialysis-dependent CKD (DD-CKD) patients, it was non-inferior to epoetin alfa over 26 weeks, with similar safety outcomes. These findings underscore the physiological regulation of EPO by HIF-PHIs, reducing the risks associated with pharmacological EPO levels. Overall, HIF-PHIs offer a transformative approach to anemia management in CKD, combining efficacy comparable to ESAs with enhanced convenience and potential additional benefits.[46,48]

Iron therapy in Patients with CKD in Hemodialysis (HD) and Non-HD

Intravenous (IV) iron supplementation is often preferred over oral administration in cases of severe anemia, particularly when rapid correction of hemoglobin (Hb) levels is required due to its superior efficacy and ability to deliver larger doses.[49] Evidence from a 2008 meta-analysis by Rozen-Zvi et al. highlighted the enhanced Hb response to IV iron in anemic patients with chronic kidney disease (CKD) undergoing hemodialysis, compared to oral iron supplementation.[50] This advantage has been supported by further studies. For example, Avni et al. demonstrated that IV iron therapy not only has a safety profile comparable to oral iron but also results in fewer gastrointestinal side effects and does not increase the risk of severe adverse events or infections.[51] A systematic review and meta-analysis by Shepshelovich et al. endorsed IV iron as the preferred treatment for patients with advanced CKD (stages 3–5 and 5D), reinforcing its recommendation over oral supplementation in this population.[52] Additionally, Sargent et al. found that in CKD stage 5 patients not yet on dialysis (CKD 5 ND), IV iron supplementation reduced mortality risk by 15%, particularly among those receiving erythropoiesis-stimulating agent (ESA) therapy. CKD patients, especially those on dialysis, are at high risk of iron deficiency anemia (IDA) due to significant iron loss during dialysis procedures.[53] First-line treatment in these cases involves administering a total loading dose of 1,000 mg of IV iron, followed by smaller maintenance doses to sustain Hb levels. Locatelli et al.[49] emphasized the superior response time of IV iron therapy, aligning with guidelines from KDIGO and European Renal Best Practice (ERBP). Furthermore, the DRIVE trial by Coyne et al. investigated the implications of elevated ferritin levels and found no evidence linking high ferritin levels to increased mortality in dialysis patients receiving IV iron.[55] Macdougall et al., through a prospective randomized controlled trial, demonstrated that proactively administering high doses of IV iron significantly improved outcomes in hemodialysis patients, reducing mortality and non-fatal cardiovascular events.[55] This strategy also minimized ESA dosage, blood transfusions, and hospitalizations, highlighting the advantages of proactive iron management. Overall, these studies collectively establish IV iron as the preferred route for treating anemia in CKD patients, offering superior efficacy, better safety, and improved patient outcomes compared to oral supplementation.

Ziltivekimab

Ziltivekimab is a human IgG1k monoclonal antibody engineered with specific Fc domain amino acid modifications to prolong its serum half-life. It operates through a distinctive mechanism of action, targeting the inflammatory processes contributing to anemia pathophysiology. Findings from the phase 2 RESCUE randomized clinical trial indicate that ziltivekimab's anti-inflammatory properties may significantly enhance hemoglobin levels and improve iron homeostasis in patients with stage 3–5 chronic kidney disease (CKD). Meanwhile, the ongoing ZEUS trial is evaluating its potential to reduce cardiovascular events in CKD patients.[57,58]

CONCLUSION

Chronic kidney disease (CKD) and its associated complications, particularly anemia, represent a growing public health challenge with significant implications for patient morbidity, mortality, and quality of life. The pathophysiology of anemia in CKD involves complex mechanisms, including erythropoietin dysfunction, iron metabolism dysregulation, and the impact of inflammation, necessitating a multifaceted approach to management. Recent advancements, such as

erythropoiesis-stimulating agents (ESAs) and hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), have expanded therapeutic options, offering opportunities for more tailored and effective treatment strategies. However, the optimal management of anemia in CKD requires addressing challenges such as therapeutic inertia, variable ESA responsiveness, and iron deficiency. Emerging therapies and ongoing research underscore the importance of individualized care plans that balance efficacy, safety, and patient-specific factors. Furthermore, proactive measures, including early detection, lifestyle modifications, and addressing modifiable risk factors, are critical in mitigating the dual burden of CKD and anemia.

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