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Review Article

Strategies for Managing Anemia in Chronic Kidney Disease

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Abstract

Anemia is a common complication in chronic kidney disease (CKD) and is associated with decreased quality of life, deteriorating kidney function, increased illness, higher mortality rates, and elevated healthcare costs. Management of CKD-related anemia aims to enhance renal function (when feasible) and bolster red blood cell production. Anemia in chronic kidney disease (CKD) stems from a variety of factors, including reduced erythropoietin (EPO) production, inadequate iron availability or functionality, and inflammation leading to heightened levels of hepcidin, among other causes. Typical treatment for CKD-related anemia involves administering oral or intravenous iron supplements in conjunction with erythropoiesis-stimulating agents (ESAs). Over the past decade, erythropoiesis-stimulating agents (ESAs) have proven effective in boosting hemoglobin (Hb) levels for many patients. However, concerns about their safety, particularly regarding increased cardiovascular risk—especially at high doses and in hyporesponsive patients—have emerged. As a result, there's been a shift towards adopting more cautious Hb targets. Iron deficiency is widespread among CKD patients, particularly in those not undergoing dialysis. While iron supplementation has traditionally been used to support anemia management, there's growing recognition of the potential benefits of intravenous iron therapy, especially in the context of heart failure. HIF prolyl hydroxylase inhibitors are promising new drugs being clinically evaluated as alternatives to ESAs for anemia treatment in CKD patients. Initial data suggest they effectively boost endogenous erythropoietin production with potential benefits like lower peak concentrations, efficacy in inflamed patients, and improved iron utilization. However, further research is needed to confirm their safety and efficacy in the long term use.

Keywords: anemia, chronic kidney disease, erythropoiesis-stimulating agents, iron, HIF-prolyl-hydroxylase inhibitors

Introduction

Anemia is a common complication in chronic kidney disease (CKD) and is associated with decreased quality of life, deteriorating kidney function, increased illness, higher mortality rates, and elevated healthcare costs.[1] Diagnosis typically involves hemoglobin levels dropping below 13.0 g/dL in men and below 12.0 g/dL in non-menopausal women.[2] Management of CKD-related anemia aims to enhance renal function (when feasible) and bolster red blood cell production. In CKD, anemia often presents as normocytic normochromic, hyperproliferative anemia, strongly associated with unfavorable outcomes and heightened mortality rates.[3] A cross-sectional analysis of NHANES data from 2007–2008 and 2009–2010 revealed that anemia was twice as prevalent among individuals with CKD compared to the general population, with rates of 15.4% versus 7.6%, respectively. The prevalence of anemia increased with the progression of CKD stages, from 8.4% at stage 1 to 53.4% at stage 5.[4] Similar findings were reported by the CKD Prognosis Consortium in a more recent study.[5] Anemia in chronic kidney disease (CKD) stems from a variety of factors, including reduced erythropoietin (EPO) production, inadequate iron availability or functionality, and inflammation leading to heightened levels of hepcidin, among other causes.[1] Typical treatment for CKD-related anemia involves administering oral or intravenous iron supplements in conjunction with erythropoiesis-stimulating agents (ESAs). Decades of research have consistently demonstrated the strong association between anemia in CKD and increased risks of mortality and hospitalization, as well as significant declines in quality of life and an elevated necessity for blood transfusions. Consequently, the combination of ESAs and iron therapy has become standard practice for managing anemia in CKD patients. ESAs address insufficient erythropoiesis, while iron supplementation ensures the presence of a crucial component for hemoglobin synthesis.[6] Fortunately, recent advancements in treatment, such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), offer promising alternatives. These medications function by enhancing natural EPO production, improving iron levels, and reducing hepcidin levels, among other benefits, potentially leading to advancements in the management of anemia in CKD patients.[1]

Erythropoiesis-stimulating agents (ESAs)

Endogenous erythropoietin (EPO) is a natural hormone made by kidney cells, encouraging red blood cell production. Although mostly produced in the kidney's peritubular cells, it also occurs in small amounts in the spleen, liver, bone marrow, lung, and brain. Oxygen levels and low hemoglobin levels influence EPO production.[7] Endogenous erythropoietin and erythropoietin stimulating agents (ESAs) prompt the growth

and development of red blood cells. They work by activating genes that encourage cell multiplication and prevent cell death. This results in an increase in overall hemoglobin and hematocrit levels in the body.[8] The initial EPO analogs, epoetin α and epoetin β, were introduced shortly after one another. They are created using recombinant DNA technology in cell cultures. Subsequently, darbepoetin alfa (DA) and methoxy polyethylene glycol-epoetin beta were developed, offering an extended half-life.[1] Not all ESAs are the same. They vary in their pharmacokinetic and pharmacodynamic characteristics, including different half-lives and affinity for the EPO receptor. This allows for less frequent dosing and easier administration, especially for non-dialysis-dependent (NDD) CKD patients using long-acting ESAs. Additionally, it's important to note that the conversion factor between short-acting and long-acting ESAs may not be linear. At higher doses, long-acting ESAs are typically more effective.[9] For example, research conducted by the Japanese Registry of Dialysis indicated that individuals treated with long-acting ESAs faced a 20% elevated risk of mortality compared to those administered short-acting ESAs.[10] Conversely, an observational study conducted in Italy among non-dialysis-dependent chronic kidney disease (ND-CKD) patients revealed a heightened likelihood of progressing to end-stage kidney disease (ESKD) and experiencing mortality among those given high doses of short-acting ESAs. Nonetheless, it was noted that patients who failed to attain hemoglobin levels exceeding 10 g/dL or those receiving the highest quartile of ESA doses were at a greater risk of cardiovascular events or death, irrespective of their treatment allocation.[11] The most severe adverse effects associated with erythropoietin-stimulating agents (ESA) include an elevated risk of blood clot formation, particularly in surgical patients. ESA use leads to increased blood viscosity due to heightened red blood cell production, thereby raising the potential for stroke and heart attacks. Furthermore, there's a heightened propensity for venous blood clot formation, necessitating careful consideration, particularly in patients with a history of clotting disorders or cardiovascular conditions.[12]

In chronic kidney disease (CKD), erythropoietin-stimulating agents (ESAs) are beneficial for patients undergoing dialysis or those who will need it soon. Recent evidence suggests that there is a clear advantage in correcting hemoglobin (Hb) levels if they are below 10 g/dL, but exceeding Hb levels of 13 g/dL may pose increased risks. Therefore, the optimal Hb target appears to lie somewhere between 10 and 12 g/dL. It's important to personalize the Hb target based on each patient's risks, baseline health conditions, and preferences.[1] Before initiating erythropoietin stimulating agent (ESA) therapy, it's crucial to conduct baseline assessments of hemoglobin and transferrin levels. Initially, hemoglobin levels should be closely monitored, ideally every week. The dosing and frequency of ESA administration should be tailored based on the patient's response to treatment. If hemoglobin levels increase to a non-anemic range, physicians should consider temporarily halting ESA therapy. Moreover, in patients exhibiting a suboptimal response to ESA therapy, supplementation with iron may be warranted, as insufficient iron availability could be a contributing factor.[12]

Iron Supplementation

Intravenous (IV) iron has proven effective in both dialysis-dependent (DDCKD) and non-dialysis-dependent (NDD-CKD) patients, boosting ferritin and hemoglobin levels while reducing the need for erythropoiesis-stimulating agents (ESAs) and blood transfusions. Unlike oral iron supplements, which are less effective in hemodialysis except for ferric citrate,IV iron is preferred due to its higher efficacy.[13] However, it can cause gastrointestinal issues like intolerance and constipation. Concerns have been raised about IV iron formulations, including potential risks of oxidative stress, endothelial dysfunction, and susceptibility to infections. Adverse reactions such as hypotension, headaches, and hypersensitivity have also been associated with IV iron administration, partly due to the release of labile iron into the circulation post-administration, which is not bound to transferrin.[1] Iron deficiency correction has been shown to reduce the need for ESAs in CKD patients, as demonstrated in the FIND: CKD trial.[14] Studies like TREAT indicate that IV iron supplementation alone, without ESAs, can increase hemoglobin levels by up to 1 g/dL, supporting the "iron fist approach" recommended in guidelines for correcting anemia. Trials such as FAIR-HF, CONFIRM-HF, and EFFECT-HF have shown that IV iron supplementation improves outcomes, symptoms, functional class, and quality of life in patients with heart failure and iron deficiency, regardless of anemia status. These benefits extend to reducing hospitalizations for heart failure. IV iron therapy has also been linked to improvements in renal function, as observed in subanalyses of studies like FAIR-HF.[15-17]

Newer, safer IV iron formulations allow for higher doses per session.[18] Iron overload, marked by an excess of iron in the body, can result in organ dysfunction. Research indicates heightened levels of iron in the liver among hemodialysis patients, possibly linked to liver fat accumulation (hepatic steatosis).[19] Individuals with non-dialysis-dependent chronic kidney disease (CKD) and elevated ferritin levels (over 500 ng/ml) might face a slightly elevated risk of mortality, although this connection warrants further investigation due to potential confounding factors.[20] The PIVOTAL study illustrated a reduced risk of adverse outcomes in new hemodialysis patients receiving a proactive high-dose iron regimen, maintaining average ferritin levels below 700 ng/ml as per study protocol. Nevertheless, the long-term safety implications and ideal iron targets necessitate additional elucidation. The PIVOTAL trial confirmed the efficacy and safety of high-dose IV iron sucrose in incident hemodialysis patients, with no increased risks of death, major adverse cardiovascular events, or infection. A sub-analysis of the PIVOTAL study revealed no significant differences in infection rates, hospitalizations, or mortality due to infections between patients receiving the proactive high-dose iron regimen and those receiving the reactive low-dose iron regimen.[21]

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors

A novel class of medications designed to treat anemia differs significantly from traditional erythropoiesis-stimulating agents (ESAs). Instead of directly activating the erythropoietin receptor, these drugs prompt the kidneys and, to a lesser extent, the liver to produce endogenous erythropoietin. Unlike ESAs, they are administered orally rather than through injection.[6] Known as HIF-prolyl-hydroxylase inhibitors (HIF-PHIs), these medications function by blocking the activity of prolyl-hydroxylase enzymes. This inhibition results in elevated levels of hypoxia-inducible factor (HIF), which in turn promotes the production of endogenous erythropoietin.[1] The HIF system regulates various physiological functions beyond erythropoiesis in response to tissue oxygen levels. During hypoxia, it activates genes controlling oxygen supply, cell viability, and diverse metabolic processes. Hypoxia-inducible factors (HIFs) regulate gene expression in response to low oxygen levels, including those essential for erythropoiesis and iron metabolism. HIF-prolyl hydroxylases (HIF-PHs) degrade HIF-α under normal oxygen conditions. However, when oxygen levels decrease, HIF-PH activity diminishes, leading to the activation of transcriptional programs that promote erythropoiesis. HIF-PH inhibitors (HIF-PHIs) prevent the degradation of HIF-α, allowing it to translocate into the nucleus alongside HIF-β, where they stimulate the transcription of

genes involved in erythropoiesis. Currently, HIF-PHI therapy stands out as the most promising treatment for anemia in chronic kidney disease (CKD). Currently, roxadustat, vadadustat, daprodustat, and enarodustat are approved PHD inhibitors for anemia treatment in CKD patients, primarily in China or Japan.[6]

Roxadustat, the forefront drug among HIF-PHIs undergoing clinical trials, has gained regulatory approval in China and Japan. In 2019, two phase 3 studies compared roxadustat with a placebo in non-dialysis-dependent (NDD) CKD patients and with epoetin alfa in dialysis-dependent (DD) CKD patients in China. Despite their smaller sample sizes and shorter durations, the former study demonstrated roxadustat's efficacy in boosting hemoglobin levels after 9 weeks compared to the placebo group.[22] Similarly, the latter study revealed that hemoglobin levels after 26 weeks were comparable to those achieved with epoetin alfa. Moreover, oral roxadustat was found to be non-inferior to parenteral epoetin alfa in treating anemia among Chinese dialysis patients, with similar safety profiles, although hyperkalemia and metabolic acidosis were more frequent in the roxadustat group.[23] Comparable outcomes were seen in a phase 3 study comparing roxadustat to ESAs in Japanese dialysis patients. A meta-analysis by Zhang L et al. in 2021 affirmed roxadustat's efficacy in raising serum hemoglobin levels, surpassing placebo response rates in NDD patients. In summary, roxadustat presents as a promising and safe treatment choice for anemia in CKD patients.[24]

The FDA's approval of daprodustat (DPD) signifies a significant advancement in treating anemia among dialysis patients with CKD, introducing the first oral option. By inhibiting HIF-prolyl hydroxylase enzymes, DPD enhances red blood cell production, resulting in elevated hemoglobin levels. Studies such as ASCEND-D have demonstrated DPD's effectiveness, showing it to be non-inferior to darbepoetin alfa. Phase II studies have already showcased DPD's efficacy in managing CKD-related anemia in both dialysis-dependent (DD) and non-dialysis-dependent (NDD) patients.[25] Ongoing research explores its potential benefits, including its impact on heart failure patients with CKD. However, attention is warranted due to adverse events like gastrointestinal bleeding and vascular calcification. In a study led by Akizawa et al., 271 Japanese hemodialysis patients received either daprodustat 4 mg/day or darbepoetin alfa, with DPD proving as effective as darbepoetin alfa in maintaining hemoglobin levels over 40–52 weeks.[26] DPD also led to a greater decrease in hepcidin levels and an increase in total iron-binding capacity compared to darbepoetin alfa. Moreover, the safety profile of daprodustat in patients undergoing hemodialysis (HD), peritoneal dialysis (PD), or non-dialysis (ND) treatment was comparable to injectable ESA in a pooled analysis of three Japanese phase 3 studies, with no new safety signals identified. Further large-scale research is imperative to assess long-term risks, including cardiovascular events and malignancy.[25]

Phase 3 trials comparing vadadustat to darbepoetin alfa in non-dialysis-dependent (NDD) CKD patients found vadadustat to meet hematologic efficacy criteria but not the specified cardiovascular safety criterion.[27] Conversely, in dialysis-dependent (DD) CKD patients, vadadustat proved noninferior to darbepoetin alfa concerning cardiovascular safety and hemoglobin level management.[28] Additionally, a study by Nangaku et al. in 2020 involving Japanese CKD patients undergoing peritoneal dialysis, both ESA users and nonusers, showed vadadustat effectively maintained hemoglobin levels within target ranges at 20 and 24 weeks without notable safety concerns.[29] These findings endorse vadadustat's potential as a safe and effective treatment for CKD-related anemia in peritoneal dialysis patients.

Multiple phase II trials, constituting the DIALOGUE program, evaluated molidustat against placebo or ESA therapy in CKD patients. These studies showcased the drug's efficacy, safety, and tolerability. Molidustat demonstrated favorable tolerability over a span of up to 36 months and emerges as a viable alternative for the long-term treatment of CKD-related anemia compared to darbepoetin and epoetin[30].

HIF-PHD inhibitors, like to ESAs, diminish the necessity for blood transfusions. In addition to promoting erythropoiesis, PHD inhibitors offer supplementary benefits that could address some ESA limitations in CKD patients. Notably, PHD inhibitors affect iron metabolism, potentially enhancing iron availability for erythropoiesis by decreasing hepcidin levels. They also exhibit a unique ancillary effect of reducing serum total cholesterol, including LDL and HDL particles, which could have implications for cardiovascular health. However, the impact of these lipid changes on cardiovascular outcomes remains uncertain[6]. Nevertheless, concerns exist regarding potential adverse effects, such as tumor progression, vascular calcification, renal cyst growth, retinopathy worsening, and increased pulmonary artery pressure. Additionally, the possibility of PHD inhibitors affecting other pathways beyond HIF-PHIs remains unknown[1]. In summary, while HIF-PHIs offer promise as an alternative treatment for anemic CKD patients, further research is necessary to evaluate their long-term safety and potential non-erythropoietic effects.

Conclusion

In summary, while current treatments for anemia in CKD patients, such as ESAs and iron supplements, have shown efficacy, they have limitations, particularly in patients who do not respond optimally. The emergence of new anti-anemic agents offers hope for improved outcomes, potentially providing better correction of anemia with a safer profile. HIF-prolyl-hydroxylase inhibitors (HIF-PHIs) are emerging as promising treatments for anemia in chronic kidney disease (CKD). By elevating hypoxia-inducible factor (HIF) levels, they stimulate endogenous erythropoietin production. Initial data suggest they could be effective alternatives to ESAs, with potential benefits including lower peak concentrations, effectiveness in inflamed patients, and improved iron utilization. However, further research is needed to confirm these findings and establish their long-term safety and efficacy.

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