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NON-SYSTEMATIC REVIEW

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Challenging patient phenotypes in the management of anaemia of chronic kidney disease

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Abstract

Background: Chronic kidney disease (CKD) is often complicated by anaemia, which is associated with disease progression and increased hospital visits, decreased quality of life, and increased mortality.

Methods: A comprehensive literature search of English language peer-reviewed articles in PubMed/MedLine published between 1998 and 2020 related to the treatment of anaemia of CKD was conducted. The United States Renal Database System and Dialysis Outcomes and Practice Patterns Study (DOPPS) data reports, the Centers for Disease Control and Prevention and the US Food and Drug Administration websites, and published congress abstracts in 2020 were surveyed for relevant information.

Results: Subgroups of patients with anaemia of CKD present a clinical challenge throughout the disease spectrum, including those with end-stage kidney disease, advanced age or resistance to or ineligibility for current standards of care (ie, oral or intravenous iron supplementation, erythropoietin-stimulating agents and red blood cell transfusions). In addition, those with an increased risk of adverse events because of comorbid conditions, such as cardiovascular diseases or diabetes, comprise special populations of patients with an unmet need for interventions to improve clinical outcomes. These comorbidities must be managed in parallel and may have a synergistic effect on overall disease severity.

Conclusions: Several therapies provide promising opportunities to address gaps with a standard of care, including hypoxia-inducible factor prolyl hydroxylase inhibitors, which stimulate haematopoiesis through promoting modest increases in serum erythropoietin and improved iron homeostasis. The critical issues in the management of anaemia of CKD in these challenging phenotypes and the clinical utility of new therapeutic agents in development for the treatment of anaemia of CKD should be assessed and the information should be made available to healthcare providers.

1 | INTRODUCTION

Anaemia affects ~15.4% of patients with chronic kidney disease (CKD) in the US, an estimated 5.7 million people.[1,2] Anaemia prevalence increases with CKD stage, ranging from 8% at stage 1 to 53% at stage 5,[1] and with age, with 28% in patients aged 18-63 years and 50% in patients aged 66-85 years.[3] Race/ethnicity and sex also impact the prevalence of anaemia of CKD with increased risk in Black, Hispanic and female patients.[4]

Compared with non-anaemic counterparts, patients with anaemia of CKD have an increased risk of hospitalisations,[5] cardiovascular (CV) events,[6] heart failure,[7] progression to dialysis dependence[8] and all-cause mortality.[9] Comorbid diabetes is linked to an increased prevalence of anaemia in CKD,[10] with greater frequency and higher severity[11] in later CKD stages. In a pooled analysis of diabetic patients with CKD, presence of anaemia was associated with an increase in cardiovascular disease (CVD) and all-cause mortality risk compared with non-anaemic counterparts.[12]

Multi-morbidity associated with anaemia of CKD adversely affects patient quality of life (QOL), with increased fatigue and decreased work productivity,[13] and leads to higher healthcare utilisation and costs.[3,14] Although the presence of anaemia may be indicative of sicker patients, a retrospective study found 38% higher adjusted mean total healthcare expense per patient per month in anaemic compared with non-anaemic patients with CKD.[14,15] Management of anaemia of CKD may improve QOL[15] and lower costs by decreasing inpatient expenditures.[14]

1.1 | Pathophysiology of anaemia of chronic kidney disease

Anaemia of CKD is primarily a function of reduced erythropoietin (EPO) levels and impaired iron homeostasis[16] leading to decreased erythropoiesis (Figure 1). Insufficient EPO production following kidney damage occurs from functional deficiency in renal EPO-producing cells[17] and desensitisation of hypoxia-sensing mechanisms.[18] Iron is necessary for haemoglobin (Hb) synthesis, and iron availability is important for adequate tissue oxygenation. Iron deficiency in anaemia of CKD can stem from absolute iron deficiency, impaired dietary absorption or functional iron deficiency, in which systemic inflammation leads to insufficient iron release from internal stores resulting in iron-deficient erythropoiesis.[16] The iron homeostasis regulator hepcidin is elevated in CKD because of inflammation[16,19] and decreased renal excretion[16] and is associated with decreased intestinal iron transport and increased iron sequestration.[19] Understanding the aetiology of anaemia of CKD and critical issues in the management of challenging patient phenotypes provide insights into treatment strategies for optimal patient care.

2 | METHODS

Information presented in this review was derived from a comprehensive literature search of English language peer-reviewed articles in PubMed/MedLine database published from January 1998 to July 2020 related to the treatment of anaemia of CKD. Key search terms included anaemia, anaemia in/of chronic kidney disease, chronic kidney disease, CKD, dialysis, end-stage kidney/renal disease, ESKD, ESRD, erythropoiesis, erythropoiesis-stimulating agent, erythropoietin-stimulating agent, ESA, functional iron deficiency, hepcidin, HIF-PH, hyporesponse, hypoxia, hypoxia-inducible factor prolyl hydroxylase, iron deficiency anaemia, etc. The United States Renal Database System (USRDS) and Dialysis Outcomes and Practice Patterns Study (DOPPS) data reports, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, verified websites from the Centers for Disease Control and Prevention and the US Food and Drug Administration, and published congress abstracts in 2020 were surveyed for relevant information. In addition, pharmaceutical product inserts, and official press releases related to clinical trial breaking news were included.

Review criteria

A comprehensive literature search of English language peer-reviewed articles in PubMed/MedLine published between 1998 and 2020 related to the treatment of anaemia of CKD was conducted. The United States Renal Database System and Dialysis Outcomes and Practice Patterns Study (DOPPS) data reports, the Centers for Disease Control and Prevention and the US Food and Drug Administration websites, and published congress abstracts in 2020 were surveyed for relevant information.

Message for the clinic

The management of chronic kidney disease (CKD) is often complicated by comorbid anaemia. Subgroups of patients with anaemia of CKD including those with end-stage kidney disease, advanced age or resistance or hyporesponsiveness to erythropoietin-stimulating agents present a clinical challenge throughout the disease spectrum. Multimodal treatment strategies and new therapeutic options that address current therapeutic challenges may be beneficial in the treatment of anaemia of CKD.

2.1 | Standard of care and its associated risks

Management of anaemia of CKD typically includes oral and intravenous (IV) iron, erythropoietin-stimulating agents (ESAs) and red blood cell (RBC) transfusions[20,21] (Table 1). Iron supplementation is often necessary to treat iron deficiency, reduce anaemia-related symptoms, allow dose sparing in patients on ESAs and avoid the need for blood transfusions.[22] Oral iron may be appropriate for non-dialysis-dependent (NDD) patients in earlier stages of the disease, as it is non-invasive, inexpensive, and can be self-administered. However, oral iron is poorly absorbed, and in patients requiring a high dose of iron to increase Hb levels, for example dialysis-dependent CKD (DD-CKD) and end-stage kidney disease (ESKD), increased pill burden with oral iron is associated with gastrointestinal side effects and decreased regimen adherence.[23] Comparatively, IV iron is effective in raising Hb levels, and its use has increased over time,[23] perhaps because of greater iron requirements with ESA treatment[24] and

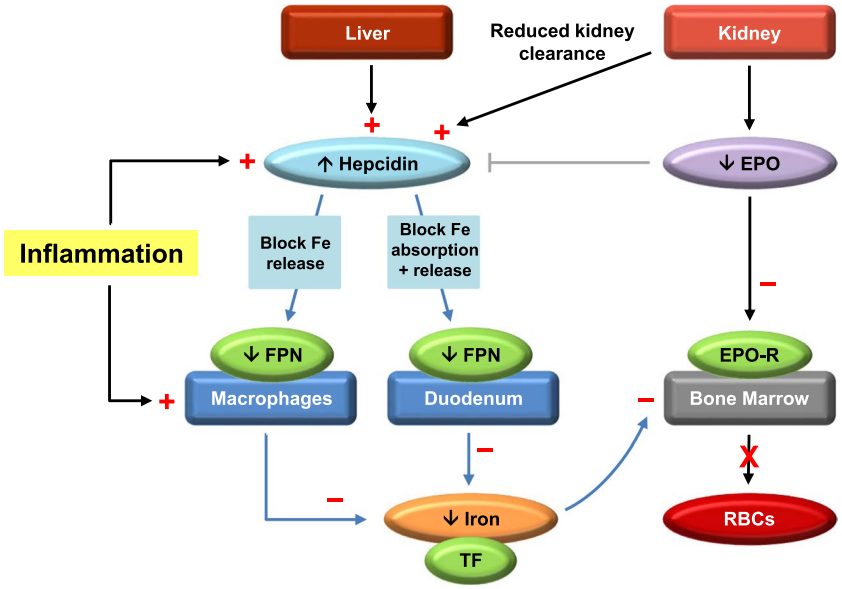

FIGURE 1 Pathophysiology of anaemia of CKD. Diagram shows aetiology of anaemia of CKD as a consequence of reduced EPO levels and impaired iron homeostasis. In CKD, inflammation and reduced renal clearance of hepcidin from kidney damage elevate hepcidin levels and leads to degradation of FPN. Decreased release of iron from internal stores (eg, dietary iron stored in the duodenum or iron from RBCs recycled by reticuloendothelial macrophages) restricts serum concentrations of TF-bound iron available to meet the demands of haematopoiesis in the bone marrow.[16,19] Inflammation also enhances macrophage uptake of iron, further depleting serum iron levels.[160] Additionally, kidney damage in CKD results in decreased EPO production, leading to deficiency in erythrocyte levels, shortened RBC lifespan, and development of anaemia.[16] Black arrows represent physiological processes. Grey line indicates inhibition. Blue arrows show hepcidin-mediated effects on iron metabolism. Positive (+) or negative (–) changes occurring with anaemia in CKD are in red. Abbreviations: CKD, chronic kidney disease; EPO, erythropoietin; EPO-R, erythropoietin receptor; Fe, iron; FPN, ferroportin; RBC, red blood cell; TF, transferrin

ESA dose-sparing practices. Concerns over IV iron include the potential for excessive accumulation, possible exacerbation of underlying systemic infection, and although uncommon, especially with high molecular weight iron dextran formulations, anaphylaxis.[20,25] For example, iron overload after IV iron therapy could lead to the generation of reactive oxygen species and further inflammation.[24] Additionally, observational studies have suggested an association between IV iron treatment and increased hospitalisation and mortality; a prospective cohort study in >30 000 haemodialysis (HD) patients found significantly higher mortality and hospitalisation risk in patients receiving ≥300 mg/month of IV iron for 4 months,[26] and a similar study in 58 000 HD patients showed a comparable trend.[27] Conversely, a large, randomised clinical trial showed significantly better outcomes in patients administered a high-dose IV iron regimen proactively vs a low-dose regimen reactively. In patients on HD, the risk of nonfatal CV events, any-cause deaths, ESA doses and need for blood transfusions were lower in those patients proactively prescribed 400 mg/month (median monthly dose of 264 mg) when ferritin concentration was <700 μg/L and transferrin saturation (TSAT) <40% compared with patients treated reactively with 0-400 mg/month of IV iron (median monthly dose of 145 mg) when ferritin concentration was <200 μg/L and TSAT < 20%.[28]

Erythropoietin-stimulating agents have similar biological action as native EPO,[38] and both short-acting (eg, epoetin alfa) and long-acting (eg, darbepoetin alfa) drugs are used for the treatment of anaemia in DD and NDD patients.[39] A few clinical trials[35,36,40,41,42] have suggested there are risks associated with the use of higher ESA doses to target higher Hb levels. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial, a 34% increased risk of the composite endpoint (death, myocardial infarction [MI], hospitalisation for congestive heart failure [CHF] and stroke) was seen with epoetin alfa in patients randomised to the higher target Hb (135 g/L) compared with lower (113 g/L) level, with no incremental improvement in QOL.[36] Secondary analyses showed that high doses of epoetin alfa and associated hyporesponse were significantly associated with an increased risk of the composite endpoint, independent of Hb achieved.[43] Increased toxicity with high-dose epoetin alfa was suggested as a contributing factor to these observations.[37] These trials along with observational data and meta-analyses indicated that using higher ESA doses to achieve higher Hb targets may be detrimental and has led to recommendations by the US Food and Drug Administration and Kidney Disease: Improving Global Outcomes (KDIGO) against the use of ESAs to target Hb levels >110 g/L[44] and Hb > 115 g/L, respectively.[20]

Blood transfusions may be necessary in patients with ESKD, ESA hyporesponders, and those precluded from ESA therapy because of, in some patients, recent stroke, pure red cell aplasia,[45] allergic reactions[46] or active cancer.[47] However, associated risks, although uncommon, include infection and severe hypersensitivity.[20,21] Additionally, alloimmunisation in patients receiving multiple blood transfusions and in multiparous women can result in

haemolytic reactions[48] and may diminish chances for successful kidney transplantation.[47]

2.2 | Patients with challenging phenotypes

The treatment of anaemia of CKD in patients who are hyporesponsive to ESAs and in those with concurrent malignancies is particularly challenging with current standard of care; in addition, patients with coexisting CVD, secondary hyperparathyroidism (SHPT) and those who are older or undergoing dialysis will require special treatment considerations.

2.2.1 | ESA hyporesponders

In ~5-10% of patients with CKD, a suboptimal response or resistance to ESAs develops, where desired Hb concentrations cannot be reached despite increasingly higher doses of ESA.[49] The prevalence of ESA resistance may range from 10% to 20% in DD patients[50,51] and may in part be related to underlying disease severity. Absolute or functional iron deficiency is the most common cause of ESA resistance[49] and can arise in the presence or absence of anaemia.[52] Patients with absolute iron deficiency have hallmark low ferritin levels (indicator of low iron storage) while patients with functional iron deficiency have adequate internal iron stores but decreased capacity to release and utilise stored iron, as indicated by normal or high serum ferritin levels but low serum TSAT (ie, low circulating iron). However, ferritin is not a specific marker for iron storage, as it is an acute phase reactant affected by inflammation, infection and malignancy; thus high levels in CKD are not always indicative of adequate iron stores.[16] Functional iron deficiency is mediated through inflammatory elevation of hepcidin levels.[19] Renin-angiotensin-aldosterone system inhibitors (RAASi), angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have been suggested to contribute to ESA hyporesponsiveness; discontinuation of these antihypertensives may be considered in some patients to regain ESA sensitivity,[49] but treatment interruption is not ideal since RAASi therapy provides cardiorenal benefits and is associated with improved survival.[53]

There is no consensus on the exact parameters defining ESA hyporesponsiveness. Per KDIGO guidelines, ESA hyporesponse at the start of treatment is characterised by no increase from baseline in Hb concentration after the first month of ESA treatment on appropriate weight-based dosing.[20] The inability to achieve or maintain Hb target levels by treatment with epoetin alfa >300 IU/kg/week subcutaneous or 450 IU/kg/week IV or darbepoetin alfa >1.5 microgram/kg/week has been considered inadequate ESA responsiveness.[21] Acute ESA hyporesponsiveness has been defined as a transient refractoriness (typically after an infectious episode) in Hb improvements with ESA dose escalation followed by response recovery within 4 months of treatment.[51] In chronic cases, ESA hyporesponsiveness can persist after 4 months of high-dose treatment[51] with a decreased likelihood of recovery with higher transfusion and mortality rates than acute cases.[54] ESA-resistant patients have higher rates of death, MI, CHF and stroke than responders.[35,37]

Inflammation plays a key role in ESA resistance and is prevalent in patients with CKD.[55] Inflammation is associated with inhibition of erythropoiesis and increased levels of hepcidin and ferritin.[56] In HD patients, serum hepcidin levels were positively correlated with ESA resistance and inflammatory markers (ie, interleukin-6 [IL-6] and high-sensitivity C-reactive protein [CRP]) and negatively with Hb levels.[57] A higher risk of progression to ESKD and mortality has been shown for patients with higher CRP levels.[58] Inflammation was an independent risk factor for heart failure in patients with CKD.[7] As inflammation influences serum ferritin and transferrin,[56] other diagnostic tests may be needed to ascertain iron status in ESA hyporesponders such as content of reticulocyte haemoglobin, CRP, percentage of hypochromic erythrocytes and soluble transferrin receptor.[59]

Addressing underlying inflammation, for example by improving general health and hygiene, optimising tunnelled catheter care to prevent infection, or by initiating the potentially less inflammatory modality of peritoneal dialysis vs HD, is key to effective treatment of anaemia of CKD[56] and may curb the development of ESA resistance. Nevertheless, inflammation is increased with catheter use even in the absence of infection, as evidenced by significantly decreased CRP levels in patients switched from a catheter to arteriovenous fistulas.[60] A systematic review found that patients with catheters had a higher risk of infection, CV events, hospitalisation and all-cause mortality compared with those using fistulas or grafts for HD.[61]

2.2.2 | Patients with concurrent malignancy

In patients with cancer, CKD can be a risk factor for malignancy, likely because of heightened inflammation and oxidative stress, or may arise consequently from cancer cell toxins or myelosuppressive and nephrotoxic anticancer therapies.[62,63] Chronic kidney disease in cancer patients can be exacerbated by anaemia stemming from chemotherapy, radiation therapy, inflammation, and repeated blood sampling.[64] Anaemia is common in cancer patients and is associated with lower treatment response rates and increased mortality.[64] As the standard of care for cancer therapy-related anaemia, ESAs may reduce the need for blood transfusions.[64] However, anaemia correction with ESAs to higher Hb targets in cancer patients receiving chemotherapy has been linked to the progression of malignancy and adverse CV events such as thrombosis, hypertension, and stroke, although the risk is not uniform across cancer types.[64] While no conclusive association has been shown between low-dose ESA use and cancer risk,[64] current guidelines recommend their use with caution and only with Hb levels <100 g/L in patients with NDD- or DD-CKD with an active or history of malignancy.[20,64] However, except for some patients with myelodysplastic syndromes, ESAs are not recommended in cancer patients with non-chemotherapy-associated anaemia.[65] For these patients, RBC transfusion may be the only

TABLE 1 Current standard of care for anaemia of CKD[20,21,29] and its advantages and disadvantages

	Advantage	Disadvantage
Oral iron	•Inexpensive •Easy to administer •Avoids an IV in patients not on dialysis[20]	•Gastrointestinal side effects are common and may limit adherence[20] •Not as efficacious as IV iron in raising Hb levels[30,31]
IV iron	•More efficacious than oral iron in raising Hb levels[30,31]	•Increased frequency of serious AEs compared with oral iron, including CV events and infection[32] •Allergic and anaphylactoid reactions (rare) have been reported, particularly with iron dextran[33] •Care must be taken to avoid iron overload[24]; high doses are associated with higher risks of mortality and hospitalisation[26,27]
ESA	•When targeting Hb levels of 90-110 g/L, decreases LVH and mortality and increases QOL[34]	•Use of high doses is associated with higher rates of death, stroke, and other CV events[35-37]
Blood transfusion	•Can be used if ESA treatment is not effective or if ESA risks are greater than benefits[20]	•Risks include fever, allergic reactions, haemolytic reactions, transfusion-related infections, and human leukocyte antigen sensitisation[20]

Abbreviations: AEs, adverse events; CKD, chronic kidney disease; CV, cardiovascular; ESA, erythropoietin-stimulating agent; Hb, haemoglobin; IV, intravenous; LVH, left ventricular hypertrophy; QOL, quality of life.

option, bringing with it concerns of allosensitisation and jeopardised future kidney transplantation.[20,64]

2.2.3 | Patients with cardiovascular disease

Chronic kidney disease and CVD are linked pathophysiological states that can exacerbate each other. Patients with comorbidities have a mortality rate at least twice as high as patients with CKD alone,[66] and most of these deaths are caused by CV complications,[67] especially among patients on dialysis.[40] Either CKD or CVD can lead to the development of anaemia, which further triggers reciprocal disease progression and is more common in patients with more severe CKD and CVD.[68] Anaemia in CKD is associated with left ventricular hypertrophy[69] and CHF,[68] stemming from tissue hypoxia and peripheral vasodilation and subsequent compensatory increases in cardiac output that place a high work burden on the heart and may result in resistance to CHF therapy and poorer clinical outcomes and survival.[68] This complex triad of anaemia, CKD, and CVD, referred to as the cardiorenal anaemia syndrome (CRAS),[68] is particularly challenging clinically because of increased morbidity and mortality, heightened systemic inflammation and iron imbalance and the need for multidisciplinary treatment approaches. Mortality risk was significantly higher in CRAS patients compared with heart failure (HF) patients with either comorbid anaemia or CKD,[70] and risks of CV complications and progression to renal replacement therapy (RRT) were higher in hospitalised HF patients with CRAS compared with HF patients with CKD without anaemia.[71] Pro-inflammatory markers are elevated in anaemic HF patients[72] and may cause progression of kidney damage[73] and cardiac remodelling.[73] As discussed, CKD alone is an inflammatory state that when combined with inflammation of CVD and anaemia further contributes to ESA hyporesponsiveness. Although IV iron therapy is beneficial, ESA use is not recommended in patients with anaemia and HF because of the lack of therapeutic benefit on CV outcomes.[74] A systematic review and meta-analysis of nine randomised clinical trials found ESA administration after acute MI and percutaneous coronary intervention to be relatively "safe," and to improve short-term (≤6 months) cardiac function,[75] but no reduction in incidence of major adverse cardiovascular events (MACE), including recurrent MI and stroke, was shown long term with epoetin beta treatment.[76] In the Trial to Reduce Cardiovascular Events With Aranesp® Therapy (TREAT), patients with anaemia of NDD-CKD and comorbid diabetes treated with darbepoetin alfa did not achieve reduction in the composite outcome of either death or a cardiovascular event but required fewer cardiac revascularisation procedures compared with placebo.[42] Clinical guidelines with an integrated treatment approach to address these obstacles are needed to improve outcomes in patients with CRAS.

2.2.4 | Patients on dialysis

In 2017 in the US, 746 557 individuals needed RRT to survive, of whom 70% received dialysis and 30% received a transplant.[77] Of 124 500 patients with incident ESKD in 2017, ~97% were initiated on dialysis and 3% started with a transplant.[77] Anaemia is prevalent in patients undergoing dialysis, up to 89% in the US.[78] Chronic inflammation is common in dialysis patients[79] and, along with lack of adequate dietary iron and functional iron deficiency,[16] can lead to declining erythropoiesis over time and worsening anaemia.[80] Retention of blood in the dialyzer adds to blood loss. Although blood loss varies by dialyzer used, estimates indicate >508 mg of total iron may be lost annually from HD.[81] Anaemia in DD-CKD patients is associated with increased hospitalisation rates, greater mortality, and higher economic burden.[82] Poor QOL is a concern in DD-ESKD patients and is associated with worse survival.[83]

Treatment with epoetin alfa[84] and darbepoetin alfa[85] in DD-CKD patients without CVD resulted in maintenance of target Hb levels, a reduced need for blood transfusions, and improvements in energy and fatigue; however, similar to NDD-CKD patients with anaemia,

ESA doses to target normal Hb levels are associated with dose-dependent adverse effects, including higher mortality rates.[86] In the US, ~80% of HD patients were given ESA therapy in 2016,[87] and ~10-20% of patients on dialysis are estimated to be hyporesponsive to ESAs.[50,51,54] Parenteral IV iron therapy can overcome functional iron deficiency in patients on dialysis with limited treatment-related adverse events and is convenient to administer by infusion during dialysis sessions. However, the optimal IV iron dose to use with various ESA doses is difficult to ascertain and complicated by poor diagnostic measures of iron status. Care must be taken to minimise potential risk of iron overload, especially in patients who are iron-resistant because of underlying inflammation and elevated levels of hepcidin.[20,88]

2.2.5 | Patients with secondary hyperparathyroidism

Secondary hyperparathyroidism, a common complication of CKD, is marked by excessive secretion of parathyroid hormone (PTH), an important regulator of serum calcium levels, in response to hyperphosphatemia from decreased kidney function and hypocalcaemia from impaired bone and mineral metabolism.[89] Parathyroid hormone is implicated in the development of renal anaemia and ESA resistance.[90] It impedes erythropoiesis by inhibiting EPO synthesis[91] and shortens the survival of RBCs.[91] Lower levels of PTH appear to improve the responsiveness to ESA treatment, as patients with relative hypoparathyroidism appeared to respond better to ESA treatment than those with stable PTH.[92] Accordingly, patients who received parathyroidectomy had reduced requirement for exogenous EPO.[91]

Treatment of SHPT may improve anaemia and associated morbidity and mortality[91] through coordinated intervention with a low-phosphorus diet and medication with phosphate binders, vitamin D analogs, and calcimimetics.[93] However, cooperative therapy is difficult to manage in patients with a constellation of CKD, SHPT, and anaemia, and lack of conclusive efficacy or potential risks may offset possible benefits.[93] Although vitamin D derivatives have been shown to suppress PTH secretion, their effect on controlling bone pain and reducing mortality are contradictory.[93] A recent randomised clinical trial in anaemic CKD patients on HD confirmed that vitamin D is dispensable for anaemia management since its administration did not improve EPO levels,[91] despite some studies suggesting that vitamin D may enhance erythropoiesis outside of its effect on PTH.[94] The most recent KDIGO guidelines do not recommend vitamin D supplementation in most adult patients with NDD-CKD in stages 3a–5, but reserve it for patients in stages 4-5 CKD with severe and progressive hyperparathyroidism.[95] Treatment of SHPT with calcimimetics has resulted in higher levels of Hb, lower doses of ESAs,[91] and decreased CV hospitalisation, but its use has been limited by high rates of gastrointestinal effects, hypocalcaemia, over-suppression of PTH and non-adherence to oral calcimimetics.[96] Multifactorial treatment considerations and risk-benefit assessments are necessary for optimal management of comorbidities in patients with CKD, SHPT and anaemia.

2.2.6 | Elderly patients

The prevalence of anaemia of CKD in older patients (≥66 years) is ~50% compared with 28% in younger patients (18-63 years) and increases with age and CKD stage.[3] Older patients often have malnutrition and/or inflammatory conditions with reduced erythropoiesis and increased hepcidin compared with younger patients,[97] which contributes to insufficient Hb. Although Hb levels decrease with age and optimal Hb targets in older patients may be lower than those in younger patients, higher Hb targets in older patients with more rigorous treatment of anaemia may not improve outcomes. In patients prescribed ESAs or iron, a significant association of high Hb levels and improved QOL was seen in patients <65 years but not in those ≥65 years, although QOL parameters are different in younger vs older patients.[98] Dose escalation with ESAs and IV iron in elderly patients is more closely associated with adverse outcomes such as CV effects, hospitalisation and mortality[97]; increased age is associated with ESA resistance,[99] and a significantly higher weekly ESA dose per kilogram body weight is required to achieve the same target Hb levels in patients ≥65 years compared with those <65 years.[97]

Stage 3-5 NDD-CKD patients aged 66-85 years with anaemia were shown to have an increased prevalence of CV conditions compared with corresponding age-matched, non-anaemic patients (arteriosclerotic heart disease [52.2% vs 36.4%], CHF [40.5% vs 20.1%] and dysrhythmia [43.8% vs 28.0%]) and compared with younger (18-63 years) counterparts (arteriosclerotic heart disease [52.2% vs 23.6%], CHF [40.5% vs 21.4%], and dysrhythmia [43.8% vs 19.5%]).[3] Similarly, there may be an increased risk of mortality in elderly HD patients with low Hb levels. Comorbidities in elderly patients with CKD can lead to reduced daily activity, which is associated with increased mortality risk.[100] Following hospital discharge, anaemia and CKD are significantly associated with 1-year mortality rates in older patients, representing post-treatment vulnerability in this population without proper follow-up.[100] Given the frequency of anaemia of CKD and associated comorbidities in the elderly, screening such patients for these disorders and mobility limitations may decrease healthcare utilisation and improve survival, particularly if accompanied by effective treatment intervention.

2.2.7 | Novel challenges from coronavirus disease 2019

The recent coronavirus disease 2019 (COVID-19) pandemic has shown a disproportionately higher disease burden and severity and poorer outcomes for patients with CKD and ESKD with or without other comorbidities.[101,102] Health records and epidemiological studies have shown stage 4-5 CKD, ESKD with dialysis, and kidney transplants to be high-risk for severe complications and hospitalisations[103]; the prevalence of kidney disease among hospitalised patients with COVID-19 was found to be as high as 13%-30% in some cohorts.[103,104] Patients with ESKD had a 37% higher risk of in-hospital death compared with non-ESKD counterparts with similar

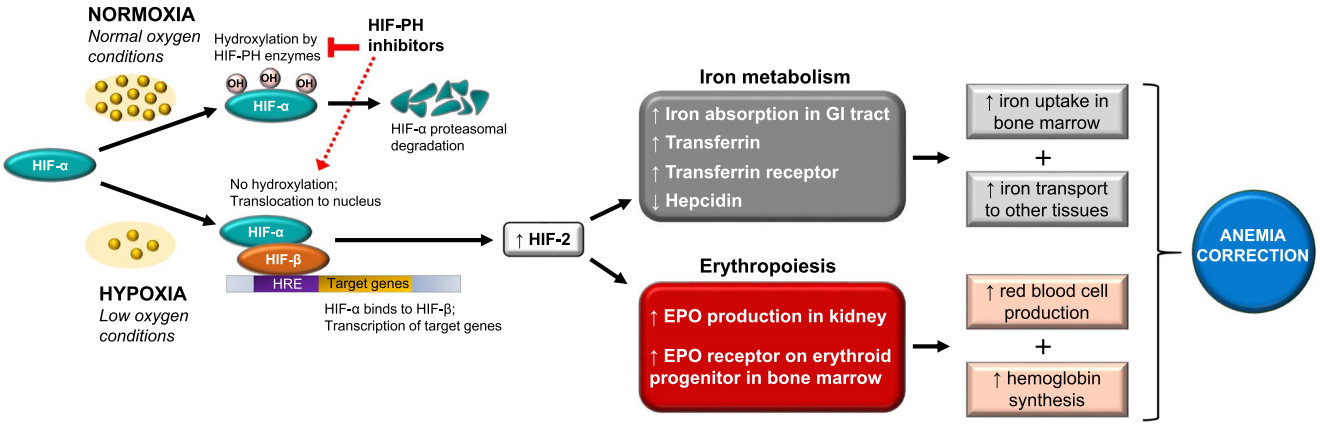

FIGURE 2 Schematic representation of HIF-PH inhibitor effects on anaemia. Under normal oxygen conditions, HIF-α is hydroxylated by HIF-PH enzymes and degraded by the proteasome. In hypoxia, HIF-α is not degraded and translocates to the nucleus where it combines with HIF-β and other coactivators to bind to the HRE and initiate transcription of target genes for iron metabolism and erythropoiesis.[11] HIF-PH inhibitors promote activation of the hypoxia-inducible pathway (dashed red arrow) by blocking the activity of HIF-PH enzymes responsible for HIF protein degradation. As a result, HIF proteins accumulate and act as transcriptional regulators of target genes whose expression has important consequences for functional iron deficiency anaemia in CKD: increased endogenous EPO expression by kidney cells and upregulation of EPO-R on the surface of bone marrow erythroid precursor cells leads to erythropoiesis, rise in Hb levels,[11] and subsequent increases in iron demands[11,109]; HIF proteins boost iron availability for EPO-induced RBC production by reducing levels of hepcidin, increasing iron absorption in the gastrointestinal tract, and mobilising iron transport to bone marrow and other tissues via upregulation of TF, TF receptor, and ceruloplasmin.[109] Anaemia correction with HIF-PH inhibitors may increase tissue oxygenation, leading to improvement in anaemia-related symptoms, such as fatigue and reduced physical and mental ability, and may potentially reduce the risk of adverse events associated with comorbidities.[11] Abbreviations: CKD, chronic kidney disease; EPO, erythropoietin; EPO-R, erythropoietin receptor; GI, gastrointestinal; Hb, haemoglobin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; HRE, hypoxia response element; OH, hydroxyl group; RBC, red blood cell; TF, transferrin

baseline demographics and comorbidities.[101] While the exact mechanism of this increased risk of adverse outcomes in patients with preexisting kidney disease is yet to be fully elucidated, it is believed that the heightened inflammation and immune system dysregulation, as well as the activation of the complement system, are believed to contribute to the pathogenesis.[101,105]

In addition to its prevalence in patients with CKD, anaemia with dysregulated iron metabolism has been observed in patients with COVID-19 and is associated with systemic inflammation and is often severe.[106] During COVID-19 infection, an immune response driven by a cytokine storm may induce a hyperinflammatory state.[101,106] Among 11 265 hospitalised patients with COVID-19, haemoglobin levels decreased and ferritin levels increased with rising inflammation, suggesting that inflammation-induced, hepcidin-mediated iron restriction in erythropoiesis may be responsible for the occurrence and exacerbation of anaemia in these patients.[106] Although ESAs have been used to treat anaemia of CKD with or without COVID-19,[107] their use in patients with CKD and COVID-19 may have reduced efficacy due to inflammation-induced resistance.[106] Furthermore, it has been suggested that ESA use may be dangerous in these patients because severe COVID-19 is characterised by venous and arterial blood clots, and ESAs tend to induce a prothrombotic state.[106] In patients on dialysis and maintenance ESA therapy, some nephrologists have recommended continuing outpatient ESA regimens in the inpatient setting but targeting lower Hb levels of 8-9 g/dL, with no dose escalation in order to mitigate the risk of thrombosis.[106] Although several putative benefits of recombinant erythropoietin have been proposed,[108] in patients with COVID-19 and anaemia with or without kidney disease, avoidance of ESA use has been suggested since the risks outweigh the benefits, even if blood transfusions may be necessary.[106,107]

2.3 | New therapeutic options in development

2.3.1 | Hypoxia-inducible factor prolyl hydroxylase inhibition

Recognition of tissue hypoxia occurs by the hypoxia-inducible factor (HIF) system. In normoxia, the oxygen-sensing subunit of HIF (HIF-α) rapidly undergoes proteasomal degradation after hydroxylation by prolyl hydroxylases (PH), but under hypoxic conditions, HIF-α is stabilised, resulting in transcription of a number of genes that support erythropoiesis, including EPO, EPO receptors and genes involved in iron metabolism[109] (Figure 2). A new class of orally administered drugs aimed at transiently stabilising HIF/HIF-α levels represents a possible treatment strategy for anaemia of CKD. These agents inhibit the activity of hypoxia-inducible factor prolyl hydroxylase (HIF-PH), leading to stabilisation of intact HIF-α. Inhibitors of HIF-PH induce EPO synthesis at significantly lower levels than the supraphysiologic levels observed with ESA therapy.[110]

Although no HIF-PH inhibitors have been approved in the US at the time of publication of this review, roxadustat, the first-in-class orally administered HIF-PH inhibitor, is in late-stage development

for the treatment of anaemia of CKD and is currently approved for the treatment of anaemia in patients with NDD- and DD-CKD in China and Japan, and the HIF-PH inhibitors vadadustat and daprodustat are approved for marketing in patients with DD- and NDD-CKD in Japan (Table 2). Roxadustat was noninferior to epoetin alfa in patients with DD-CKD[111] and superior to placebo in those with NDD-CKD[112] in raising Hb levels with similar frequency of adverse events, except hyperkalaemia, which was reported more often in the roxadustat treatment groups. Phase 3 studies in Japan suggested that roxadustat was noninferior to ESA therapy and effective at maintaining Hb levels within a target range in ESA-naïve patients undergoing HD[113] or peritoneal dialysis.[114]

In DD-CKD patients with anaemia, preliminary data from several recent global phase 3 trials, including the US-based SIERRAS,[143] the European PYRENEES,[145] and the worldwide HIMALAYAS trials[146] have shown the noninferiority of roxadustat to epoetin alfa in increasing Hb levels. Significant improvements from baseline Hb levels and reduction in IV iron use were seen in patients with DD-CKD with roxadustat vs epoetin alfa in the worldwide ROCKIES[144] trial. In addition, roxadustat was associated with a reduction in hepcidin levels from baseline compared with little change after epoetin alfa in DD-CKD[111] and vs placebo in NDD-CKD patients.[112] Apparent inflammation based on high CRP levels did not affect the Hb response with roxadustat; in a sub-analysis of patients with elevated CRP levels, roxadustat treatment led to greater increases in Hb compared with epoetin alfa, indicating that roxadustat may benefit patients with inflammation and anaemia of CKD.[111] In NDD-CKD patients with anaemia, significant increases from baseline in Hb levels were observed with roxadustat treatment vs placebo in preliminary data from several phase 3 trials, including the ALPS, ANDES, and OLYMPUS trials.[145,147,148]

An additional effect of roxadustat is the improvement in lipids; a decrease in total and low-density lipoprotein (LDL) cholesterol and triglycerides, and improvement in LDL to high-density lipoprotein ratio has been shown.[111] In an open-label, randomised, non-comparative clinical trial in ESA-naïve Japanese patients with DD-CKD, daprodustat treatment provided an increase in mean Hb from baseline after 4 weeks and attainment of target mean Hb after 8 weeks, which was maintained for 24 weeks. No treatment-related serious adverse events were reported.[121] In Japanese patients with NDD-CKD, preliminary results showed noninferiority of daprodustat to ESA in achieving target Hb levels and no clinical differences in adverse events of special interest, including ocular, cardiovascular, and cancer-related adverse events.[122] Similar efficacy results were reported in phase 3, randomised, active-controlled studies with vadadustat in Japanese patients with DD-[152] and NDD-CKD[153]; however, in preliminary safety results from patients with NDD-CKD, vadadustat did not meet the primary safety endpoint of noninferiority vs darbepoetin alfa with time to first occurrence of MACE.[155]

Phase 2b trials of molidustat,[131,132,156] enarodustat[128,129] and desidustat[126] have reported similar results. Notably, all HIF-PH inhibitors have hepcidin-lowering effects, which may reduce IV iron requirements and increase dietary iron absorption and iron release from internal stores.[111,112,118,126,128,129,131,149,150,151,156]

Associated with the stimulation of numerous genes related to the cellular response to hypoxia, HIF-PH inhibitors may also have non-haematologic effects such as angiogenesis, tumour growth, and fibrosis. Although such responses have not been observed in clinical trials, ongoing studies will further evaluate the long-term safety and efficacy of these agents.[110]

2.3.2 | Hepcidin antagonism

Early clinical studies investigating the ability of hepcidin antagonists (ie, PRS 080, L-oligonucleotide Lexaptepid Pegol [NOX-H94] and the humanised monoclonal antibody [mAb] LY2787106) to improve functional iron deficiency in patients with anaemia of CKD by increasing iron availability through binding and inhibition of hepcidin have shown promising preliminary results. The development of these particular agents has been discontinued, and the clinical utility of anti-hepcidin-based approaches remains to be evaluated.[157,158]

Other strategies to modify hepcidin levels currently in preclinical development include decreasing hepcidin production via ligand sequestration or small molecule inhibition of the signalling pathway involved in hepcidin transcription (ie, bone morphogenetic pathway); downregulation of the inflammatory pathway by neutralising IL-6 with mAbs or small interfering RNA-mediated targeting of hepcidin or hepcidin regulator mRNA; neutralisation of hepcidin with specific mAbs; interference of hepcidin-ferroportin interaction without blocking iron export using either small molecule inhibitors or anti-ferroportin antibodies; and inhibition of ferroportin receptor endocytosis or increased production of ferroportin receptor.[159]

3 | CONCLUSIONS

For a substantial subset of patients with CKD, anaemia management remains suboptimal and challenging. In particular, for patients who are hyporesponsive to ESAs or have other common comorbid conditions such as diabetes, CVD, functional iron deficiency, and heightened inflammatory status, current standard of care may be inadequate. Newer treatment options, such as HIF-PH inhibitors, that lower hepcidin levels and provide more physiologic levels of EPO and maintain higher Hb levels without major adverse outcomes may be beneficial.

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TABLE 2 Hypoxia-inducible factor prolyl hydroxylase inhibitors

Drug name	Study design		Dosing frequency in clinical trials	Outcomes from clinical trials	Status[a]
	DD-CKD	NDD-CKD			
Daprodustat (GSK-1278863)	Phase 2 RCTs NCT02019719[115] NCT01587924[116] NCT02075463[117] NCT01977482[118] NCT01047397[119] Phase 3 RCTs NCT02829320[121] NCT02969655[125] NCT03029208[124] NCT02879305[124] NCT03400033[124] NCT02791763[124]	Phase 2 RCTs NCT01977573[120] NCT01587898[116] NCT01047397[119] Phase 3 RCTs NCT02876835[124] NCT03409107[124] NCT02791763[124]	QD[121-123]	↑ Hb ↓ Hepcidin ↓ Ferritin ↑ TIBC	Approved in patients with anaemia of DD-CKD and NDD-CKD in Japan[124]
Desidustat (ZYAN1)	Phase 3 RCTs NCT04215120[127]	Phase 2 RCTs CTRI/2017/05/008534[126] Phase 3 RCTs NCT04012957[127]	3x/week[126]	↑ Hb ↓ Hepcidin ↑ TIBC	Phase 3 clinical trials are ongoing[127]
Enarodustat (JTZ-951)	Phase 2 RCTs JapicCTI-152892[128] Phase 3 RCTs JapicCTI-173700[130] JapicCTI-173701[130] JapicCTI-173702[130] JapicCTI-183938[130] NCT04027517[130]	Phase 2 RCTs JapicCTI-152881[129] Phase 3 RCTs JapicCTI-173699[130] JapicCTI-183870[130]	QD[128,129]	↑ Hb ↓ Hepcidin ↓ Ferritin ↑ TIBC ↓ TSAT	NDA filed in Japan in November 2019 in patients with anaemia of DD-CKD and NDD-CKD[130]
Molidustat (BAY-853934)	Phase 2 RCTs NCT01975818[131] NCT02064426 (OLE)[132] Phase 3 RCTs NCT03351166[133] NCT03418168[133] NCT03543657[133]	Phase 2 RCTs NCT02021370[131] NCT02021409[131] NCT02055482 (OLE)[132] Phase 3 RCTs NCT03350321[133] NCT03350347[133]	QD[131]	↑ Hb ↓ Hepcidin ↓ Ferritin ↑ or stable TIBC ↓ or stable TSAT	Phase 3 clinical trials are ongoing[133]

(Continues)

TABLE 2 (Continued)

Drug name	Study design		Dosing frequency in clinical trials	Outcomes from clinical trials	Status[a]
	DD-CKD	NDD-CKD			
Roxadustat (FG-4592)	Phase 2 RCTs NCT01596855[134] NCT01147666[135] NCT01414075[136] Phase 3 RCTs NCT02652806[111] NCT02779764[113] NCT02780141[113] NCT02273726[143] NCT02174731[144] NCT02278341[145] NCT02052310[146]	Phase 2 RCTs NCT01599507[134] NCT01244763[137] NCT00761657[138] Phase 3 RCTs NCT02652819[112] NCT01750190[147] NCT01887600[145] NCT02174627[148]	3x/week[111,112,113,114,139,140]	↑ Hb ↓ Hepcidin ↓ Ferritin (variable in ESKD patients) ↑ Transferrin ↑ TIBC ↓ or stable TSAT	Approved in patients with anaemia of DD-CKD and NDD-CKD in China and Japan[141,142] NDA filed in December 2019 in Canada, Mexico, Taiwan, Philippines, and Singapore in patients with anaemia of DD-CKD and NDD-CKD[141] NDA Filed in US in Feb 2020 in patients with anaemia of DD-CKD and NDD-CKD[141]
Vadadustat (AKB-6548)	Phase 2 RCTs NCT02260193[149] Phase 3 RCTs[154] NCT02865850 NCT02892149 NCT03242967 NCT03402386 NCT03439137 NCT03461146 NCT04313153	Phase 2 RCTs NCT01906489[150] NCT01381094[151] Phase 3 RCTs[142] NCT02680574 NCT03329196	QD[150,152,153]	↑ Hb ↓ Hepcidin ↓ Ferritin ↑ TIBC	Approved in patients with anaemia of DD-CKD and NDD-CKD in Japan[142]

Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; ESKD, end-stage kidney disease; Hb, haemoglobin; NDA, new drug application; NDD-CKD, non-dialysis-dependent chronic kidney disease; OLE, open-label extension; QD, once daily; RCT, randomised clinical trial; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

[a]Status at the time of manuscript publication; none of these agents has been approved in the US.

DISCLOSURES

David S. Goldfarb, MD: Consultant, Alnylam, AstraZeneca, Retrophin, Synlogic; Research, Akebia, Dicerna; Owner, Dr Arnie's, Inc Sheena Pramod, MD: has nothing to disclose. The authors have not received any funding or honoraria for their work.

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole. All authors and medical writers from inScience Communications wrote the first draft of the manuscript. All authors participated in subsequent drafts, approved the submission of the manuscript, and are fully accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study. All presented data are from published studies.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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