Managing Anemia across the Stages of Kidney Disease in Those Hyporesponsive to Erythropoiesis-Stimulating Agents

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Keywords

Anemia · Chronic kidney disease · Erythropoiesis-stimulating agent hyporesponse · Heparin hypoxia-inducible factor · Prolyl hydroxylase inhibitor

Abstract

Background: Patients with CKD frequently have anemia that results from iron-restricted erythropoiesis and inflammation. Anemia of CKD is currently managed with iron supplements and erythropoiesis-stimulating agents (ESAs) to promote erythropoiesis and with RBC transfusion in severe cases. Hyporesponse to ESAs, or the need for larger than usual doses to attain a given hemoglobin (Hb) level, is associated with increased morbidity and mortality and presents a pressing clinical challenge, particularly for patients on dialysis. This paper reviews ESA hyporesponse and potential new therapeutic options in the management of anemia of CKD.

Summary: The most common causes of ESA hyporesponse include iron deficiency and inflammation, and to a lesser degree, secondary hyperparathyroidism, inadequate dialysis, malnutrition, and concomitant medications. Management of ESA hyporesponse is multipronged and involves treating low level infections, ensuring adequate nutrition, and optimizing iron status and dialysis modality, although some patients can remain refractory. Inflammation directly increases production and secretion of hepcidin, contributes to an im-

paired response to hypoxia, and suppresses proliferation of erythroid progenitors. Coordination of renal and hepatic erythropoietin (EPO) production and iron metabolism is under the control of hypoxia-inducible factors (HIF), which are in turn regulated by HIF-prolyl hydroxylases (HIF-PHs). HIF-PHs and hepcidin are therefore attractive potential drug targets particularly in patients with ESA hyporesponse. Several oral HIF-PH inhibitors have been evaluated in patients with anemia of CKD and have been shown to increase Hb and reduce hepcidin regardless of inflammation, iron status, or dialysis modality. These sustained effects are achieved through more modest increases in endogenous EPO compared with ESAs. **Key Messages:** Treatments that address ESA hyporesponse remain a significant unmet clinical need in patients with anemia of CKD. New therapies such as HIF-PH inhibitors have the potential to address fundamental aspects of ESA hyporesponse and provide a new therapeutic option in these patients.

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Introduction

Anemia is common in patients with CKD and is associated with increased morbidity and mortality [1–3]. Anemia of CKD results from low erythropoietin (EPO) production by the failing kidney [4] and immune activa-

Table 1. Definitions of ESA hyporesponse

Source	Definition of ESA hyporesponse
NKF-KDOQI [21]	450 units/kg per week i.v. EPO or 300 units/kg per week s.c. EPO
KDIGO [11]	No increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing
NICE best practices/The Renal Association [18]	Failure to reach the target Hb level despite s.c. epoetin dose >300 IU/kg/week (450 IU/kg/week i.v. epoetin) or darbepoetin dose >1.5 µg/kg/week
ERI [16]/EHRI [22]	Weight-adjusted weekly ESA dose divided by the Hb value >12.7–20.0 IU weekly/kg/Hb, g/dL

NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; EHRI, ESA hyporesponsiveness index; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ERI, ESA response index.

tion, which inhibits iron absorption and mobilization, suppresses EPO production, and decreases erythrocyte survival, all of which lead to iron-restricted erythropoiesis [5]. This pattern is now recognized as anemia of inflammation.

Anemia of CKD is currently managed with oral or intravenous (IV) iron and erythropoiesis-stimulating agents (ESAs) to promote erythropoiesis and with RBC transfusion in severe cases and as a last resort in most patients. However, in patients with cancer, per the American Society of Oncology and American Society of Hematology guidelines, transfusions are preferred to ESAs in those receiving myelosuppressive chemotherapy; ESAs are not recommended in most patients with non-chemotherapy-associated anemia or when myelosuppressive chemotherapy is anticipated to be curative [6].

Correction of anemia with the supplemental approach of iron and ESAs is effective in many patients and is associated with increased hemoglobin (Hb) levels, reduced need for blood transfusions, improved exercise tolerance and health-related quality of life, and reductions in left ventricular mass [7–9]. However, dosing with ESAs to target normalized Hb levels (i.e., Hb target ~13.5 g/dL) is associated with an increased incidence of adverse clinical outcomes (death, myocardial infarction, and hospitalization for congestive heart failure) [10, 11]. As a result, use of ESAs to achieve Hb targets >11.5 g/dL is not recommended [10, 11]. Rather, the current US Food and Drug Administration guidelines recommend considering the lowest approved effective dose of ESA.

Some patients do not respond to ESAs or require a larger than usual dose of ESA to attain a given Hb level. This condition, known as ESA hyporesponse or resistance, is associated with increased morbidity, mortality,

and healthcare resource utilization [12–16], and is a pressing clinical challenge. The objective of this review is to (1) provide an overview of factors leading to ESA hyporesponse; (2) evaluate the clinical use of relatively high doses of ESAs, and (3) discuss the role of emerging therapeutics for the treatment of anemia of CKD in patients hyporesponsive to ESAs.

Prevalence and Characteristics of ESA Hyporesponse

There is no universally accepted definition of hyporesponse or resistance to an ESA (Table 1) [11, 17–22]. In practice, it often means failure to achieve a target Hb concentration despite receiving a higher than usual dose of a given ESA or a requirement for increasing doses of an ESA to maintain a target Hb level [20]. For epoetin alfa, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and National Institute for Health and Care Excellence (NICE) definitions for ESA hyporesponse equate to a dose greater than the maximum recommended starting dose (50–100 units/kg/thrice weekly) [17, 21, 23]. Similarly, the NICE hyporesponse definition equates to a dose >3-fold the recommended starting dose for darbepoetin alfa (0.45 µg/kg/week) [21, 24].

While it is believed that the majority of patients with CKD stages 3–5 have relative epoetin deficiency [25], ESA hyporesponse is less common and its incidence and prevalence vary widely depending on the characteristics of the population studied and the criteria used to define ESA hyporesponse. For example, recent estimates of prevalence range from 12.5% when both Hb level and ESA dose were included in the definition [26], to 30.3% when only

Fig. 1. Factors associated with ESA hyporesponse. ESA, erythropoiesis-stimulating agent; RAAS, renin-angiotensin-aldosterone system; HIF, hypoxia inducible factor; HIF-PH, HIF prolyl hydroxylase; PTH, parathyroid hormone.

change from baseline in Hb was considered in patients with baseline Hb <11 g/dL [27]. Regardless of the definition, ESA hyporesponse is associated with increased all-cause mortality in patients with CKD when compared with patients who respond as expected to ESAs [12, 13, 16, 20, 28–30]. Moreover, poor response to ESAs has also been associated with adverse outcomes in patients with anemia of diabetic kidney disease [14], and with anemia in heart failure [31].

Dose escalation does not ameliorate anemia in patients who are hyporesponsive to ESAs. Indeed, use of high doses of ESAs may contribute to the adverse clinical outcomes as shown in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial. Patients in CHOIR had CKD and a baseline Hb of <11 g/dL and were randomized to achieve a target Hb of 11.3 or 13.5 g/dL with epoetin alfa dosed once weekly [32]. The incidence of the primary outcome (composite endpoint of death, congestive heart failure, stroke, and myocardial infarction) was significantly higher in patients assigned to the higher Hb

target of 13.5 g/dL [32]. Significantly, a secondary analysis that examined epoetin alfa dose as a potential contributor to these adverse outcomes showed that those patients who failed to achieve the assigned Hb target had higher event rates [33]. This trend was evident in both groups, and within each group, patients who received high epoetin alfa doses ($\geq 20,000$ U) had higher event rates than patients who received low epoetin alfa doses ($< 20,000$ U) [33]. Inability to achieve the target Hb and use of high-dose epoetin alfa were each also significantly associated with increased risk of the primary endpoint, composite time to death, myocardial infarction, hospitalization for congestive heart failure, or stroke in unadjusted analyses [33]. However, in adjusted models, only high-dose epoetin alfa was associated with a significantly increased hazard of the primary end point, suggesting that the use of high doses of ESAs in the setting of ESA hyporesponse may do more harm than good [33]. In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) in patients with diabetes mellitus and moderate anemia of CKD,

treatment with darbepoetin alfa at a median monthly dose of 176 µg, designed to target a Hb level of 13.0 g/dL, was associated with a 2-fold increased risk of stroke compared with placebo [34]. An increased risk of stroke was similarly observed in the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial in patients with heart failure who met the TREAT inclusion criteria [35]. Collectively, these observations suggest that the risks versus benefits of ESAs – especially high-dose ESA therapy needed to target higher Hb levels or address ESA hyporesponse – need to be carefully weighed.

The type of ESA may play a role in the risk of adverse outcomes, but the relative risk among individual ESAs remains controversial. In a large, long-term, randomized trial, patients with CKD receiving epoetin beta pegol had no increase in risk of all-cause mortality, nonfatal myocardial infarction, or stroke compared to those receiving either epoetin alfa or darbepoetin alfa [36], in agreement with prior meta-analyses that found no significant safety differences among ESAs [37–39]. A recent pooled analysis of prospective cohorts in Italy with non-dialysis-dependent (NDD) CKD stages 1–5 showed that the risk of the composite of end-stage kidney disease or death was not impacted by the type of ESA (e.g., short-acting [epoetin alfa or epoetin beta] or long-acting [darbepoetin alfa or epoetin beta pegol]) when all dosing levels were pooled but did increase at higher standardized ESA doses [40]. Notably, patients receiving high doses of short-acting ESAs had a 2-fold increased risk of the composite endpoint compared with those receiving low short-acting ESA doses and a 56% increased risk compared with those receiving high long-acting ESA doses [40]. Conversely, a nationwide cohort study of 194,698 patients on dialysis in Japan found that the death rate was 13% higher in patients receiving long-acting (darbepoetin alfa or epoetin beta pegol) versus those receiving short-acting (epoetin alfa, epoetin beta, or epoetin kappa) ESAs [41]. Reasons for these discrepancies remain unclear but could be related to differences in CKD severity (e.g., dialysis dependence vs. not) or regional and ethnic differences among study populations.

Causes of ESA Hyporesponse

Although disease severity and comorbidities may, in part, contribute to ESA hyporesponse, the most common causes include iron deficiency and inflammation, and to a smaller degree, secondary hyperparathyroidism (SHPT), inadequate dialysis, and concomitant medications (Fig. 1).

Iron Deficiency

Absolute iron deficiency in patients with CKD results from increased blood loss due to frequent blood draws, residual blood in hemodialysis tubing, and decreased dietary intake or reduced absorption of iron from the gastrointestinal tract [42, 43]. Consequently, there is a severe reduction in the quantity of iron stored in the bone marrow, liver, and spleen, which is needed during periods of increased demand for Hb synthesis, for example, in response to treatment with ESAs [44]. Clinically, a transferrin saturation (TSAT, a measure of circulating iron) of $\leq 20\%$ and serum ferritin (a marker of overall iron stores) of ≤ 100 ng/mL are diagnostic for absolute iron deficiency in patients with NDD-CKD or in those on peritoneal dialysis, while serum ferritin of ≤ 200 ng/mL is diagnostic for absolute iron deficiency in patients with CKD on hemodialysis [44]. Functional iron deficiency, or iron-restricted erythropoiesis, occurs when adequate bodily iron stores are present but release of iron from macrophages into the circulation is blocked due to inflammation and/or increased hepcidin production [45, 46] or does not occur rapidly enough to support an increased rate of erythropoiesis, for example, during treatment with ESAs [47]. Hepcidin is produced by the liver and sequesters iron by traveling in the circulation and binding to ferroportin, the only known transmembrane iron exporter, on enterocytes, macrophages, and hepatocytes, causing its internalization and degradation [48, 49]. Loss of transmembrane iron transport interrupts absorption and recycling of iron and promotes iron sequestration by preventing release from intracellular stores [46]. TSAT $\leq 20\%$ and elevated serum ferritin levels (>100 ng/mL) are indicative of functional iron deficiency [5, 44]. In a large, open-label, randomized controlled trial in patients with dialysis-dependent (DD)-CKD, proactive treatment with high-dose IV iron was associated with use of lower ESA doses and decreased the risk of hospitalizations, as compared with a low-dose, reactive IV iron regimen [50]. This supports the notion that correcting iron deficiency may improve ESA response, although whether any of the patients were hyporesponsive to ESAs was not reported [50]. However, in a retrospective study of patients with DD-CKD from the CROWNWeb database, a greater proportion (26.5%) of patients who were hyporesponsive to ESAs had iron deficiency with TSAT $\leq 20\%$ compared with 10.9% in those who responded normally to ESAs [16]. This occurred despite similar rates of IV iron use in the 2 months prior to meeting the hyporesponse criteria, suggesting IV iron therapy alone may not be sufficient to address ESA hyporesponse [16].

Inflammation

Inflammation is the common denominator in the anemia frequently observed in patients with chronic illnesses including CKD and contributes to an impaired response to hypoxia and ESA hyporesponse [5]. Low-level inflammation directly increases production and secretion of hepcidin by hepatocytes [45]. Specifically, signaling via inflammatory cytokines such as interleukin (IL)-1 β , tumor necrosis factor alpha (TNF- α), and IL-6 leads to increased hepcidin levels [48, 49]. In patients with NDD-CKD, a positive correlation was shown between hepcidin level and ESA dose [51], and between hepcidin and the ESA response index (ERI, the average ratio of weight-adjusted ESA dose to Hb used as a measure of ESA hyporesponse; Table 1) [52]. Interestingly, markers of inflammation are also correlated with ESA resistance and anemia [27, 52–56]. IL-6 and C-reactive protein (CRP) levels are significantly higher in patients who are hyporesponsive to ESAs [53, 57], and IL-6 levels are a strong predictor of ESA resistance in patients on hemodialysis [57]. Moreover, in a recent study, patients on hemodialysis in the highest tertile of ERI had higher mean IL-6, high-sensitivity (hs) CRP, ferritin, and hepcidin levels and lower Hb levels, RBC counts, and hematocrit than patients in lower tertiles [56].

Regional and racial differences in inflammation and ESA dose have been reported. A recent longitudinal study of patients enrolled in the Dialysis Outcomes Practice Patterns Study found dialysis patients in Japan had lower median CRP levels (2 vs. 3 mg/L) and lower mean weekly ESA doses (5,200 vs. 7,800 U/week) compared with those in Australia, New Zealand, and Europe [58]. Nevertheless, acute increases in inflammation increased ESA dose requirements and incidence of ESA hyporesponse in both populations [58]. These data suggest an intricate association between inflammation, hepcidin, and ESA hyporesponse. Currently, CRP level as a surrogate for systemic inflammation in dialysis patients is not measured in clinical practice in the USA [59].

The hypoxia-inducible factor (HIF) pathway plays a critical role in the normal physiologic response to hypoxia, including the upregulation of EPO [60]. In CKD, HIF is not activated as the reduced oxygen delivery to the kidney coupled with reduced kidney tissue oxygen consumption due to CKD-induced structural and functional changes creates a pseudonormoxic state. This impairs production of endogenous EPO as the oxygen gradient is preserved despite reduced oxygen delivery to the kidney [61]. Inflammation may directly impair EPO production as IL-1 β and TNF- α inhibit EPO transcription *in vitro* via

the transcription factors NF- κ B and GATA-2 [62]. This is compounded by suppression of proliferation of erythroid progenitors by chronic inflammation in the hematopoietic microenvironment [63].

The most common causes of CKD are diabetes mellitus and/or hypertension [64], which are themselves common comorbidities and are associated with inflammation [65–67]. Interestingly, a recent retrospective study found that patients with DD-CKD who were hyporesponsive to ESAs had higher rates of hypertension and other cardiovascular diseases including heart failure, coronary heart/artery disease, and arrhythmia, and higher rates of cardiovascular event-related hospitalizations prior to meeting the criteria for ESA hyporesponse, as compared with patients with a normal ESA response [16], further supporting a connection between inflammation-associated conditions and ESA hyporesponse.

Secondary Hyperparathyroidism

SHPT is a chronic condition characterized by elevated levels of parathyroid hormone (PTH). SHPT develops early in the course of CKD, worsens as CKD progresses, and affects the majority of patients with advanced CKD, particularly those on dialysis [68–70]. Interestingly, there is an inverse correlation between PTH and Hb levels [71, 72], and elevated levels of PTH are significantly associated with ESA hyporesponse in patients on hemodialysis [73]. The exact mechanism(s) of anemia and ESA hyporesponse in SHPT remain unclear but may involve the suppression of endogenous EPO production by PTH, as patients have been reported to have increased EPO levels after undergoing parathyroidectomy [74]. Similarly, patients receiving PTH-lowering therapies in several small studies showed improved Hb levels and, in some cases, were able to reduce their dose of ESA [75–77]. However, these effects were relatively modest or not evident in larger controlled trials [74]. Additionally, PTH may contribute to anemia by inducing fibrosis in bone marrow and decreasing RBC survival or production [74]. Finally, an observational study of patients with DD-CKD found increased risk of ESA hyporesponse in patients in the lowest (5–440 pg/mL) and highest (8,621–76,000 pg/mL) quintiles of fibroblast growth factor 23, a protein commonly dysregulated in SHPT [78].

Concomitant Medications

Drugs that inhibit the renin-angiotensin-aldosterone system (RAAS) are frequently used to treat comorbid hypertension; slow the progression of CKD, particularly in patients with proteinuria; and improve cardiovascular

outcomes [79]. Most trials have excluded patients with advanced CKD (estimated glomerular filtration rate <30 mL/min/1.73 m²) though evidence exists that RAAS inhibitors may also provide benefit in these patients [80–82]. Treatment with RAAS inhibitors has been associated in a number of studies with ESA hyporesponse in patients with DD-CKD [55, 83], although 1 study showed no such association [84]. In cohorts of patients with NDD-CKD [85] or with CKD and predominantly not on dialysis [27], there are reports of both increased and decreased ESA hyporesponse in patients receiving RAAS inhibitors. Additionally, a study in patients with heart failure reported a protective effect of RAAS inhibitors on ESA responsiveness [31]. Due to the potential to inhibit erythropoiesis, RAAS inhibitor use should be carefully evaluated in patients hyporesponsive to ESAs. Pentoxifylline, a vasodilator, has been proposed as a potential treatment for ESA hyporesponse; however, in a small randomized, double-blind, placebo-controlled trial, patients treated with pentoxifylline had no significant improvement in ERI relative to those receiving placebo but did have modest relative increases in Hb (0.76 g/dL) [86]. In secondary analyses, pentoxifylline treatment was not associated with alterations to markers of oxidative stress [87] or significant reductions in hepcidin relative to placebo [88].

Interestingly, in patients with DD-CKD, treatment with statins has been suggested to ameliorate ESA hyporesponse [89–91]. In patients in predialysis, long-term statin therapy was inversely associated with ESA hyporesponse [92]. Likewise, an analysis of patients on hemodialysis showed that those receiving a statin had lower hsCRP levels than patients not on statins and a lower ERI and required lower ESA doses [90].

Therapeutic Options and Strategies to Improve ESA Response

Management of Infection

Management of anemia of CKD in patients who are hyporesponsive to ESAs involves a range of strategies (Fig. 1). Treating active infections, if present, and improving nutritional status are basic measures that may be helpful in all patients [93]. Dialysis catheters and non-functioning arteriovenous grafts may be a source of infection and inflammation and have been linked to ESA hyporesponse [94, 95].

Optimization of Dialysis

Optimizing dialysis is associated with reduction in inflammatory mediators, improved ERI, and improvements in response to ESAs [96–98]. For example, hemofiltration is associated with a more rapid decrease in ERI than low-flux bicarbonate dialysis [99] or high-flux hemodialysis [100]. Similarly, the use of ultrapure dialysate reduces ESA requirements, possibly associated with reduced inflammation [101, 102], while increased dialysis efficiency for small molecules is correlated with reductions both in hepcidin levels and ERI and, consequently, lower weekly ESA requirements [99, 103]. Finally, increased dialysis time and/or frequency can be beneficial as switching from a conventional thrice weekly 3.5–4-h hemodialysis to three to five 8-h nocturnal sessions is associated with decreased ESA resistance [104].

Correction of Iron Deficiency

Iron deficiency is a notable cause of ESA hyporesponse [11]. A thorough assessment of iron status and correction of possible absolute or functional iron deficiency will ensure that any apparent ESA hyporesponse is real and not due to an easily corrected iron deficiency. As already discussed, in patients with DD-CKD, high-dose IV iron is not associated with an increased incidence of adverse clinical outcomes or infections and allows for lower ESA doses when compared with low-dose IV iron [50]. These recent data suggest that high-dose IV iron may be safe to administer and may lower ESA requirements. However, concerns remain regarding long-term use of high-dose IV iron [105], and iron administration does not address the fundamental mechanism that results in ESA hyporesponse.

Optimization of iron status, ESA dose, and dialysis parameters improves anemia in many patients; however, a proportion of patients remain refractory to ESAs and are in need of alternative therapies. Several novel drug classes that target the fundamental defects that lead to ESA hyporesponse are in development, including HIF-prolyl hydroxylase (HIF-PH) inhibitors and hepcidin antagonists.

Targets for New Therapeutic Options

Hypoxia-Inducible Factor

Coordination of renal and hepatic EPO production and iron metabolism is under the control of HIF [60]. HIF comprises 2 subunits (HIF- α and HIF- β) that dimerize in the nucleus and then bind to hypoxia response elements

(For legend see next page.)

to induce transcription of many target genes, including the genes encoding EPO and its receptor [106, 107]. HIF- α is widely distributed in the cytoplasm and nucleus and bears 2 proline residues that are functional oxygen sensors [107]. Hydroxylation of one or both of these residues on HIF- α by HIF-PHs results in the binding of von Hippel-Lindau tumor suppressor protein, which marks the complex for rapid ubiquitination and proteasomal degradation [107]. HIF-PHs are exquisitely sensitive to changes in oxygen saturation, as small reductions in tissue oxygen levels reduce their enzymatic activity [108].

The oxygen-sensing properties of HIF-PHs are the key elements in regulating erythropoiesis. When oxygen delivery to tissues is sufficient (i.e., under normoxic conditions; Fig. 2), these enzymes are active, HIF- α is rapidly degraded before it can dimerize with HIF- β , and as a result, EPO gene transcription does not occur [60]. In contrast, HIF-PHs are inactive under hypoxic conditions; thus, HIF- α remains available to interact with HIF- β and a cascade of events results in coordinated erythropoiesis [60, 109], including production of EPO in the kidney and the expression of proteins, which facilitate iron absorption by enterocytes such as divalent metal transporter 1 and duodenal cytochrome B reductase [4].

HIF-PH Inhibitors

It follows that inactivation of HIF-PHs will allow HIF- α and HIF- β to dimerize in the nucleus, bind to hypoxia response element, induce gene expression, and ultimately stimulate production of endogenous EPO, improve iron metabolism, and promote erythropoiesis [110]. Accordingly, HIF-PHs represent an attractive therapeutic target and several orally administered HIF-PH inhibitors have been developed and evaluated in patients

with anemia of CKD, including those patients with NDD-CKD and DD-CKD. Five agents in this class (roxadustat, daprodustat, vadadustat, molidustat, and enarodustat) have been approved in China and Japan for the treatment of anemia of CKD [60, 111–114].

Collectively, data from clinical trials of HIF-PH inhibitors, namely roxadustat [115–127], daprodustat [128–135], desidustat [136], enarodustat [137, 138], molidustat [139–143], and vadadustat [144–149], have clearly shown these agents are efficacious in increasing Hb and decreasing hepcidin levels in patients with anemia of CKD (Table 2). Indeed, a recent meta-analysis of 22 trials found that HIF-PH inhibitors provided a 0.96 and 1.78 g/dL greater weighted mean increases of Hb levels from baseline compared with control (placebo or ESA) in patients with DD-CKD or NDD-CKD, respectively [150]. Moreover, in 21 studies that measured serum hepcidin, HIF-PH inhibitors led to a 40.42 μ g/L greater weighted mean reduction in hepcidin relative to controls [150].

In patients with anemia of CKD not receiving ongoing ESA therapy, treatment with daprodustat was associated with increases in Hb concentration, decreases in serum hepcidin levels, and either increases [128] or no change in endogenous EPO levels [131]. Additionally, several studies have shown that Hb levels remain stable after switching from ongoing ESA therapy to treatment with an oral HIF-PH inhibitor [131, 140, 144–146]. In a phase 2 study of patients with DD-CKD and receiving ESA therapy, switching to oral roxadustat was associated with increased Hb levels and decreased hepcidin levels and promoted EPO levels in the physiologic range [117]. Mean Hb levels were maintained or increased in a dose-dependent manner during roxadustat treatment despite lower EPO levels than those observed with ESAs.

Fig. 2. Hypoxia, HIF, and regulation of erythropoiesis. **a** In a normally functioning kidney, HIF-PHs sense and utilize oxygen (O_2) to promote the rapid degradation of the HIF- α subunit of the HIF transcription factor and EPO is not expressed. Hepcidin expression by the liver is minimal. When hypoxia occurs, HIF-PHs become inactive, allowing the HIF- α subunit to dimerize with the HIF- β subunit to promote the expression of EPO, resulting in coordinated erythropoiesis. **b** In anemia of CKD, the normal oxygen gradient persists due to adaptive changes that result in reduced kidney oxygen delivery and consumption. This prevents activation of the HIF pathway and, coupled with damage to renal tubular fibroblasts, prevents appropriate increases in EPO. This is exacerbated by suppression of EPO transcription by inflammatory cytokines such as IL-1 β and TNF- α . Furthermore, IL-1 β , TNF- α , and IL-6 stimulate production of the peptide hepcidin in the liver, which reduces the expression of the iron exporter FPN on the surface of many tissues, including macrophages and in the duode-

num, limiting the availability of iron for erythropoiesis. At the same time, diminished kidney function reduces the clearance of hepcidin, contributing to its accumulation in the circulation, thus further restricting iron. Collectively, this reduces erythropoiesis. Administration of ESAs mimics the function of EPO and directly stimulates erythropoiesis in the bone marrow but have minimal impact on iron homeostasis. On the other hand, HIF-PH inhibitors increase HIF- α and activate the HIF pathway and thus lead to production of endogenous EPO. Additionally, HIF-PH inhibitors indirectly suppress hepcidin expression, which restores FPN activity and allows mobilization of iron from internal stores. Red arrows denote changes brought about by CKD and inflammation, and green arrows denote effects of HIF-PH inhibitors. HIF, hypoxia inducible factor; HIF-PH, HIF prolyl hydroxylase; EPO, erythropoietin; IL, interleukin; TNF- α , tumor necrosis factor alpha; FPN, ferroportin; ESAs, erythropoiesis-stimulating agents.

Table 2. Prolyl hydroxylase inhibitors in clinical development for the treatment of anemia in patients with CKD

Author, phase, registration	Patients, N	Treatment	Pharmacologic effects				
			Hb	hepcidin	TIBC	TSAT	ferritin
<i>Roxadustat</i>							
Chen et al. [121], 3, NCT02652819	CKD 3–5, ND, non-ESA (154)	Roxadustat 70 or 100 mg ^{d,e} versus PBO	↑	↓	↑	↓	↓
Chen et al. [120], 3, NCT02652806	ESRD, HD, PD, stable ESA (305)	Roxadustat 100 or 120 mg ^{d,e} versus epoetin alfa	↑ (NI)	↓	↑	↓	↓
Akizawa et al. [122], 3, NCT02952092	HD, stable ESA (303)	Roxadustat 70 or 100 mg ^d versus darbepoetin alfa	NC, NI	NC	↑	↓	↓
Akizawa et al. [119], 3, NCT02780141, NCT02779764	HD, non-ESA (75)	Roxadustat 50 or 100 mg ^d	TNC	↑	↑	↓	↓
	HD, stable ESA (164)	Roxadustat 70 or 100 mg ^d no comparator	↑	↑	↑	↓	↓
Akizawa et al. [123], 3, NCT02780726	PD non-ESA (13), stable ESA (43)	Roxadustat 50 or 70 mg ^d (non-ESA), or roxadustat 70 or 100 mg ^d (stable ESA) no comparator	↑	↓	NR	↓ or NC ^b	↓ or NC ^b
Coyne et al. [124], 3, NCT01750190	CKD 3–5, ND, non-ESA (922)	Roxadustat 70 or 100 mg ^d versus PBO	↑	↓	↑	↓	↓
Shutov et al. [127], 3, NCT01887600	CKD 3–5, ND, non-ESA (594)	Roxadustat 70 or 100 mg ^d versus PBO	↑	↓	NR	↓	↓
Provenzano et al. [126], 3, NCT02052310	Incident HD or PD (1,043), non-ESA	Roxadustat 70 or 100 mg ^d versus epoetin alfa	↑	↓	↑	NC	↓
Fishbane et al. [125], 3, NCT02174627	CKD 3–5, ND (2731)	Roxadustat 70 mg versus PBO	↑	↓	↑	NC	↓
Basarab et al. [115], 2, NCT01414075	HD, PD, non-ESA (60)	Roxadustat 60–300 mg ^d ; maximum dose of 2.5 mg/kg with no iron, oral iron, or IV iron	↑	↓	↑	↑ ^c	↑ ^c
Provenzano et al. [117], 2, NCT01147666	HD, stable ESA (144)	Roxadustat 1–2 mg/kg ^d versus epoetin alfa	↑/NC ^d	↓	↑	↓	↓
Provenzano et al. [116], 2, NCT01244763	CKD 3–4 (145)	Roxadustat 1.0–1.7 mg/kg ^d or roxadustat 50, 70, or 100 mg ^d no comparator	↑	↓	↑	↓	↓
Chen et al. [118], 2, NCT01599507, NCT01596855	CKD 3–5 ND, non-ESA (91)	Roxadustat 1.1–1.75 or 1.50–2.25 mg/kg ^d versus PBO	↑	↓	↑	↓	↓
	HD, stable ESA (87)	Roxadustat 1.1–1.8 or 1.5–2.3 or 1.7–2.3 mg/kg ^d versus epoetin alfa	↑	↓	↑	↓	↓
<i>Daprodustat</i>							
Akizawa et al. [133], 3, NCT02969655	HD, ESA (267)	Daprodustat 4 mg/d versus darbepoetin alfa	NC ^c , NI	↓	↑	NC	↓
Tsubakihara et al. [134], 3, NCT02829320	HD, non-ESA (28)	Daprodustat 4 mg/d no comparator	↑	↓	↑	↓	↓
Nangaku et al. [135], 3, NCT02791763	CKD 3–5, ND	Daprodustat 2 mg/d (ESA-naïve) versus epoetin beta pegol	TNC	↓	↑	↓	↓
Cizman et al. [130], 2, NCT02075463	ESA-naïve (100), stable ESA (117)	Daprodustat 4 mg/d (ESA) versus epoetin beta pegol	↑	NC	NR	↑	↓
Meadowcroft et al. [132], 2, NCT01977482	HD, chronically hyporesponsive to ESA (15)	Daprodustat 12 mg/d no comparator	↑	↓	↑	↓	↓
Brigandi et al. [128], 2, NCT01047397	HD, stable ESA (171)	Daprodustat 4–12 mg/d versus ESA ^{a,b}	↑	↓	↑	↓	↓
	CKD 3–5 ND (70)	Daprodustat 10–100 mg/d versus PBO	↑	↓	↑	↓	↓
	HD (37)	Daprodustat 10 or 25 mg/d versus PBO	↑	↓	↑	NC	↓
Holdstock et al. [131], 2, NCT01977573	CKD 3–5, ND, non-ESA, stable ESA (252)	Daprodustat 1–4 mg/d versus ESA	↑ or NC ^d	↓	↑	↓	↓
Holdstock et al. [129], 2, NCT01587898, NCT01587924	ND (73), non-ESA	Daprodustat 0.5–5 mg/d versus PBO	↑	↓	↑	↓	↓
	HD (83), stable ESA	Daprodustat 0.5–5 mg/d versus ESA	NC	NC	↑	↑	↓
<i>Desidustat</i>							
Parmar et al. [136], 2, CTR1/2016/02/006665	CKD, non-ESA (117)	Desidustat 100–200 mg/d versus PBO	↑	↓	↑	↓	NR
<i>Enarodustat</i>							
Akizawa et al. [137], 2, JapicCT1-152892	HD, stable ESA (85)	Enarodustat 2–6 mg/d	↑	↓	↑	↓	↓
Akizawa et al. [138], 2b, JapicCT1-152881	CKD 3–5 ND non-ESA (94) or stable ESA (107)	Enarodustat 2–8 mg/d versus PBO	↑eNC ^f	↓	↑	↓	↓
<i>Molidustat</i>							
Akizawa et al. [143], 3, NCT03351166	HD, non-ESA (25)	Molidustat 75 mg/d	↑	NR	NR	NR	NR
Macdougall et al. [140], Akizawa et al. [139], 2, NCT02021370, NCT02021409, NCT01975818	ND, non-ESA (121)	Molidustat 25–100 mg/d versus PBO	↑	↓	↑	↓	↓
	ND, stable ESA (124)	Molidustat 25–75 mg/d versus ESA	NC ^c	↓	NC	NC	↓
	HD, stable ESA (199)	Molidustat 25–150 mg/d versus ESA	NC ^c	NC	NC	NC	↑
<i>Vadadustat</i>							
Nangaku et al. [148], 3, NCT03402386	CKD, PD, stable ESA (40), and non-ESA (2)	Vadadustat 300 mg/d	↑	↓	↑	↓	↓
Nangaku et al. [149], 3, NCT03439137	HD, stable ESA (323)	Vadadustat 300 mg/d versus darbepoetin alfa	NC	↓	↑	NC	NC
Nangaku et al. [147], 2, NCT03054337, NCT03054350	CKD, ND (51)	Vadadustat 150, 300, or 600 mg versus PBO	↑	↓	↑	↓	↓
	HD (60)	Vadadustat 300 or 450 mg/d or 450 mg i.i.v. ^g no comparator	↑	↓	↑	↓	↓
Haase et al. [146], 2	HD, stable ESA (94)	Vadadustat 300 or 450 mg/d versus PBO	NC ^d	↓	↑	↑	↓
Martin et al. [145], 2, NCT01381094	CKD 3–4 ND (93), non-ESA	Vadadustat 240–630 mg/d versus PBO	↑	↓	↑	NR	↓
Pergola et al. [144], 2, NCT01906489	CKD 3–5 ND, ESA-naïve (107), non-ESA (63), stable ESA (40)	Vadadustat 150–600 mg/d versus PBO	↑	↓	↑	NR	↓

D, dialysis; ESA, erythropoiesis-stimulating agents; ESA-naïve, never previously exposed to ESA therapy; Hb, hemoglobin; HD, hemodialysis; Hep, hepcidin; NC, no change; ND, non-dialysis; NI, non-inferior versus continued ESA therapy; non-ESA, not receiving ESA therapy prior to the study; NR, not reported; PBO, placebo; PD, peritoneal dialysis; stable ESA, receiving ESA therapy prior to study; TIBC, total iron-binding capacity; t.i.w., thrice weekly; TSA/T, transferrin saturation. ^a Patients weighing 40 to <60 kg received oral roxadustat at an initial dose of 70 mg (non-dialysis [121]) or 100 mg t.i.w. (HD or PD [120]); patients weighing ≥60 kg received oral roxadustat at an initial dose of 100 mg (non-dialysis [121]) or 120 mg t.i.w. (HD or PD [121]) titrated to achieve an Hb level of 10.0–12.0 g/dL. ^b No change in the stable ESA group. ^c TSA/T decreased in patients not receiving iron supplements. ^d No change in patients previously receiving stable ESA. ^e In the group not previously receiving stable ESAs. ^f Dosed 3 times weekly. ^g ESA started after receiving PBO for 4 weeks.

Hb levels improved with roxadustat treatment in each of 2 phase 3 trials in patients with CKD in China, including patients with NDD-CKD and DD-CKD. In patients with anemia of NDD-CKD not receiving ESAs, roxadustat produced significantly greater increases in Hb than placebo [121], and in patients with DD-CKD receiving stable ESA therapy at baseline, roxadustat therapy was non-inferior to continuing ESA therapy [120]. Recent global, long-term studies have corroborated these findings. In a phase 3 randomized, double-blind trial of 922 patients with NDD-CKD in the USA, South America, New Zealand, Australia, and Asia, patients receiving roxadustat had a least-squares mean increase in Hb that was 1.85 g/dL greater than those receiving placebo [124]. A phase 3 study of 1,043 patients with CKD on dialysis for >2 weeks and ≤4 months found similar mean increases in Hb in patients treated with roxadustat (2.57 g/dL) compared with epoetin alfa (2.36 g/dL) [126]. Preliminary analyses of 3 phase 3 trials in patients with NDD-CKD found those treated with roxadustat had consistent, significant improvements in Hb ranging from 1.8 to 2.0 g/dL compared with placebo (0.2–0.4 g/dL) irrespective of geographic location [151]. Furthermore, 96.4 and 99.0% of patients receiving roxadustat had Hb >10.0 g/dL after 6 and 12 months of treatment, respectively [152].

Similar findings have been observed in phase 3 studies of other HIF-PH inhibitors. For example, in patients with DD-CKD in Japan, daprodustat was non-inferior to darbepoetin alfa in maintaining Hb levels when switched from stable ESA [133], and in 2 global studies in patients on incident or maintenance dialysis, vadadustat was non-inferior to darbepoetin alfa [153]. Likewise, interim (36 weeks) analysis of phase 3 studies in patients with NDD-CKD in Japan showed molidustat to be non-inferior to darbepoetin alfa in maintaining [141] or improving [142] Hb levels in patients who converted from stable ESA or who were ESA-naïve, respectively.

In patients with NDD-CKD with evidence of systemic inflammation, as indicated by elevated CRP levels, the baseline ESA dose was positively correlated with baseline CRP level [117], which is notable as inflammation is a suspected contributor to ESA hyporesponse. After switching from ESA therapy to roxadustat, Hb increases were independent of the baseline CRP level, and the average weekly dose required to maintain Hb levels was independent of baseline CRP level [117, 120]. In contrast, among patients who continued ESA therapy, Hb levels were consistently lower in patients with elevated CRP levels, despite receiving consistently higher ESA doses [120]. Preliminary analysis of recent global phase 3 trials has rein-

forced these findings as treatment with roxadustat resulted in similar increases in Hb across hsCRP concentration quintiles both in patients with DD-CKD (1.18–1.36 g/dL) [154] and NDD-CKD (1.90–1.96 g/dL) [155]. These results suggest that patients with anemia of CKD respond to roxadustat regardless of inflammatory status, providing a clear differentiation from ESAs. Furthermore, hepcidin levels decreased in patients randomized to roxadustat [120, 121], whereas there was no change in hepcidin levels in patients on placebo or ESA therapy. Reductions in hepcidin and improvements in Hb have been observed regardless of baseline CRP level and with or without iron supplementation [115]. In patients randomized to roxadustat alone, or with either oral or IV iron, the largest decreases in hepcidin levels occurred in those patients who received no exogenous iron, suggesting patients with DD-CKD may not require IV iron therapy during roxadustat treatment [115]. In phase 3 studies, decreased hepcidin with roxadustat was coincident with mean increases in total iron-binding capacity from baseline (18.2 μmol/L in patients with NDD-CKD and 10.0 μmol/L in DD-CKD) and mean decreases in serum ferritin (–93 μg/L in NDD-CKD and –119 μg/L in DD-CKD) from baseline, and similar improvements in iron parameters have been observed among multiple HIF-PH inhibitors (Table 2) [120, 121]. Collectively, these data suggest HIF-PH inhibitors improve iron homeostasis and may ameliorate functional iron deficiency.

The efficacy of HIF-PH inhibitors specifically in patients hyporesponsive to ESAs has been evaluated in a few instances. In a small phase 2 study, treatment with daprodustat for 12 weeks resulted in an increase or maintenance of Hb in the target range of 10.5–11.0 g/dL in 40% of patients chronically hyporesponsive to ESAs [130]. Interestingly, in a phase 3 trial, patients with DD-CKD in the highest tertile of ERI received a median weekly dose of darbepoetin alfa of 25.8 μg/week compared with 10.4 μg/week in the lowest ERI tertile; however, in patients randomized to daprodustat, the median daily dose was similar, 4 and 6 mg/day, between the lowest and highest ERI tertiles, respectively [133]. In preliminary analysis of an uncontrolled study of 64 patients on hemodialysis who were resistant to ESAs, treatment with roxadustat was associated with a slight increase in Hb and a significant decrease in PTH, a suspected contributor to ESA hyporesponse, after 8 weeks [156]. Among patients without diabetes in the study, conversion to roxadustat was also associated with an increase in Hb from 10.3 to 10.7 g/dL [157].

The safety of HIF-PH inhibitors is an area of ongoing investigation, including assessment of cardiovascular

outcomes and all-cause mortality. An analysis of 18 trials found no difference in the risk of adverse events or severe adverse events between HIF-PH inhibitors and controls (placebo or ESA) [150]. Despite this, concerns related to hyperkalemia, hypertension, thromboembolism, and comorbid malignancy or cardiovascular events persist owing to inconclusive evidence from trials to date or theoretical consequences of HIF activation [158]. Whether select adverse events are specific to individual HIF-PH inhibitors or are common to the class remains an open question and awaits future publications and/or data.

Data pertaining to the effects of treatment with an HIF-PH inhibitor on hard outcomes continue to emerge. In a single study of 836 patients on maintenance dialysis in central Europe, all-cause mortality was 15.4% with roxadustat and 12.1% with epoetin alfa or darbepoetin alfa [159]. Recently reported phase 3 studies in patients with NDD-CKD stages 3–5 found no significant difference in the risk of mortality [124] or in the incident mortality rate [127] in patients treated with roxadustat compared with placebo. In a phase 3 study of patients on dialysis >2 weeks and ≤4 months, the number of fatal treatment-emergent adverse events was similar between the roxadustat and epoetin alfa groups [126]. Recently, vadadustat did not meet the outcome of non-inferiority in time to first major adverse cardiovascular event (a composite of death, myocardial infarction, and stroke) versus darbepoetin alfa in patients with NDD-CKD [160], but was non-inferior to darbepoetin alfa in time to first major adverse cardiovascular event in patients with DD-CKD [153].

While HIF transcription factors regulate numerous biological processes including angiogenesis, glucose and cholesterol metabolism, and cell growth, motility, and death [60, 161, 162], adverse effects related to these processes have not been observed. Long-term safety of HIF-PH inhibitors beyond phase 3 trials, including non-erythropoietic effects, remains to be determined, and the comparative efficacy, safety, and cost-effectiveness of HIF-PH inhibitors relative to ESAs remain areas of active investigation [163].

Hepcidin Antagonists

Hepcidin is an attractive target in anemia of inflammation because elevated hepcidin levels are associated with iron sequestration and anemia [5]. Several hepcidin antagonists have been evaluated in humans. Single intravenous infusions of an anti-hepcidin l-oligoribonucleotide (lexaptetid, NOX-H94) suppressed hepcidin activity and prevented inflammation-associated iron sequestration in healthy volunteers [164]. In a subsequent study in healthy

volunteers, lexaptetid produced dose-dependent increases in serum iron concentration, serum ferritin, and TSAT after single and multiple IV doses [165].

Alternative strategies to block the effects of hepcidin include preventing its expression or interaction with ferroportin since hepcidin itself may be difficult to target due to its relatively high circulating levels and high turnover rate [166]. To these ends, monoclonal antibodies that target ferroportin (LY2928057) and bone morphogenetic protein 6 (LY3113593), a key regulator of hepcidin expression, have been developed. Their use increased serum iron and TSAT in healthy volunteers, and LY3113593 led to decreased hepcidin levels [166]. In phase 1 studies in patients with CKD, these antibodies either slowed the decline (LY2928057) or increased (LY3113593) Hb levels and both decreased ferritin relative to placebo [166]. Improvements in iron status appeared greater with LY2928057 than with LY3113593 in patients with CKD; however, the study of LY2928057 did not meet the pre-specified threshold for Hb efficacy, suggesting the agent may not be effective as monotherapy. Lexaptetid and LY2928057 increased serum hepcidin concentrations, which is of concern in patients with CKD as increased hepcidin expression is associated with CV events [165–167]. Potentially as a result of these considerations, the development of these agents appears to have been discontinued and their future remains unclear.

Considerations in Light of Coronavirus Disease 2019

Accumulating evidence from studies of SARS-CoV-2, the novel virus that caused the ongoing coronavirus disease 2019 (COVID-19) pandemic, shows that older patients and those with chronic illnesses such as CKD are at increased risk of infection, severity of disease, and mortality [168, 169]. An analysis of data from 257 critically ill patients in 2 New York City hospitals found that critically ill patients with COVID-19 had a median age of 62 years and that 82% had at least one chronic illness, while 14% had CKD [170]. Moreover, severe COVID-19 is characterized by a hyperinflammatory state and an observational study reported COVID-19 is associated with iron deficiency and hyperferritinemia that appear to persist up to 2 months after COVID-19 onset [171]. The vulnerability of patients with CKD, especially those on traditional hemodialysis requiring 3 times weekly visits to a dialysis center, is evident and self-isolation is necessary to reduce the risk of COVID-19 transmission [172–174]. Similarly, patients with anemia of CKD receiving IV iron

or an ESA require visits to an infusion center and are thus at higher risk of transmission. Treatment options that reduce the need for inter-person contact would be particularly valuable under such circumstances. Moreover, it has recently been suggested that ESAs may provide little benefit in patients with COVID-19 due to increased inflammation, but the full scope of this remains to be determined [175]. Here, orally administered alternatives to ESAs such as HIF-PH inhibitors and home dialysis modalities present strategies that could improve outcomes and alleviate the burden on patients with anemia of CKD and healthcare resources during crises.

Limitations

This review is limited by factors common to emerging therapies. As HIF-PH inhibitors are a relatively new class of therapeutic agents, there are discrepancies in the number of published studies among the various HIF-PH inhibitors. Further, data on patients hyporesponsive to ESAs are limited in part because these patients collectively carry a high disease burden and are often excluded from studies. Despite these limitations, multiple lines of indirect evidence suggest HIF-PH inhibitors should be explored further in this difficult-to-treat patient population.

Conclusions

ESA hyporesponse is associated with poor outcomes in patients with anemia of CKD. The use of high doses of ESA may be an underlying reason for increased morbidity and mortality. Disturbed iron homeostasis and inflammation are major contributors to the etiology of anemia in patients with CKD and may largely be responsible for ESA hyporesponse. Clinicians should therefore strive to eliminate sources of inflammation and infection, ensure adequate dialysis and nutrition, and correct absolute and functional iron deficiency in patients with ESA hyporesponse. Novel agents such as HIF-PH inhibitors and hepcidin antagonists, which address the fundamental defects that give rise to inflammatory anemia, are in clinical development. Although no studies to date have evaluated their efficacy specifically in patients hyporesponsive to ESAs, several lines of evidence suggest that HIF-PH inhibitors may offer advantages to these patients. Treatment with HIF-PH inhibitors is associated with increased Hb levels and improved iron metabolism, including decreased hepcidin levels, regardless of inflammation, iron

status, or dialysis modality; effects mediated through modest increases in endogenous EPO levels and improved iron mobilization and absorption. Accordingly, these agents appear to represent feasible therapeutic options for patients with anemia of CKD and may be particularly useful in patients hyporesponsive to ESAs.

Acknowledgements

Brian Woolums, PhD, and Meri Pozo, PhD, CMPP of inScience Communications (New York, NY, USA), provided editorial support funded by AstraZeneca.

Statement of Ethics

The manuscript was developed in compliance with the Good Publication Practice 3 (GPP3) guidelines.

Conflict of Interest Statement

M.R.W. serves as a scientific advisor to AstraZeneca; Boehringer Ingelheim; Janssen Pharmaceuticals, Inc.; Merck Sharp & Dohme; Otsuka Pharmaceutical Co.; and Vifor Pharma.

Funding Sources

The development of the manuscript was supported by AstraZeneca.

Author Contributions

The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript and takes responsibility for the integrity of the work as a whole. The author had full editorial control of the manuscript and provided his final approval of all content. The author has not received funding for this work.

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