Iron Therapy Challenges for the Treatment of Nondialysis CKD Patients

Francesco Locatelli, Sandro Mazzaferro,† and Jerry Yee‡*

Abstract

The clinical consequences of untreated, severe anemia in patients with nondialysis CKD can be significant, but disparities exist in the anemia treatment guidelines and position papers issued from working groups and associations across the world. These differ in hemoglobin target and iron levels and their emphasis on various iron markers and other clinical outcomes. Not surprisingly, disparities are observed in anemia treatment strategies among patients with nondialysis CKD across different areas of the world. Over the past decade, the prescription and dosage of both iron therapies and erythropoiesis-stimulating agents have shifted, with notable regional differences observed. Moreover, there is ongoing debate regarding oral versus intravenous administration of iron. Compared with oral iron therapy, which often leads to gastrointestinal adverse events, low patient adherence, and low efficacy, intravenous iron administration has been associated with potential serious adverse events, such as anaphylaxis. New iron–based compounds and drugs currently under development are reviewed to describe their potential benefits in the treatment of anemia in patients with CKD. New oral compounds, including iron–based phosphate binders, heme iron polypeptide, and liposomal iron, show different rates of absorption with possibly different efficacy and improved tolerability. These new potential therapies offer health care providers additional anemia treatment options for their patients with CKD; however, the management of anemia in the CKD population continues to present challenges that require prospective studies to identify the optimal iron therapy for patients.

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*Department of Nephrology, Dialysis and Transplantation, Alessandro Manzoni Hospital, Lecco, Italy; †Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, Sapienza University, Rome, Italy; and ‡Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, Michigan

Correspondence: Dr. Francesco Locatelli, Manzoni Hospital, Nephrology, via dell'eremo 9/11, Lecco, Italy 23900. Email: f.locatelli@ospedale.lecco.it

Introduction

Guidelines for treating anemia in patients with CKD, particularly patients with nondialysis (ND) -CKD, vary, especially across different areas of the world (1–8). In addition, the growing number of patients with CKD and anemia and the increasingly insufficient number of nephrologists have led primary care physicians, particularly those in the United States, to take on the burden of care for many of these patients (9). There are clinical and logistical concerns in treating to correct anemia in this patient population because of the scarcity of evidence regarding treatment of patients with ND-CKD compared with the dialysis CKD population. There are several causes, including the lack of access to facilities for intravenous (iv) administration, conflicting reports regarding safety of treatments, and poor tolerability and efficacy of oral preparations, particularly in patients with CKD stage 5. These concerns have caused confusion as to how to optimize anemia therapy for patients with ND-CKD and led some health care providers to choose not to treat anemia in these patients at all. However, untreated moderate to severe anemia in patients with CKD has been associated with left ventricular hypertrophy, congestive heart failure, and coronary heart disease (9). Additionally, untreated anemia can have consequences regarding the patient's overall health–related quality of life (HRQoL). Moreover, recent experimental (10) and clinical (11) evidence points to iron status as a modulator of fibroblast growth factor 23 (FGF23) and phosphate metabolism, thus broadening iron's potential clinical implications. Conversely, the consequence of excess iron can promote oxidative stress, leading to protein oxidation and lipid peroxidation. These processes may accelerate cellular apoptosis as shown in nonclinical studies; however, the association with advancing cardiovascular disease is proposed but not yet confirmed (12). A consensus is required to aid health care providers in choosing the best therapeutic plan to treat iron deficiency anemia in patients with ND-CKD. An overview of the current understanding of anemia in CKD, underlying mechanisms of erythropoiesis, and iron absorption is provided in Figure 1.

Current Treatment Guidelines

Taking into account these various anemia therapy approaches, treatment guidelines and position papers by a number of societies and working groups across the world have been developed. Guidance regarding patients with ND-CKD include the Kidney Disease Improving Global Outcomes (KDIGO) (1) and the Kidney Disease Outcomes Quality Initiative (2) guidelines and position papers from the Canadian Society of Nephrology (3–6), the National Institute for Health and Care Excellence (NICE) (7), and European Renal Best Practice (8) (Table 1). Although there are some exceptions, these guidelines and position papers are generally consistent regarding the

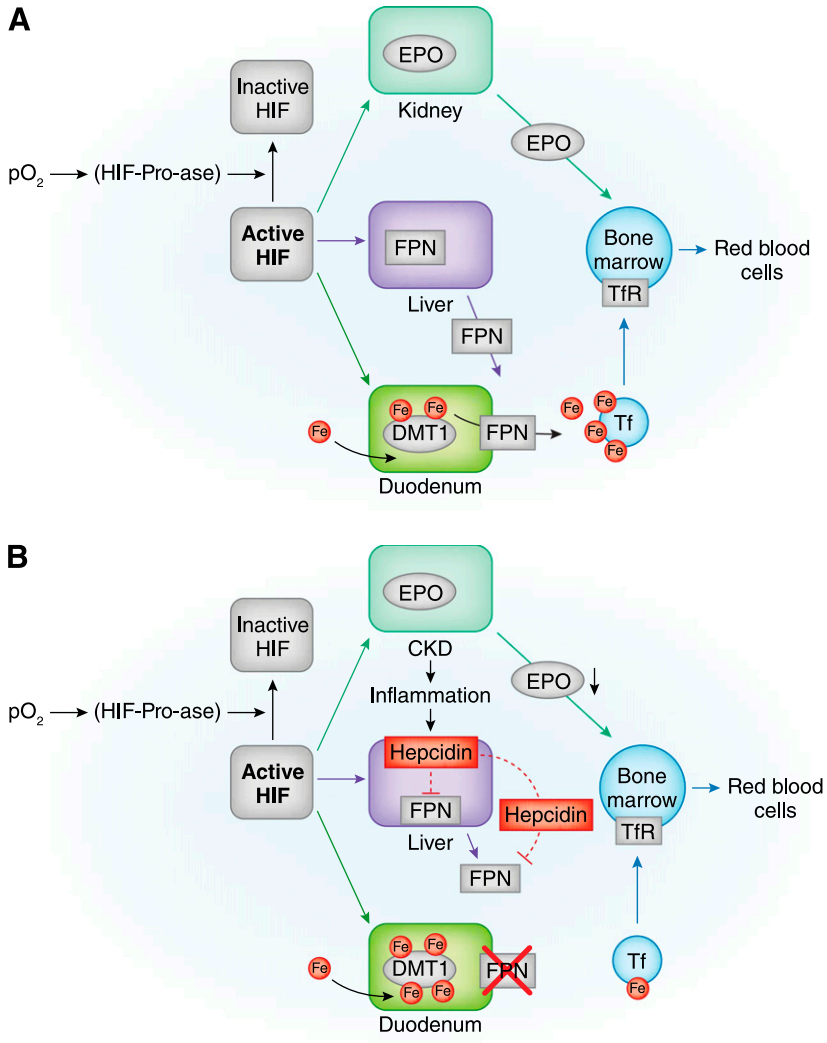

Figure 1. | **Anemia, erythropoiesis, and iron absorption in normal subjects and patients with CKD**. (A) In normal subjects, by inhibiting hypoxia–inducible factor–prolyl–hydroxylases (HIF-Pro-ase), hypoxia stabilizes hypoxia-inducible factor (HIF), thus increasing its activity. In time, the HIF signaling cascade increases renal synthesis of erythropoietin (EPO), liver synthesis of ferroportin (FPN), and duodenal synthesis of divalent metal transporter 1 (DMT1). By targeting duodenal cells, FPN favors iron transfer into blood. In blood, iron is bound to transferrin (Tf) and transported to transferrin receptor (TfR) –expressing cells. Bone marrow cells supplied with iron and stimulated by EPO can efficiently increase red blood cell production. (B) In chronic inflammatory states, like chronic renal failure , increments in HIF do not efficiently increase renal synthesis of EPO or liver synthesis of FPN. This last effect also results from increased liver synthesis of epcidin, an inflammatory cytokine capable of inhibiting both FPN liver synthesis and its binding to duodenal cells. Intestinal absorption of iron is blunted with possibly increased intracellular iron concentrations. With lower iron availability and inadequate EPO stimulation, bone marrow cannot efficiently increase red blood cell production. (C) Iron supply in chronic renal failure can be obtained by either oral or intravenous administration. The oral route can be regarded as physiologic but is hampered by reduced efficiency of intestinal absorption and gastrointestinal side effects; the unphysiologic intravenous administration is hindered by possible toxic effects through production of labile plasma iron (LPI). Lines indicate activation, and dashed lines indicate inhibition. Fe, iron; I.V., intravenous; pO_2, partial pressure of oxygen.

definition of hemoglobin (Hb) thresholds of anemia. However, they are less consistent in recommendations regarding iron supplementation and erythropoiesis–stimulating agent (ESA) use and defining target Hb ranges and maximum ferritin levels. Regional differences in treatment preferences are also evident, because the position papers from outside of the United States, including those from the NICE and the Canadian Society of Nephrology, generally consider HRQoL effects, whereas the United States–based guidance does not emphasize HRQoL parameters. However, all of the guidelines and position papers agree that any iron deficiency should be addressed before initiating ESA therapy and suggest that the decision to prescribe ESAs should be on the basis of Hb levels and clinical factors. These guidelines and position papers are updated periodically to reflect new research results; however, because of differences in how clinical trial results are evaluated and the lack of strong evidence supporting particular approaches, the interpretation of these results can be conflicting and lead to widely different treatment recommendations. In particular, studies of iron therapy have not provided clear results as opposed to the evidence supporting ESA use.

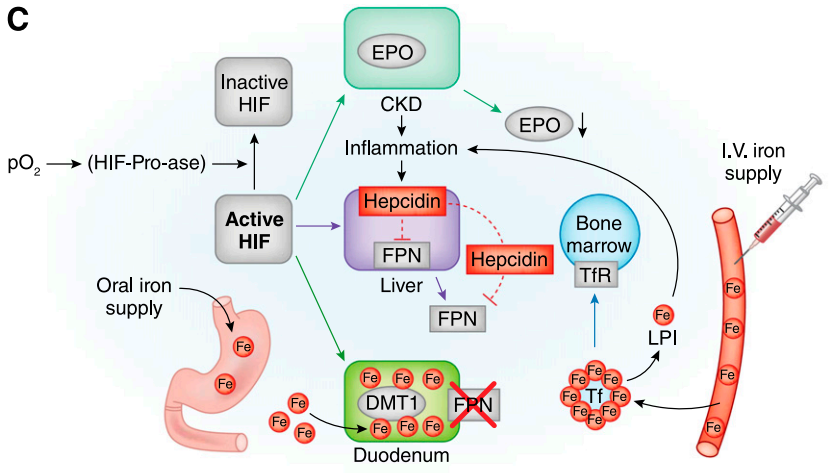

Figure 1. | **Continued**.

As reflected in the various criteria used in the guidelines and position papers described above, the evaluation of therapies for anemia presents a challenge to health care providers, because so many measures of effectiveness need to be considered, including efficacy targets, safety evaluations, and HRQoL. The most frequently used efficacy measurements to assess anemia therapies are Hb, ferritin (as a marker of iron stores), and transferrin saturation (TSAT; as a marker of available iron). Apoferritin is a hollow protein sphere that surrounds a core of hydrous ferric oxide, in which up to 4500 iron atoms can be stored bound to oxygen in the ferric state (13). Although all ferritins contain the same core structure, there are variations in the ferritin molecule depending on cell type and function (13,14). Interestingly, serum ferritin is derived from the same gene sequence as intracellular ferritin; however, serum ferritin is iron poor, because it consists predominantly of L-chain subunits, and there may be a combination of ferritin and apoferritin (not combined with iron) (15). In addition, there is current controversy regarding whether serum ferritin contains iron. Ferritin serves to sequester iron for storage; thus, when intracellular iron increases, ferritin synthesis increases, and expression of cell surface transferrin receptors decreases (16). The iron storage disorder called hereditary hemochromatosis, an autosomal recessive genetic disorder that usually results from defects in the *HFE* gene, although rare, should also be taken into consideration when evaluating patients with CKD for anemia (17). However, the specificity and sensitivity of ferritin and TSAT for the evaluation of iron status are not ideal, especially when evaluating iron repletion and excess iron, because they can be affected by other causes, such as inflammation (ferritin) and malnutrition (TSAT), providing misleading results (18).

Consequently, investigation into other biomarkers of iron deficiency has begun. Reticulocyte Hb content has been shown to be a more stable and sensitive marker of iron deficiency than ferritin or TSAT in a clinical trial of erythropoietin (EPO) -treated patients on dialysis but is not routinely tested in patients with ND-CKD (19). Other measures include the percentage of labile plasma iron (20), soluble transferrin receptor 1 (21), and hepcidin levels (22,23), but these assays must be further refined before general use (24,25).

In addition to efficacy measurements, the safety of treatments to correct iron deficiency anemia has become a growing concern, because severity of associated adverse events (AEs) needs to be carefully monitored. Also, although often neglected (26), the patient's overall HRQoL, including physical functioning, pain, general health and vitality, social functioning, and mental and emotional health (27), is another outcome to consider when choosing a treatment plan and biomarker targets. For example, HRQoL should be considered when choosing an upper Hb target, particularly in younger patients without comorbidities, because physical activity would be important to most of these patients.

ESA Therapy

Since the approval of recombinant human EPO by the Food and Drug Administration (FDA) in 1989, ESAs have become a key component of anemia treatment plans for patients with CKD. Therapy with ESAs is intended to stimulate erythropoiesis and consequently, increase Hb levels; however, as described above, target Hb levels are debated as well as the correlation between high Hb levels and HRQoL. Some studies have shown that higher Hb levels have a significant association with improved HRQoL scores, including both physical and mental summary scores and general health scores (28,29). In the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial, significantly better HRQoL measures were observed in the group treated with epoetin to maintain high Hb levels (130–150 g/L) over the group with a lower Hb target (105–115 g/L) (30). In the Correction of Hemoglobin and Outcomes in Renal insufficiency (CHOIR) Study, primary analysis of the composite events of death, myocardial infarction, hospitalization caused by congestive heart failure, and stroke showed a higher rate in patients with ND-CKD treated with weekly epoetin targeting a higher Hb level compared with those targeting a lower Hb level (135 versus 113 g/L; 17% versus 13.5%; $P=0.03$) (31).

Table 1. Summary of current clinical guidelines to treat anemia in adult patients with nondialysis-dependent CKD

Guideline	Diagnosis of Anemia	ESA Use	Iron Use	Hb Target	TSAT/Ferritin Target	Phosphorus Target	Adjuvants
KDIGO (1,83)	Hb<130 g/L in men >15 yr; Hb<120 g/L in women >15 yr	Initiate ESA therapy in those with Hb<100 g/L after all other correctable causes of anemia have been addressed and symptoms of anemia are present and for avoiding transfusions; therapy should be individualized for each patient[a]	1- to 3-mo trial of oral iron or iv iron[b] if TSAT is <30% and ferritin is <500 μg/L or ESA therapy is to be avoided or decreased (if already on ESA therapy)	Hb≤115 g/L in adults on ESA therapy but should be on the basis of individual patients	TSAT>30%/ferritin >500 μg/L	CKD stages 3–5: Maintain serum phosphorus within the normal range	Not recommended: androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline
KDOQI (2,84)	Hb<135 g/L in adult men; Hb<120 g/L in adult women	Initial ESA dose and ESA dose adjustments determined by the patient's Hb level, target Hb level, rate of increase in Hb level, and clinical circumstances[c]	Oral or iv iron administered to maintain ferritin >100 μg/L and TSAT>20% during ESA treatment[d]	Hb>110 g/L; ESA-treated patients should not be routinely maintained at Hb≥130 g/L	TSAT≥20%/ferritin >100 and <500 μg/L	Stages 3 and 4 CKD: ≥2.76 and <4.61 mg/dl; stage 5 CKD: >3.50 and <5.51 mg/dl	Not routinely recommended: L-carnitine and ascorbate; not recommended: androgens
Canadian Society of Nephrology (3–6,85)	Hb<135 g/L in men ≥18 yr; Hb<120 g/L in women ≥18 yr	Initiate ESA therapy when iron stores have been corrected, other reversible causes of anemia have been treated, and Hb level is sustained at <100 g/L in patients not receiving ESA therapy[e]; for patients receiving ESA therapy, target Hb is 110 g/L	Oral or iv iron to maintain target concentrations of TSAT and ferritin[f]; iron is not recommended for patients without evidence of classic iron deficiency whose Hb is >110 g/L	Hb<110 g/L (acceptable Hb range =100–120 g/L)	TSAT>20%/ferritin >100 μg/L; iron should be considered if patient is below target Hb or requires high ESA doses and has ferritin >800 μg/L and TSAT<25%	Does not recommend monitoring phosphorus for stage 3 CKD; stages 4 and 5 CKD: Maintain within normal range	Not recommended: androgens; insufficient evidence to recommend: L-carnitine, vitamin C, ultrapure dialysis, pentoxifylline, statins, vitamin B6, and quotidian dialysis
NICE (7)	Hb<110 g/L or development of symptoms attributable to anemia (tiredness, shortness of breath, lethargy, and palpitations)	ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency; ESAs not recommended in the presence of comorbidities or a prognosis that is likely to negate the benefits of correcting the anemia[g]	Oral or iv iron to maintain hypochromic RBC, reticulocyte, or TSAT and ferritin targets	100–120 g/L; rate of Hb increase should be between 10 and 20 g/L per mo in patients on ESA therapy[h]	Recommend using hypochromic RBC >6% (unless ferritin is >800 μg/L) or reticulocyte count >29 pg (unless ferritin is >800 μg/L); if tests are not available, TSAT>20%/ferritin >100 μg/L; maintain ferritin <800 μg/L in patients on iron therapy	Recommend following British, American, and European treatment guidelines	Not recommended: androgens, vitamin C, folic acid, and carnitine

Table 1. (Continued)

Guideline	Diagnosis of Anemia	ESA Use	Iron Use	Hb Target	TSAT/Ferritin Target	Phosphorus Target	Adjuvants
ERBP (8,86)	Hb<135 g/L in adult men ≤70 yr; Hb<132 g/L in adult men >70 yr; Hb<120 g/L in adult women	In low-risk patients or those in whom a clear benefit in quality of life can be foreseen, ESA therapy can be considered at Hb<120 g/L; in high-risk patients, ESA therapy should be initiated at Hb values between 90 and 100 g/L[i]	Oral or iv iron if TSAT is <20% and ferritin is <100 μg/L or if Hb increases without ESA therapy, TSAT is <25%, and ferritin is <200 μg/L; in patients on ESA therapy in whom increase in Hb or decrease in ESA dose is desired, oral or iv iron may be given when TSAT is <30% and ferritin is <300 μg/L	100–120 g/L; not >130 g/L for patients receiving ESA therapy; approximately 100 g/L in high-risk patients	TSAT≥20%/ferritin = 100 μg/L; should not exceed TSAT>30%/ferritin >500 μg/L	For CKD stages 3–5, maintain within normal range	Not recommended

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TSAT, saturated transferrin; KDIGO, Kidney Disease Improving Global Outcomes; iv, intravenous; KDOQI, Kidney Disease Outcomes Quality Initiative; NICE, National Institute for Health and Care Excellence; RBC, red blood cell; ERBP, European Renal Best Practice.

[a]ESA dosing should be on the basis of the individual patient Hb, body weight, and clinical circumstances and should be adjusted on the basis of Hb, rate of change in Hb, current ESA dose, and clinical circumstances. The choice of ESA should be on the basis of the balance of pharmacodynamics, safety information, clinical outcome data, cost, and availability. Subcutaneous dosing is recommended for administration of ESA therapy to patients with nondialysis CKD. Initiation of ESA therapy should be with great caution, if at all, in patients with active malignancy or a history of stroke.

[b]The route of iron administration should be on the basis of the severity of iron deficiency, the availability of venous access, response to prior oral iron therapy, side effects with prior iron therapy, patient compliance, and cost.

[c]The route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and class of ESA used in adults. The anticipated frequency and pain of administration and the potential effects on the child and family should also be considered in pediatric patients. Convenience favors subcutaneous administration and less frequent ESA administration in adult patients with nondialysis CKD.

[d]Clinicians should judge the individual patient's clinical status and ESA responsiveness and base iron treatment decisions on this assessment.

[e]ESAs should be administered subcutaneously on the basis of improved efficacy and convenience.

[f]Oral iron is the preferred first–line therapy in patients with nondialysis CKD. In patients who do not meet serum ferritin or TSAT targets on oral iron or in whom oral iron is not tolerated, iv iron may be used. The medical decision regarding the use of iron therapy should be guided by results of iron status tests together with Hb levels, ESA dose, and patient status.

[g]When ESA has been initiated, the effectiveness of the ESA should be assessed after an agreed on interval. Where appropriate, a mutual decision between the clinician, the patient with anemia and CKD, and the family/caregivers should be made on whether to continue ESA therapy. The patient and clinician should agree to the route of ESA administration taking into account the individual patient's clinical course, pain of injection, frequency of administration, lifestyle and preferences, efficacy, and cost.

[h]When determining individual Hb targets for patients with anemia and CKD, take into account patient preferences, symptoms, comorbidities, and the required treatment.

[i]The decision on whether and when to begin ESA therapy in patients with nondialysis CKD should be individualized and take into account the rate of fall of Hb, prior response to iron therapy, risk of transfusion, risks related to ESA therapy, and the presence of symptoms attributable to anemia. Hb values should not routinely be allowed to fall to <100 g/L in patients with nondialysis CKD. Therapy with ESAs should not be started if there is a temporary and obvious cause of anemia that is potentially reversible. Risk factors for stroke, a history of malignancy, or the presence of active malignancy should be considered when weighing the risk-to-benefit ratio of ESA therapy.

Attempting to attain the higher Hb concentrations required higher doses of epoetin, and these doses were associated with more AEs. The CHOIR Study also indicated no significant increase in overall HRQoL outcomes at higher Hb values. The placebo–controlled Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), which evaluated patients with CKD and type 2 diabetes, found no differences in the composite primary end point of mortality and cardiovascular comorbidities, whereas there was increased risk of stroke and neoplasia in ESA-treated patients; however, a secondary analysis showed that patients in the ESA group reported a significant improvement in fatigue compared with those in the placebo group as well as numerically, but not significantly, higher improvements in other HRQoL measures in the ESA group (32).

In the United States, EPO dosages decreased by about 20% from 2005 to 2009 among patients with ND-CKD (33). Additionally, an analysis of ESA use among the ND-CKD population in the United States before and after the release of results from the TREAT showed that, in the 2 years after the release of the study results, ESA use declined 38% and 22% among patients with ND-CKD stage 3 or 4, respectively (34). Also, a 15% decrease was observed in Hb levels >120 g/L among patients with ND-CKD (33,35). In 2011, the FDA changed ESA prescribing to remove the target Hb range of 10–12 g/dl and replaced it with the recommendation to consider initiating ESA treatment when Hb is <10 g/dl and symptoms of anemia are present (36).

In contrast to the trends observed in the United States, between 2008 and 2013 in Sweden, ESA doses slightly increased among patients with ND-CKD (37). In Taiwan, restrictive criteria for ESA reimbursement were introduced by the National Health Insurance Administration in 1996, resulting in much lower ESA dosing and use (38). These guidelines provide strict criteria for when ESA therapy can be initiated in patients with ND-CKD (serum creatinine >6 mg/dl and a hematocrit <28% to maintain a hematocrit level not exceeding 30%), limiting its use in this patient population (38).

Iron Therapy

The treatment guidelines universally recommend iron therapy to correct iron deficiency in patients with ND-CKD (Table 1); however; the type of iron therapy and route of administration have been topics of much controversy, with differences observed regionally. In patients with ND-CKD in Sweden, oral iron therapy decreased from 15.1% in 2008 to 11.0% in 2013, whereas iv iron administration increased from 3.8% in 2008 to 5.5% in 2013 (37). Although changes in iron therapy administration among the ND-CKD population have not been collected in the United States or many other regions of the world, trends in recent years in the United States among the dialysis CKD population have shown an increase in iv iron administration (39). The reason for these regional differences in iron use could be because of differences in guidelines, but there are not enough data regarding the ND-CKD population at this time to draw such conclusions. The CKD Outcomes and Practice Patterns Study team is a collaborative research relationship among experts in France, Germany, Brazil, and the United States that uses its international scope to facilitate comparisons of nephrology practices in different countries. The overall goal is to develop an evidence base for the effective treatment of advanced CKD, thereby improving care and outcomes for future patients. Numerous topics are currently being explored, including anemia; thus, these studies may provide insight into these trends in the future.

Changes in iron therapy trends have been observed regionally and over the past decade, and ferritin levels in the dialysis population have shown increasing variation among countries, with the United States presenting with the highest national average of ferritin and Japan showing the lowest (40). These country-specific differences are not as clearly identified in the ND-CKD population. In the latest study from Sweden of patients with ND-CKD, average serum ferritin levels did not change significantly over the period from 2008 to 2013, despite increases in iv iron use over that same period (37). It would be interesting to identify whether the increase in ferritin levels within the United States CKD population occurs earlier during disease management or if the increase in ferritin coincides with the incidence of dialysis. Despite the recognition that ferritin is a poor marker of iron stores, it remains to be identified if elevated levels of ferritin contribute to poorer outcomes, especially in patients with ND-CKD. For example, a prospective study in patients with ND-CKD showed a dose dependency between iv iron doses and liver iron concentration; however, no dose dependency was observed in changes in serum ferritin or TSAT concentrations (18,41–43).

Iron supplementation can be administered by iv and oral routes (1,2,7,8). The KDIGO guidelines recommend that, for patients with ND-CKD who require iron supplementation, the route of iron administration should be selected on the basis of severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or iv iron therapy, patient adherence, and cost (1). Health care providers have begun reconsidering oral iron therapy over iv iron therapy, particularly for the ND-CKD population, for multiple reasons, including safety concerns regarding the regulation of iv iron, ease of administration, vein preservation for future vascular access, and cost. Typical AEs associated with oral iron administration are nausea, vomiting, constipation, and a metallic taste, which are usually reported as relatively mild in intensity (44).

iv Iron Therapies

iv Iron was evaluated for treating anemia as early as 1932 (45), but the 10% ferric ammonium citrate formulation produced severe AEs. Updated iv iron formulations were introduced for treating anemia beginning in 1964. Early iv iron formulations, such as high molecular weight dextran, raised concerns of severe anaphylactoid reactions (46). Newer formulations have sought to reduce immunogenicity by reducing the size and branch characteristics of the polysaccharide, which may reduce some of the safety issues associated with earlier formulations (47).

Moreover, treatment with iv iron has also raised more serious safety concerns, such as for renal injury (48), cardiovascular injury (49), calciphylaxis (50), and labile iron

toxicity (51). The administration of iv iron has been shown to cause oxidative stress from large amounts of iron being introduced in the blood during a single infusion (48). In an *in vitro* study comparing iv iron dextran, iron sucrose, iron gluconate, and iron oligosaccharide, all formulations produced oxidative stress, which was shown by increases in lipid peroxidation (52). However, differences in cell death were observed in this study where ferric sucrose caused the highest rate of cell death, followed by ferric glucose, ferric dextrose, and ferric oligosaccharide, indicating significantly different toxicity profiles (52). These *in vitro* data have been supported by animal studies (53) as well as studies in patients on hemodialysis (54,55) and patients with ND-CKD (56). In a study of patients with ND-CKD treated with iv ferric carboxymaltose, levels of both oxidative stress and inflammatory markers increased after iron treatment, regardless of response to the iron therapy (56). Oxidative stress markers analyzed included oxidized low–density lipid protein, protein carbonyl groups, erythrocyte superoxide dismutase, and glutathione peroxidase. Glutathione peroxidase activity was lower in nonresponders compared with responders; however, levels of all other oxidative stress markers did not show significant differences between the two groups. The long-term effects of such iron–induced oxidative stress have not been determined.

Recent clinical trial results have continued to present conflicting efficacy and safety conclusions regarding the use of iv iron to treat anemia in the ND-CKD population. In the randomized, clinical trial the Randomized Trial to Evaluate Intravenous and Oral Iron in Chronic Kidney Disease (REVOKE) that investigated iv iron sucrose (200 mg once every 2 weeks for a total of 1 g) versus oral ferrous sulfate (325 mg three times daily for 8 weeks) in patients with ND-CKD and moderate to severe anemia, efficacy measurements were similar between the two treatment groups. However, the trial was terminated early because of an increased risk of serious AEs, particularly cardiovascular AEs and infections, in the iv iron treatment group (57). In contrast, another randomized clinical trial known as the Ferinject Assessment in Patients with Iron Deficiency Anemia and Non-Dialysis-Dependent Chronic Kidney Disease Study evaluated the difference between iv ferric carboxymaltose (high [1000 mg followed by 500–1000 mg every 4 weeks depending on ferritin level] and low [200 mg followed by 200 mg every 4 weeks] doses) and oral iron therapy (100 mg ferrous sulfate twice daily) in the same population and found that iv iron therapy was more effective in reaching and maintaining Hb levels and reduced the need for additional anemia management (58). The investigators did not observe the same increase in serious AEs as those reported in the REVOKE. Similarly, in an open-label clinical trial comparing iv ferric carboxymaltose (1000 mg up to three times over 8 weeks) with oral ferrous sulfate (325 mg three times daily), statistically significant increases in Hb, ferritin, and TSAT were observed in the iv versus oral group, with significantly fewer treatment–related AEs in the iv iron group (59). A recent phase 3, open-label clinical study compared the use of iv iron isomaltoside 1000 (500–1000 mg weekly) with oral ferrous sulfate (100 mg twice daily) in ESA-naïve patients with ND-CKD over 8 weeks and found that the iv iron group had statistically significant improvement of iron deficiency markers, including Hb, serum ferritin, and TSAT concentrations, over the oral iron group (60). A similar number of AEs was reported in each treatment group; however, a larger percentage of patients in the oral ferrous sulfate group (4.3% versus 0.9%) discontinued the trial because of AEs. Thus, safety results in regards to iv iron administration are different among studies, and the long-term consequences of continued iv iron are yet to be determined.

Other considerations for iv versus oral iron administration include ease of administration and cost. Oral iron is inexpensive and administered at home. Patients receiving iv iron are required to visit a health care facility for treatment by a skilled health care professional. Although considered rare, AEs (especially with first treatment or initiation of a new formulation), including acute chest and back tightness, allergic reactions, or anaphylactic shock (61), can occur, and, thus, the iv iron therapies should only be administered in facilities where resuscitation and treatments for anaphylaxis are readily available (62). Although rare, the chance of allergic reactions with iron treatment prompted the European Medicines Agency to release new recommendations to manage the risk of allergic reactions with iron-containing medicines in 2013 (63). In addition, recurrent infusions of iron can lead to problems with venous anatomy and quality, thereby compromising future vascular access construction (1), which needs to be preserved for potential future hemodialysis treatments.

Oral Iron Therapies

The use of oral iron in medicine has a more colorful history (64). Although oral ferrous sulfate was empirically prescribed as early as the 1700s to treat "chlorosis" in adolescent girls, which was characterized by "pale color, palpitation of the heart," and "confusion of the spirits," it was only in the 1830s that any rationale for this treatment for anemia was provided (64). Still, it remained contested into the late 1890s whether inorganic iron could be incorporated into Hb, and the relationship between oral iron and anemia was finally accepted with the advent of radioactive tracer experiments in the late 1930s that showed gut iron absorption (64).

The bioavailability of oral iron sources has been a major concern for the treatment of anemia. Iron is absorbed in the intestine in a highly regulated metabolic cycle. Hepcidin has been shown to be an important regulator of iron metabolism by inhibiting release of intestinal iron being absorbed into the blood (65). Hepcidin inhibition increases during states of inflammation, such as inflammation experienced by patients with CKD, and during iron overload, resulting in decreased iron absorption (Figure 1) (65,66). Thus, new oral iron therapies are required to provide efficacy with better patient compliance. The most promising of the new therapies along with conventional options for oral iron supplementation are reviewed in Table 2, and a summary of oral iron therapies is also provided in Table 2.

Iron Salts

Iron salts have historically been the most common form of oral iron supplementation used in patients with ND-CKD. Iron salts exist as the ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms. For gut absorption, iron must be in the ferrous

Table 2. Oral iron supplementation therapies in patients with nondialysis-dependent CKD

Therapy	Chemical Formula	Therapy Duration	Efficacy Measures[a]			Adverse Events		Studies in Nondialysis CKD
			Hb	Fer	TSAT	Frequency, %[b]	Most Common Adverse Events[c]	
Ferrous sulfate	$FeSO_4$	8 wk	X	X	X	68.1	Stool discoloration, URI, diarrhea, traumatic injury, fall, constipation, dyspnea, chest pain, dizziness, UTI, hyperkalemia, hypertension	Agarwal *et al.* (57)
Ferrous sulfate	$FeSO_4$	52 wk	X	X	X	81.7	Diarrhea, constipation, hypertension, peripheral edema, dyspepsia, UTI, nasopharyngitis	Macdougall *et al.* (58)
Ferrous sulfate	$FeSO_4$	56 d	X	—	X	59.2	Constipation	Qunibi *et al.* (59)
Ferrous sulfate	$FeSO_4$	12 mo	—	—	—	NR	NR	McMahon *et al.* (87)
Ferrous sulfate	$FeSO_4$	6 wk	—	X	X	20[d]	Constipation, stool discoloration, nausea, diarrhea	Agarwal *et al.* (88)
Ferrous sulfate	$FeSO_4$	29 d	X	—	—	NR	NR	Charytan *et al.* (89)
Ferrous sulfate	$FeSO_4$	56 d	X	X	X	19	Constipation, diarrhea, nausea, vomiting	Van Wyck *et al.* (90)
Ferrous sulfate	$FeSO_4$	3 mo	X	—	—	NR	NR	Aggarwal *et al.* (91)
Ferrous sulfate	$FeSO_4$	5.2 mo	X	X	NR	NR	NR	Stoves *et al.* (92)
Ferrous fumarate	$C_4H_2FeO_4$	21 d	X	X	X	52	Constipation, diarrhea	Spinowitz *et al.* (93)
Ferric citrate	$FeC_3H_5O(COO)_3$	12 wk	X	X	X	68.3	Diarrhea, constipation, abdominal discomfort, abdominal distension[e]	Yokoyama *et al.* (94)
Ferric citrate	$FeC_3H_5O(COO)_3$	12 wk	X	X	X	69.3	Stool discoloration, diarrhea, constipation, nausea, vomiting, URI	Block *et al.* (74)
Heme iron		6 mo	X	X	X	NR	Constipation, abdominal cramps, muscle cramps, bloating, diarrhea, nausea	Nagaraju *et al.* (80)
Liposomal iron	$Fe_4(P_2O_7)_3$	3 mo	X	—	—	3.1[d]	—	Pisani *et al.* (81)

Hb, hemoglobin; Fer, ferritin; TSAT, transferrin saturation, X, evidence of therapeutic efficacy for the given measure; URI, upper respiratory tract infection; UTI, urinary tract infection; —, lack of efficacy evidence; NR, not reported.

[a]Assessed at the conclusion of treatment.

[b]Unless otherwise noted, percentage of subjects experiencing at least one adverse event.

[c]Unless otherwise noted, most common treatment–emergent adverse events occurring in ≥5% of participants.

[d]Percentage of subjects experiencing at least one treatment–related adverse event.

[e]Most common treatment–emergent and –related adverse events occurring in ≥5% of participants.

form; thus, dietary ferric iron is reduced to the ferrous form to be absorbed (67). Prescribed oral iron salt preparations are in the ferrous form, including ferrous sulfate, ferrous fumarate, ferrous gluconate, and polysaccharide iron complex (68). Among these, ferrous sulfate is by far the most frequently prescribed for treating anemia in patients with ND-CKD (44). These oral iron salts have been shown to increase Hb, ferritin, and TSAT in this population (69,70). Administration of these iron salts can produce a rapid release of iron ions in the gastrointestinal tract, leading to oxidative stress and resulting AEs, particularly those affecting the gastrointestinal tract (67,71). Mild to moderate AEs of constipation, nausea, vomiting, and diarrhea are often reported in trials of oral iron salts, such as ferrous sulfate, but serious AEs related to treatment are rare. Recent evidence has also suggested that unabsorbed oral iron can lead to changes in the intestinal microbiome by stimulating the growth of bacterial pathogens, which threaten the natural microbiota of the gut and lead to additional AEs (72). Because of frequent gastrointestinal side effects, patients with ND-CKD often have reduced adherence to oral iron therapy (44).

Iron–Based Phosphate Binders

Ferric citrate is an oral compound comprising trivalent iron with citrate. Originally developed and approved for use as a phosphate binder, it is water soluble and dissociates into ferric iron and citrate in the intestinal lumen (73). In a phase 2 study in patients with ND-CKD to evaluate the change in serum phosphate and TSAT, ferric citrate increased measures of iron repletion, including Hb, ferritin, and TSAT (74). As with other iron preparations, the most frequently observed AEs with ferric citrate were gastrointestinal (74). A phase 3 trial (NCT02268994) is currently underway in the United States to evaluate the effect of ferric citrate on changes in Hb compared with placebo in patients with ND-CKD. Sucroferric oxhydroxide is another iron–based phosphate binder recently approved for treatment of patients with CKD; however, the clinical trials showed no clinical or statistical increase in iron parameters when used as a phosphate binder in patients with CKD on dialysis (75).

Recent studies of the molecular mechanism of phosphate homeostasis have suggested a link between hyperphosphatemia and iron deficiency through the key regulatory hormone FGF23 (11). In addition, a historical population–based study found that higher phosphorus levels in patients with early CKD resulted in a greater chance of having anemia (76). Interestingly, ferric citrate, being administered with meals as a phosphate binder, has been shown to reduce FGF23 and increase iron parameters in ND-CKD (74).

Heme Iron Polypeptide

Heme iron polypeptide is an oral iron therapy that uses the heme porphyrin ring to supply iron to sites of absorption in the intestinal lumen (77). Because heme iron is absorbed *via* a different receptor than in nonheme (ionic) iron, the bioavailability of heme iron polypeptide in healthy individuals is significantly greater than that for nonheme iron (78). However, this increase has not uniformly translated into markedly improved outcomes in clinical studies (79). Nevertheless, heme iron polypeptide increases levels of Hb, ferritin, and TSAT in patients with ND-CKD (80).

As with other forms of oral iron supplementation, AEs associated with heme iron polypeptide therapy are primarily related to the gastrointestinal system in patients with ND-CKD. These AEs occurred at a frequency similar to that observed with iv iron therapy, including constipation, abdominal cramps, muscle cramps, bloating, diarrhea, and nausea (80).

Liposomal Iron

Liposomal iron is an oral iron preparation in which iron, as ferric pyrophosphate, is carried within a phospholipid membrane. Liposomal iron does not directly contact the intestinal mucosa before its release by liver enzymes. Consequently, this method of iron supplementation is associated with high gastrointestinal absorption, high bioavailability, and a low incidence of side effects (77).

Liposomal iron is an investigational drug currently under study. AEs associated with liposomal iron therapy in patients with ND-CKD occur at a lower frequency than typically observed for other oral or iv iron supplementation strategies (81). These AEs are generally mild and primarily related to the gastrointestinal system, with the most common being constipation, diarrhea, nausea, and headache. This therapy increases iron stores and Hb levels in patients with ND-CKD, but early data suggest that it does so less effectively than iv iron therapy (81).

Other Approaches to Treat Iron Deficiency Anemia in Patients with CKD

Although ESAs and iron therapy continue to be the main therapies used in the treatment of anemia in patients with CKD, other approaches to anemia treatment are currently being investigated in clinical studies. These include hypoxia–inducible factor stabilizers and hepcidin modulators (82). In addition to ESA and iron therapies, these could offer alternative or complementary therapies for the treatment of anemia in patients with CKD.

Conclusions

Despite disparities regarding target iron levels and the absence of reliable markers of iron deficiency, the importance of correcting iron deficiency in patients with CKD is indisputable. Oral iron therapies offer safe and effective options to treat iron deficiency anemia in patients with CKD in a physiologic way. In contrast to iv iron therapies, oral iron treatments require few resources for administration and are not associated with potential serious AEs. However, traditional oral iron treatments are not optimal because of increased gastrointestinal AEs, lack of patient adherence, and very often, lack of efficacy in patients with stage 5 CKD. Overall, treatments currently under development for iron deficiency anemia may represent an improvement in therapeutic options to treat iron deficiency anemia.

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